

Review article

Allergy and sports

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Introduction

At the beginning of the third millennium, physical exercise is often seen as a kind of panacea (a Greek word meaning “a cure for every sickness”); there is no doubt that it induces an increase in an individual’s socialization and self-esteem, but it also has positive physiologic and psychologic effects, improving the functioning of the cardiovascular, respiratory, and muscular systems, and leading to modifications in diet. Sports competitions are now an important part of economic, social, and cultural life, and leading athletes represent a model to be imitated by the majority of young people and children. Thus, a large proportion of the young population practice exercise and sports in order to achieve the best results from their bodies.

Because allergic illnesses in industrialized countries affect 10–25% of the population (1), it may reasonably be hypothesized that this percentage will be the same for athletes and amateurs of various sporting disciplines.

Could it be that a well-trained amateur or a professional athlete faces some problems of a pseudoallergic type when performing physical exercise? Or is it conceivable that an allergic subject can practice sports at the expert level and, indeed, become a champion?

These issues will be examined in this review article.

Sports activity induces modifications of some immunologic parameters

The different studies performed so far in this field are

not very easily comparable owing to the different modalities of exercise (acute, prolonged, training season, etc.) or different sports (running, cycling, swimming, football, etc.) examined up to now. The methods employed to perform these studies have also been extremely varied: they range from the simple evaluation of leukocyte counts to that of the different lymphocyte subpopulations; from their response to mitogens to the study of cytokine production.

Physical exercise can bring about modifications of various immunologic parameters. These studies could be an interesting point of research for that, as well as for the pathogenesis of recognized allergic disorders arising from sports.

Various studies have revealed modifications in mononucleate blood cells (2–10). In general, increased levels of all the lymphocyte subclasses have been found during acute exercise, and some authors describe a fall in the CD4/CD8 ratio (11). At the end of the exercise, values fall below normal levels; according to a number of authors (2, 12, 13), both the duration and the suppression of the values depend on the intensity and duration of the exercise itself. The concentration of neutrophils increases during exercise, and continues to increase when exercise has finished (13); their oxidizing activity is reduced (14).

Controversial data have been obtained on the activity of natural killer (NK) cells: they can be found to increase during exercise (15), subsequently decreasing at the end of the effort (perhaps following the prostaglandins produced by the activated monocytes [16]), or to be unchanged (17, 18), or to be reduced (19). A meta-

analysis of 94 studies evaluating NK cell counts showed that there is a marked increase at the end of exercise (catecholamin-mediated demargination of cells?), whereas the cell count dropped after exercise to less than half of normal levels (20).

The production of cytokines appears to increase as a response to acute exercise; proinflammatory cytokines (IL-1, IL-6 [21], and TNF- α) (22) are found at increased values after prolonged exercise (a 20-km run, for instance); increased IL-1 β is found in the muscular tissue (23), and increased activity of IL-1 can be noted (24), although other authors (22) have found a suppression of their production 1 h after exercise. It is thought that IL-1 and TNF- α may be responsible for muscular proteolysis, since the injection of these cytokines in animals causes a release of branched chain amino acids from the skeletal muscle (25).

As far as B cells are concerned, their modification during physical exercise has not yet been fully clarified; there seems to be a reduced *in vitro* functionality after the traditional stimuli used in the laboratory, and this is generally reversible (26).

No modifications have been found in IgE and its production (27).

It is worth noting the finding (28) of a marked decrease of salivary IgA levels in athletes during and after a training season. This could be a predictive marker of infectious risk for athletes (29), and also for allergic patients performing various physical activities.

To explain the susceptibility of some elite athletes to infections (especially of the upper respiratory tract) during the competition season, one of the first hypotheses to be proposed is the so-called "open window" (5, 30, 31), meaning that between 3 and 72 h after exercise (according to the parameters being measured) there may be an increased risk of clinical events (32). This can be considered an important factor increasing, as we shall see, the risk of exercise-induced asthma.

Allergy and exercise

The three principal disorders which correlate allergic diseases with exercise and the practice of sport are the following:

- 1) exercise-induced asthma (EIA)
- 2) exercise-induced anaphylaxis (EIA_n)
- 3) exercise-induced urticaria (EIU).

Exercise-induced asthma (EIA)

EIA (the word *asthma* comes from the Greek word $\alpha\sigma\theta\mu\alpha$, as Hippocrates denoted breathing with difficulty) was first described around 2000 years ago, probably by Aretaeus of Cappadocia (33, 34). Asthma has recently been defined as a "chronic

inflammatory disease of the respiratory tract in which a number of cells have an important pathogenic role, including mastocytes, eosinophils, and the T lymphocytes. In susceptible individuals this specific inflammation provokes recurring episodes of dyspnoea, a sense of suffocation, thoracic constrictions and coughing, above all during the night and in the early hours of the morning" (35). Generally, it is divided into "allergic" (or extrinsic) and "nonallergic" (or intrinsic) (36). The accumulation of eosinophils in the airways, the production of various proinflammatory cytokines leading to the activation of endothelial cells inducing, in turn, adhesion molecules such as ICAM-1, ICAM-2, and ICAM-3 (37), VCAM-1, selectins, and RANTES, leads to a complex inflammatory process which ends with several clinical expressions that depend both on the various stimuli and on individual responses based, for asthmatic subjects, mainly on atopy (38–45).

Exercise may trigger asthma attacks. EIA represents the major risk for an allergic patient taking exercise, but, at the same time, exercise can cause serious respiratory problems also in nonasthmatic subjects.

Clinical aspects of EIA

About 75–80% of asthmatic subjects out of therapy (38) may experience an asthma attack when practicing physical activity, but in recent years, even in apparently healthy, asymptomatic, and nonallergic subjects, some episodes of EIA have been described. Moreover, EIA is one of the main causes of asthma attacks in young children, often being the first symptom of atopy.

The term "exercise-induced bronchoconstriction" (EIB) is sometimes (46) used to distinguish a physiologic response to hyperpnea, and to the drying out of the mucous membranes, from a true disease.

There is a close link between EIA and sports: it is our task, by means of appropriate therapies, to allow asthmatic athletes to achieve their maximum potential; on the other hand, it has been observed that many endurance athletes, despite being asymptomatic at the beginning of their career, may develop asthma symptoms during the years of athletic activity, particularly when the activity is continued after the age of 28 (47).

The symptoms are easily identifiable. They include coughing, dyspnea, thoracic constriction, and wheezing occurring several minutes after physical exertion has stopped (generally 2–10 min, peaking at around 10–15 min); they disappear spontaneously, however, after a period of time varying between 30 and 60 min (38, 48). The bronchospastic crisis (which may be slight or extremely serious, with even fatal consequences) is followed by a 2–3-h period during which renewed exertion generally does not create any kind of problem, or at most very slight symptoms.

Regardless of the mechanism which gives rise to exercise-induced asthma (vascular or osmolar hypoth-

esis) (38, 49–53), two factors are essential for EIA to be induced: the first one is the type of physical activity (exercise requiring more hyperventilation induces EIA more easily); the second one is the environment, since EIA is more frequent when the air is cold and dry. Moreover, if the bronchial reactivity is very high, a moderate ventilatory increment is sufficient to induce the symptoms; if bronchial reactivity is moderate (as, for example, in the case of a patient with pollen allergy during the interseasonal period), ventilation has to reach high levels in order to represent an adequate stimulus (54, 55).

Allergic subjects are a typical example of this situation: in spring, for example, a notable increase in the number of cases of EIA has been found; this is due both to the inhalation of various pollens, and to an increase in bronchial reactivity owing to the inflammation of the airways observed during that period. The same is true for other seasons with a corresponding increase in other pollens (*Ambrosia*, *Compositae*, *Parietaria*, olive, and others). Individuals who show sensitivity also (or only) to perennial allergens (mites, for example) are those who, because of the chronic basic inflammation of the airways, are usually more subject to episodes of EIA.

Recently, new potential hazards for allergic subjects have been described: if diving with compressed-air tanks seems to increase airway hyperresponsiveness (56–60), pollens trapped in a scuba air tank can also induce very dangerous asthma attacks underwater (61, 62).

Diagnosis

A bronchoprovocation test with physical exercise is essential. After a 5–8-min run (63) under suitable environmental conditions, the test allows the reproduction of the situations which can normally provoke an attack of EIA. By subsequently measuring the parameters of the flow-volume loop (FEV_1 in particular) at 5-min intervals up to 30 min, it is possible to determine whether the subject is positive for EIB (54, 55). A subject is considered positive when the FEV_1 is reduced by at least 10% (in athletes) or 15% (in sedentary subjects) compared to base values. In the case of a positive outcome of the test, it is essential for the extent of the problem to be evaluated, and therapeutic safeguards put into effect for the patient under examination.

EIA and athletes

EIA has been reported, for instance, in US Olympic Winter Sports athletes (64, 65), affecting about 25% of them, particularly cross-country skiers, and with a prevalence of women over men; in Finnish cross-

country skiers also, the percentage was the same, with a prevalence of atopic subjects (66). The same was found for runners (67).

Recently, there have been reports that the EIA screening of elite athletes shows remarkable differences between laboratory and field exercise challenges (68). In fact, exercise done during competition induces the symptoms more easily than in laboratory tests.

Which sport for the allergic patient?

One of the main problems currently confronting allergists is what kind of physical exercise or sport can be suggested for allergic subjects. The main questions are as follows:

- 1) Can asthmatics practice sports?
- 2) What kind of sport is suitable for asthmatics?
- 3) How is an asthma attack to be prevented?
- 4) How is an asthma attack to be treated?

Of course, there is general agreement that asthmatic children not only can but should practice sports. Exercise is beneficial both for the growth and for the psychological status of asthmatic children, who often consider themselves – and are likewise considered by their parents and relatives – as seriously ill persons, incapable of achieving good performance in sports.

It is often incorrectly believed by some physicians, too, that an asthmatic is not fit for sports. In fact, there is a long list of world athletes who have been able to reach the highest levels of success (taking part in world championships, the Olympic Games, and so on), despite being asthmatic; some of them have achieved quite brilliant performances.

Among them, we may recall Miguel Indurain (69), the famous cyclist, and Kurt Grote (US Olympic Gold Medalist in the 400 m relay swimming in the 1996 Olympics).

Another point is that there is a clear difference between power and endurance sports in terms of anaerobic and aerobic performance. It is well known that some sports involve less risk for asthmatic subjects. For instance, swimming is better than running, probably because the reduced gradient of temperature between the inhaled air and the airways decreases the effect of air on the aspecific bronchial reactivity, which is typical of the asthmatic patient.

The asthmatic subject today has a whole range of measures to prevent an attack during exercise. Exercise is to be performed when the patient is clinically symptomless, but this status should also correspond to a peak respiratory flow rate (PEF) of $\geq 80\%$. The exercising individual should avoid areas and seasons where pollens are at high concentration (e.g., grass fields in springtime or indoor rooms where mites can be present). For instance, a positive skin prick test to such allergens was found in 41% of a group of Australian

athletes involved in Olympic sports (70) and in 28% of 118 athletes of the Italian Olympic team (71); thus, elite athletes may often find themselves participating in competitions during already scheduled periods, which in general are not determined on the basis of the pollen season (70).

Running, the highest-risk sport for asthmatics – apart from being a discipline per se, with various different events – is also a training method used in almost all sports to increase aerobic capacity. It is possible to observe subjects who do not complain of any symptom while practicing their own discipline, but who manifest symptoms during training runs.

Swimming, as previously reported, is commonly suggested for asthma patients: the warm, damp air of the swimming pool avoids the drying-out and cooling of the bronchial mucous membrane which, as we have seen, is the cause of EIB, and ventilatory demands are limited. It is, however, necessary to pay attention to the high levels of chlorine as an aspecific irritant, as well as to the possible presence of mites or mold in the changing rooms and other communal areas.

Medium-risk sports are team sports (particularly volleyball and basketball) in which the alternation of aerobic and anaerobic phases, as well as the relatively brief periods of continuous exercise (in any case, usually under 5–8 min), results in a lower risk of bronchospasm; medium- to low-risk sports are those which do not require high ventilatory levels (fencing and artistic gymnastics, for example, are primarily indicated) (54), but, even in these cases, it is necessary to pay careful attention to the environmental conditions for allergy patients, or to the presence of aspecific irritants.

The evaluation of the bronchial hyperreactivity is fundamental: if this proves to be high and not reversible by adequate pharmacologic therapy, even sports such as swimming are inadvisable. On the other hand, if the bronchial hyperreactivity can be prevented or reduced by treatment, even an asthmatic can practice any sport. Considerable restrictions remain, however, for any underwater activity using breathing apparatus, high-altitude sports (hang gliding or mountaineering, for example), and motor sports (54, 55).

Asthma and viral infections

This topic is apparently not strictly related to allergy, but we will see that the relationships between viral infection, allergy, and sports are closer than they may at first appear. Infections of the respiratory tract by rhinoviruses, but also RSVs, parainfluenza, adenoviruses, influenza, and coronaviruses may exacerbate or induce an asthma attack (72), especially in young children.

It has recently been demonstrated that the altered response of the airways during a viral infection probably exhibits the same mechanism as that observed

during an asthma attack (73). In allergic subjects, in fact, the infiltration of the inflammatory cells, even at the level of the bronchial lumen, is supported by an increased expression of ICAM-1 (74), and 90% of human rhinovirus variants (HRVs) use this superficial glycoprotein as a receptor (75–78). If we take into consideration the fact that alterations of the immune defenses may occur for those who practice competitive sports, exposing the subject to a higher risk of viral infections, it is clear that asthmatic subjects performing exercise are at risk also from this point of view.

Prevention and treatment of EIA

There is general agreement that EIA can be prevented by some classes of drugs (79) (some of which are prohibited by current antidoping legislation).

β₂-agonists. Salbutamol, terbutaline, and salmeterol are the only drugs allowed by antidoping laws, and they may be administered only by inhalation and only for the prevention and/or cure of EIA and EIB. The use of the drug must be reported in writing to the appropriate medical authority (80). In addition to the well-known effects of these drugs, they have the advantage of favoring the replacement of water lost during the inhalation of dry air (38).

Cromones. Particularly indicated for children, these drugs (cromolyn and nedocromil), with their short-term action of about 90 min, protect most athletes (even those who are prick-test negative) from EIA if administered beforehand (81). Their activity probably stabilizes the membrane of the mast cells, reducing the release of histamine, leukotrienes, and other mediators.

Corticosteroids. It is well known that the systemic use of corticosteroids is reserved for the most serious cases (III and IV stage, according to GINA). In any case, they are prohibited by the antidoping laws. Conversely, the use of the topical steroids budesonide, fluticasone, flunisolide, and beclomethasone is the standard prolonged treatment of asthmatic subjects, and their use is allowed by the antidoping regulations, provided that the appropriate authorities are notified.

Antileukotrienes. The strategic place of leukotrienes in the pathogenesis of asthma has opened new possibilities for EIA treatment. EIA is the only key indication for the leukotriene receptor antagonists (zafirlukast and montelukast), and the drugs can also be administered in combination with β₂-agonists and/or cromones. In the case of episodic exertion, β₂ stimulants remain the drugs of choice for prevention and treatment, while antileukotrienes are employed

when there is regular exertion, particularly in the case of children when exercise cannot be scheduled (82, 83). As far as dope testing is concerned, there are no restrictions (so far) on this class of drugs.

For other classes of drugs, such as anticholinergic inhalants and orally administered theophyllines, there are no restrictions. As far as antibiotics are concerned, the only necessary caution concerns the formulation for intramuscular administration, inasmuch as local anesthetics, often used in association, are classed as doping substances. Antihistamines are prohibited only if used in association with β_2 stimulants, sedatives, or ephedrine; they are in any case prohibited in the international competitions organized by the trapshooting, archery, and biathlon federations.

Some antiasthmatic drugs are often used improperly even by nonasthmatic athletes in order to improve their competitive performance; in fact, some β_2 stimulants (clenbuterol) (84) behave like anabolic steroids, and have been used especially by cyclists, bodybuilders, and weight lifters.

Nonpharmacologic prevention, on the other hand, is based on the following strategies, which are not always easy to put into practice:

- 1) Nasal breathing: this aids the warming of inhaled air, and gives rise to lower stimulation of the bronchial mucous membrane. Some authors have advocated the use of nasal dilators to reduce the airflow limitation in the nose and lungs (85, 86). At this point, it is worth remembering that allergic rhinitis, as an important factor which can predispose to or induce asthma, needs to be duly treated, mainly in children, in order to prevent EIA.
- 2) The use of an anticold mask.
- 3) The practice of performing warm-up exercises (87) consisting of brief exertions of between 15 and 30s, alternating with rest periods lasting 60–90s.

There is, however, a certain percentage of allergic subjects with bronchial asthma able to practice either competitive or noncompetitive physical activities without any apparent problem.

A relevant point to remember is that correctly administering allergen-specific immunotherapy (88) to allergic subjects can reduce bronchoreactivity, allowing them to perform better.

Not being in a position to avoid pollen seasons (unless they can change hemisphere), asthma patients should avoid zones (such as grass fields) with high concentrations of allergens. A weekly pollen bulletin in many countries helps patients to assess the environmental situation. The Sydney Olympic Games, for example, were held during the southern spring, with consequently high spring pollen concentrations; a warning was announced that numerous pollen-allergic athletes taking part in competitions involving prevalently aerobic activity ran a risk of asthma (70).

Another important issue is the close relationship and confidence between the patient and the doctor. There is agreement on the simple rules that have to be followed:

- 1) Do not underestimate breathing difficulty after exercise, believing it to be simply the consequence of a heavier workload than normal or a normal effect of exercise.
- 2) Do not underestimate episodes of dry and persistent coughing (more frequent in children after physical exercise), considering it a simple "irritation" of the airways.
- 3) Do not underestimate excessive tiredness or headaches, accompanied by a sense of thoracic constriction and general feeling of malaise, that may arise after exercise: they may in themselves be the only manifestations of exercise-induced asthma in its initial phase.

In 1996, of the 699 athletes in the American Olympic squad, 107 (15.3%) had suffered from asthma in previous years, 97 (13.9%) received antiasthma therapies, and 117 (16.7%) took antiasthma drugs or were diagnosed as having bronchial asthma. Numerous asthmatic athletes won medals in their events (89). This demonstrates that, despite preconceptions, it is possible for those with bronchial asthma to compete at the same level as nonasthmatic individuals, both in sports and in everyday life.

Exercise-induced anaphylaxis (EIA_n)

Anaphylaxis, a name coined in 1902 by Charles Richet (1913 Nobel Prize winner) and his colleague Paul Jules Portier, to describe "the opposite of protection (phylaxis)" (90), is the most serious phenomenon in the field of allergology; the form arising from physical exercise is a relatively recent syndrome (first described in 1979) (91, 92). Its clinical manifestations can be extremely varied, ranging from pruritus, erythema, and urticaria to angioedema, gastrointestinal symptoms, laryngeal symptoms, and vascular collapse (93).

There are two types of EIA_n:

- 1) postprandial (food-dependent, FDEIA_n)
- 2) non-food-dependent.

In the first case, the symptoms may arise a few hours after the consumption of foodstuffs, which thus represent the predisposing factor. The literature includes cases of EIA_n following the consumption of a wide variety of foods (94–96). EIA_n following the consumption of snails in patients demonstrating cutaneous hypersensitivity to dust mites has also been described (97), the cross-reactivity between aeroallergens and foodstuffs being well known. Although the prognosis for this disease has not been clearly defined, a reduction in attacks has been shown in 45% of subjects upon the elimination of the foodstuff in question.

In non-food-dependent EIA, hyperemia and hyperthermia can, in subjects who have mast-cell instability, provoke an activation of the mast cells and eosinophils with massive and ubiquitous liberation of their mediators (98).

Mention should also be made of the so-called aquagenic anaphylaxis (from contact with water), as well as of drug-dependent EIA (99).

The diagnosis of EIA may follow a well-defined protocol, first described by Romano et al. (100). It is important that patients with suspected food-dependent EIA receive allergologic testing in the form of prick tests with a wide panel of commercial allergens (airborne allergens and food allergens, including seasonal foods) and fresh foods, as well as CAP System RAST. Avoidance of all test-positive foods (or of all meals, for patients whose reaction does not appear to be related to a specific food) for 4 h before exercise seems to prevent further EIA episodes.

Some authors also describe a case in which the EIA depends mainly on the amount, and not on the type, of allergic food ingested (101).

Exercise-induced urticaria (EIU)

Urticaria, which has been well known since ancient times (described by Hippocrates [460–370 BC]), was named by Frank in 1792 (from the Latin name for the stinging nettle *Urtica urens*). EIU is one of several different kinds of urticaria. These include EIU itself, physical urticaria (or urticaria factitia, or dermatographism), and various forms induced by cold or heat, by compression, by exposure to solar rays, by vibrations, and by water, as well as the cholinergic form.

The cold-induced form reveals itself in various ways. Among athletes, the most common is the primary acquired form; erythematous-pomphoid lesions develop in areas exposed to the cold, the wheals occurring after a few minutes and persisting for 0.5–1 h (102). Sometimes the pattern can be so serious that it might be related to EIA, with symptoms leading to shock, especially after a swim.

Delayed pressure-induced urticaria is characterized by a deep and painful pomphoid reaction which develops 3–12 h after a pressure stimulus, and which can last up to a day. In general, it affects young subjects in body areas under an increased pressure on the tissue (for example, the feet after a run, the buttocks of a cyclist, the hands of athletes who use their hands in their sports, or even in areas where a particular piece of equipment with belts, straps, or slings leads to an increase in pressure).

Solar urticaria may affect all those athletes exposed to solar rays, revealing itself in erythema and wheals within 5 min of exposure to rays of a particular length,

and this may vary from person to person (UVA, 320–400 nm; UVB, 290–320 nm; visible light, 400–700 nm).

Aquagenic urticaria is a particular form of physical urticaria; it is provoked by simple contact of the cutis with water at body temperature. The lesions, indistinguishable from those of cholinergic urticaria, appear at 2–3 min and 30 min–1 h after contact, and regress after about 30 min (102).

Other minor aspects of allergic disorders during sporting activity are related to contact dermatitis caused by different substances or situations. There have been descriptions of dermatitis in swimmers arising from phenol-formaldehyde resin and benzoyl peroxide contained in swimming goggles (103), or from diphenylthiourea or other substances in wet suits (104, 105). There are also reports of the “sea bather eruption” (a form of pruritic dermatitis probably due to *Cnidaria* larvae in Florida, the Caribbean, and Bermuda) (106, 107).

Lichenoid photodermatitis in footballers (108) and dermatitis due to formaldehyde resins in athletic tape have been also described (109).

Concluding remarks

The relationship between allergy and exercise has been clearly shown by a number of clinical pictures, ranging from simple dermatitis to potentially fatal anaphylaxis. The mechanisms of EIA, EIB, EIU, and EIA may have been clarified in general terms, and their diagnosis, prevention, and treatment are beginning to be well defined and standardized, mainly thanks to the extraordinarily rapid growth of research in the fields of allergy and immunology.

Studies concerning the effects of exercise on the immune system may also yield further data and contributions to studies on allergy and sports.

Relevant points to be stressed are that during exercise other important systems are activated: the neurologic (110) and endocrine (111) systems may greatly affect immunoallergic responses, and we should be aware of this aspect when performing studies on athletes in the field and in the laboratory.

Nutritional factors (112) (foods, vitamins, amino acids, and integrators) are also of great relevance; this is another sports-related field of research whose effects are generally beneficial, but its relevance to allergy is also important, as we have seen in the case of food allergy, EIA, and EIU.

The number of allergic sportsmen and sportswomen is destined to increase rapidly over the next two decades: this implies that the studies performed so far on allergy and sports, which have been briefly outlined in this review article, need to be better standardized and brought out of the laboratories into the practical field.

We are now in possession of a whole range of techniques by which we can measure and individually quantify physical effort, in order to evaluate an athlete's potential, as well as to assess the level of atopy, bronchial reactivity, cell subpopulations, and mediators, all of which allows us to provide allergic subjects with appropriate counseling and correct guidelines for behavior and treatment.

In short, we now have the armamentarium to allow us to help our allergic patients to realize their full

athletic potential; perhaps, as doctors, some of us will some day have the satisfaction of having helped produce a champion.

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References

1. European Allergy White Paper. Allergic diseases as a public health problem. Braine-l'Alleud: UCB Institute of Allergy, 1997.
2. KEAST D, CAMERON K, MORTON AR. Exercise and the immune response. *Sports Med* 1988;**5**:248–267.
3. DEL GIACCO SR, MANCONI PE, DEL GIACCO GS. Esercizio fisico e sistema Immune. *G It Allergol Immunol Clin* 1998;**1**:143–144.
4. DEL GIACCO SR, MANCA E, AMBROSINI B, et al. Modification of immunological parameters in athletes during acute exercise. *Allergy* 2000;**55 Suppl 63**:69.
5. HOFFMAN-GOETZ L, PEDERSEN BK. Exercise and the immune system: a model of the stress response? *Immunol Today* 1994;**15**:382–387.
6. BRINES R, HOFFMAN-GOETZ L, PEDERSEN BK. Can you exercise to make your immune system fitter? *Immunol Today* 1996;**17**:252–254.
7. BOUSQUET J, CHANEZ P, MERCIER J, PRÉFAUT C. Monocytes, exercise, and the inflammatory response. *Exerc Immunol Rev* 1996;**2**:35–44.
8. MACKINNON LT. Current challenges and future expectations in exercise immunology: back to the future. *Med Sci Sports Exerc* 1994;**26**:191–194.
9. NIEMAN DC. Exercise, upper respiratory tract infection, and the immune system. *Med Sci Sports Exerc* 1996;**17**:128–139.
10. PEDERSEN BK, NIEMAN DC. Exercise and immunology: integration and regulation. *Immunol Today* 1998;**19**:204–206.
11. PEDERSEN BK, HOFFMANN-GOETZ L. Exercise and the immune system: regulation, integration and adaptation. *Physiol Rev* 2000;**80**:1055–1081.
12. PEDERSEN BK, KAPPEL M, KLOKKER M, et al. The immune system during exposure to extreme physiologic conditions. *Int J Sports Med* 1994;**15 S-3**:116–121.
13. MCCARTHY DA, DALE MM. The leucocytosis of exercise. A review and model. *Sports Med* 1988;**6**:333–363.
14. ORTEGA E, COLLAZOS ME, MAYNAR M, et al. Stimulation of phagocytic function of neutrophils in sedentary men after acute moderate exercise. *Eur J Appl Physiol* 1993;**66**:60–64.
15. MACKINNON LT. Exercise and natural killer cells. What is the relationship? *Sports Med* 1989;**7**:141–149.
16. PEDERSEN BK, TVEDE N, CHRISTENSEN LD, et al. Natural killer cell activity in peripheral blood of highly trained and untrained persons. *J Sports Med* 1989;**10**:129–131.
17. NIEMAN DC, MILLER AR, HENSON DA, et al. Effects of high vs. moderate-intensity exercise on natural killer cell activity. *Med Sci Sports Exerc* 1993;**25**:1126–1134.
18. PALMØ J, ASP S, DAUGAARD JR, et al. Effect of eccentric exercise on natural killer cell activity. *J Appl Physiol* 1995;**78**:1442–1446.
19. NIELSEN HB, SECHER NH, KAPPEL M, et al. Lymphocyte, NK and LAK cell responses to maximal exercise. *Int J Sports Med* 1996;**17**:60–65.
20. SHEPHARD RJ, SHECK PN. Effects of exercise on natural killer cell counts and cytolytic activity: a meta-analysis. *Sports Med* 1999;**28**:177–195.
21. BRUUNSGAARD H, GALBO H, HALKJAER-KRISTENSEN J, et al. Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage. *J Physiol (Lond)* 1997;**15**:833–841.
22. WEINSTOCK C, KONIG D, HARNISCHMACHER R, et al. Effect of exhaustive stress on the cytokine response. *Med Sci Sports Exerc* 1997;**29**:345–354.
23. CANNON JG, FIELDING RA, FIATARONE MA, et al. Increased interleukin 1 beta in human skeletal muscle after exercise. *Am J Physiol* 1989;**26**:R451–R455.
24. EVANS WJ, MEREDITH CN, CANNON JG, et al. Metabolic changes following eccentric exercise in trained and untrained men. *J Appl Physiol* 1986;**61**:1864–1868.
25. NAWABI MD, BLOCK KP, CHAHREBARTI MC, et al. Administration of endotoxin, tumor necrosis factor, or interleukin 1 to rats activates skeletal muscle branched-chain alpha-keto acid dehydrogenase. *J Clin Invest* 1990;**85**:256–263.
26. TVEDE N, HEILMANN C, HALKJAER-KRISTENSEN J, et al. Mechanisms of B-lymphocyte suppression induced by acute exercise. *J Clin Lab Immunol* 1989;**30**:169–173.
27. ELIAKIM A, WOLACH B, KODESH E, et al. Cellular and humoral immune response to exercise among gymnasts and untrained girls. *Int J Sports Med* 1997;**18**:208–212.
28. GLEESON M, McDONALD WA, PYNE DB, et al. Salivary IgA levels and infectious risk in elite swimmers. *Med Sci Sports Exerc* 1999;**31**:67–73.
29. NEHLSEN-CANNARELLA SL, NIEMAN DC, FAGOAGA OR, et al. Saliva immunoglobulins in elite women rowers. *Eur J Appl Physiol* 2000;**81**:222–228.
30. NIEMAN DC. Special feature for the Olympics: effects of exercise on the immune system: exercise effects on systemic immunity. *Immunol Cell Biol* 2000;**78**:496–501.
31. NIEMAN DC, PEDERSEN BK. Exercise and immune function. Recent developments. *Sports Med* 1999;**27**:73–80.
32. PETERS EM. Exercise, immunology and upper respiratory tract infections. *Int J Sports Med* 1997;**18 S-1**:S 69–77.
33. ADAMS F. The extant works of Aretaeus, the Cappadocian. London: Sydenham Society, 1856.
34. ANDERSON SD. Exercise-induced Asthma. In: CARLSEN KH, IBSEN TB, editors. Exercise induced asthma and sports in asthma. Copenhagen: Munksgaard, 1999:11–17.

35. NHLBI/WHO Workshop Report. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Washington DC: National Institutes of Health, 1995, publ. no. 95-3659.
36. BURROWS B, MARTINEZ FD, HALONEN M, et al. Association of asthma with serum IgE levels and skin-test reactivity to allergens. *New Engl J Med* 1989;**320**:271-277.
37. DOUGLAS IS, LEFF AR, SPERLING AI. CD4+ T cell and eosinophil adhesion is mediated by specific ICAM-3 ligation and results in eosinophil activation. *J Immunol* 2000;**164**:3385-3391.
38. CRIMI E, BARTALUCCI C, BRUSASCO V. Asthma, exercise and the immune system. *Exerc Immunol Rev* 1996;**2**:45-64.
39. ROT A, KRIEGER M, BRUNNER T, et al. RANTES and macrophage protein 1 alpha induces the migration and activation of normal human eosinophil granulocytes. *J Exp Med* 1992;**176**:1489-1495.
40. ROSSI GA, CRIMI E, LANTERO S, et al. The late-phase asthmatic reaction is associated with an early recruitment of eosinophils in the airways. *Am Rev Respir Dis* 1991;**143**:379-383.
41. SEDGWICK JB, CALHOUN WJ, VRTIS RF, et al. Comparison of airway and blood eosinophil function after *in vivo* antigen challenge. *J Immunol* 1992;**149**:3710-3718.
42. GRUNSTEIN MM, HAKONARSON H, MASKERI N, KIM C, CHUANG S. Intrinsic ICAM-1/LFA-1 activation mediates altered responsiveness of atopic asthmatic airway smooth muscle. *Am J Physiol Lung Cell Mol Physiol* 2000;**278**:1154-1163.
43. DIGNETTI P, CIPRANDI G, CANONICA GW. Ruolo dei leucotrieni nella patogenesi delle malattie allergiche. *Allergy Respir Dis Today* 1999;**1**:18-24.
44. DOUCET C, BROUTY-BOYE D, POTTIN-CLEMENCEAU C, et al. IL-4 and IL-13 specifically increase adhesion molecule and inflammatory cytokine expression in human lung fibroblasts. *Int Immunol* 1998;**10**:1421-1433.
45. SANMUGALINGHAM D, DE VRIES E, GAUNTLETT R, et al. Interleukin-5 enhances eosinophil adhesion to bronchial epithelial cells. *Clin Exp Allergy* 2000;**30**:255-263.
46. KALLINGS LV, EMTNER M, BACKLUND L. Exercise-induced bronchoconstriction in adults with asthma. Comparison between running and cycling and between cycling at different air conditions. *Ups J Med Sci* 1999;**104**:191-198.
47. CARLSEN KH. Asthma and Allergy in Athletes. In: CARLSEN KH, IBSEN TB, editors. Exercise induced asthma and sports in asthma. Copenhagen: Munksgaard, 1999:18-22.
48. MCFADDEN ER, GILBERT IA. Exercise induced asthma. *N Engl J Med* 1994;**330**:1362-1367.
49. WILSON J. The bronchial microcirculation in asthma. *Clin Exp Allergy* 2000;**30 S-1**:51-53.
50. ANDERSON SD, SCHEFFEL RE, et al. Sensitivity to heat and water loss at rest and during exercise in asthmatic patients. *Eur J Respir Dis* 1987;**63**:459-471.
51. EGGLESTON PA, KAGEY-SOBOTKA A, LICHTENSTEIN LM. A comparison of the osmotic activation of basophils and human lung mast cells. *Am Rev Respir Dis* 1987;**135**:1043-1048.
52. CRIMI E, BALBO A, MILANESE M, et al. Airway inflammation and occurrence of delayed bronchoconstriction in exercise-induced asthma. *Am Rev Respir Dis* 1992;**146**:507-512.
53. MCFADDEN ER Jr, NELSON JA, SKOWRONSKI ME, LENNER KA. Thermally induced asthma and airway drying. *Am J Respir Crit Care Med* 1999;**160**:221-226.
54. TODARO A. Physical activities and sports in asthmatic patients. *Minerva Med* 1983;**74**:1349-1356.
55. TODARO A. Exercise-induced bronchodilatation in asthmatic athletes. *J Sports Med Phys Fitness* 1996;**36**:60-66.
56. TEZLAFF K, NEUBAUER B, REUTER M, FRIEGE L. Atopy, airway reactivity and compressed air diving in males. *Respiration* 1998;**65**:270-274.
57. BOUTET S, SALVIA P, POTIRON M. Asthma and diving with a cylinder. *Allerg Immunol (Paris)* 1999;**31**:245-249.
58. WOLF SL, TWAROG F, WEILER JM, et al. Discussion of risk of scuba diving in individuals with allergic and respiratory disease: SCUBA Subcommittee. *J Allergy Clin Immunol* 1995;**96**:871-873.
59. SCHANKER HM, SPECTOR SL. Scuba diving in individuals with asthma. *Allergy Asthma Proc* 1996;**17**:311-313.
60. BENTLIFER GE. Warn asthmatics of scuba diving risks. *Chest* 1997;**112**:298.
61. ASTARITA C, GARGANO D, DI MARTINO P. Pollen trapped in a scuba tank: a potential hazard for allergic divers. *Ann Intern Med* 2000;**132**:166-167.
62. D'AMATO G, NOSCHESI P, RUSSO M, et al. Pollen asthma in the deep. *J Allergy Clin Immunol* 1999;**104**:710.
63. RANDOLPH C. The free running athletic screening test. *Ann Allergy Asthma Immunol* 1998;**81**:275a-275g.
64. WILBER RL, RUNDELL KW, SZMEDRA L, et al. Incidence of exercise-induced bronchospasm in Olympic winter sport athletes. *Med Sci Sports Exerc* 2000;**32**:732-737.
65. WEILER JM, RYAN EJ 3rd. Asthma in United States Olympic athletes who participated in the 1998 Olympic Winter Games. *J Allergy Clin Immunol* 2000;**106**:267-271.
66. HELENIUS IJ, TIKKANEN HO, SARNA S, HAAHTELA T. Asthma and increased bronchial responsiveness in elite athletes: atopy and sport event as risk factors. *J Allergy Clin Immunol* 1998;**101**:646-652.
67. HELENIUS IJ, TIKKANEN HO, HAAHTELA T. Occurrence of exercise induced bronchospasm in elite runners: dependence on atopy and exposure to cold air and pollen. *Br J Sports Med* 1998;**32**:125-129.
68. RUNDELL KW, WILBER RL, SZMEDRA L, et al. Exercise-induced asthma screening of elite athletes: field versus laboratory challenge. *Med Sci Sports Exerc* 2000;**32**:309-316.
69. Miguel Indurain: the allergic extraterrestrial. *Allergy* 1997;**52** [Newsletter, Dec issue, 3-4].
70. KATELARIIS CH, CARROZZI FM, BURKE TV, BYTH K. A springtime Olympics demands special consideration for allergic athletes. *J Allergy Clin Immunol* 2000;**106**:260-266.
71. BONINI S. AIDA Study Group. Allergy and infectious diseases in Italian athletes selected for the Sydney Olympics. Abstract No. P-357; ICACI 2000, Sydney, Australia.
72. GERN JE, BUSSE WW. The role of viral infections in the natural history of asthma. *J Allergy Clin Immunol* 2000;**2**:201-212.
73. GRUNSTEIN MM, HAKONARSON H, MASKERI N, CHUANG S. Autocrine cytokine signaling mediates effects of rhinovirus on airway responsiveness. *Am J Physiol Lung Cell Mol Physiol* 2000;**278**:L1146-1153.
74. CIPRANDI G, PRONZATO C, RICCA V, BAGNASCO M, CANONICA GW. Evidence of intracellular adhesion molecule-1 expression on nasal epithelial cells in acute rhinoconjunctivitis caused by pollen exposure. *J Allergy Clin Immunol* 1994;**94**:738-746.
75. BELLA J, ROSSMANN MG. ICAM-1 receptors and cold viruses. *Pharm Acta Helv* 2000;**74**:291-297.
76. KAUL P, BIAGIOLI MC, SINGH I, TURNER RB. Rhinovirus-induced oxidative stress and interleukin-8 elaboration involves p47-phox but is independent of attachment to intercellular adhesion molecule-1 and viral replication. *J Infect Dis* 2000;**181**:1885-1890.

77. VAN KEMPEN M, BACHERT C, VAN CAUWENBERGE P. An update on the pathophysiology of rhinovirus upper respiratory tract infections. *Rhinology* 1999;**37**:97–103.
78. BELLA J, ROSSMANN MG. Review: rhinoviruses and their ICAM receptors. *J Struct Biol* 1999;**128**:69–74.
79. SMITH BW, LABOTZ M. Pharmacologic treatment of exercise-induced asthma. *Clin Sports Med* 1998;**17**:343–363.
80. KINTZ P, DUMESTRE-TOULET V, JAMEY C, et al. Doping control for beta-adrenergic compounds through hair analysis. *J Forensic Sci* 2000;**45**:170–174.
81. ANDERSON SD, HENRIKSEN JM. Management of exercise-induced asthma. In: CARLSEN KH, IBSEN TB, editors. *Exercise induced asthma and sports in asthma*. Copenhagen: Munksgaard, 1999:99–108.
82. DIGNETTI P, CIPRANDI G, CANONICA GW. Ruolo degli antileucotrieni nella terapia dell'asma. *Allergy Respir Dis Today* 1999;**2**:69–74.
83. ALLEGRA L, CANONICA GW, DONNER CF, et al. Asthma controller therapy: role of antileukotrienes, a new therapeutic class. *Monaldi Arch Chest Dis* 1999;**54**:136–145.
84. SPANN C, WINTER ME. Effect of clenbuterol on athletic performance. *Ann Pharmacother* 1995;**29**:75–77.
85. WILDE AD, ELL SR. The effect on nasal resistance of an external nasal splint during isometric and isotonic exercise. *Clin Otolaryngol* 1999;**24**:414–416.
86. WILDE AD, ELL SR. Effect on nasal resistance of an external nasal splint and isotonic exercise. *Br J Sports Med* 1999;**33**:127–128.
87. DE BISSCHOP C, GUENARD H, DESNOT P, VERGERET J. Reduction of exercise-induced asthma in children by short, repeated warm ups. *Br J Sports Med* 1999;**33**:100–104.
88. World Health Organization Position Paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Geneva: WHO, 1998.
89. WEILER JM, LAYTON T, HUNT M. Asthma in United States Olympic athletes who participated in 1996 Summer Games. *J Allergy Clin Immunol* 1998;**102**:722–726.
90. RICHEL C. Anaphylaxis. Liverpool: Constable, 1913.
91. MAULITZ RM, PRATT DS, SCHOCKET AL. Exercise-induced anaphylactic reaction to shellfish. *J Allergy Clin Immunol* 1979;**63**:433–434.
92. SHEFFER AL, AUSTEN KF. Exercise-induced anaphylaxis. *J Allergy Clin Immunol* 1980;**66**:106–111.
93. SENNA G, MEZZELANI P, PACOR ML. Anafilassi da esercizio fisico. *Recenti Prog Med* 1993;**84**:203–209.
94. ROMANO A, DI FONSO M, VENUTI A, et al. Food-dependent exercise-induced anaphylaxis: report of two cases. *Int J Sports Med* 1992;**13**:585–587.
95. PAULS JD, CROSS D. Food-dependent exercise-induced anaphylaxis to corn. *J Allergy Clin Immunol* 1998;**101**:853–854.
96. KANO H, JUJI F, SHIBUYA N, et al. Clinical courses of 18 cases with food-dependent exercise-induced anaphylaxis. *Arerugi* 2000;**49**:472–478.
97. LONGO G, BARBI E, PUPPIN F. Exercise-induced anaphylaxis to snails. *Allergy* 2000;**55**:513–514.
98. CASTELLS MC, HORAN RF, SHEFFER AL. Exercise-induced anaphylaxis (EIA). *J Allergy Clin Immunol* 1999;**17**:413–424.
99. VAN WIJK RG, DE GROOT H, BOGAARD JM. Drug-dependent exercise-induced anaphylaxis. *Allergy* 1995;**50**:992–994.
100. ROMANO A, DI FONSO M, GIUFFREDA F, et al. Diagnostic work-up for food-dependent, exercise-induced anaphylaxis. *Allergy* 1995;**50**:817–824.
101. HANAKAWA Y, TOHYAMA M, SHIRAKATA Y, et al. Food-dependent exercise-induced anaphylaxis: a case related to the amount of food allergen ingested. *Br J Dermatol* 1998;**138**:898–900.
102. GREAVES M. Chronic urticaria. *J Allergy Clin Immunol* 2000;**4**:664–672.
103. AZURDIA RM, KING CM. Allergic contact dermatitis due to phenol-formaldehyde resin and benzoyl peroxide in swimming goggles. *Contact Dermatitis* 1998;**38**:234–235.
104. BOEHNCKE WH, WESSMANN D, ZOLLNER TM, HENSEL O. Allergic contact dermatitis from diphenylthiourea in a wet suit. *Contact Dermatitis* 1997;**36**:271.
105. BALESTRERO S, COZZANI E, GHIGLIOTTI G, GUARRERA M. Allergic contact dermatitis from a wet suit. *J Eur Acad Dermatol Venereol* 1999;**13**:228–229.
106. FREUDENTHAL AR, JOSEPH PR. Seabather's eruption. *N Engl J Med* 1993;**329**:542–544.
107. BURNETT JW. Seabather's eruption. *Cutis* 1992;**50**:98.
108. BALABANOVA M, KASANDGIEVA J, POPOV Y. Lichenoid dermatitis in 3 professional footballers. *Contact Dermatitis* 1993;**28**:166–168.
109. SHONO M, EZOE K, KANIWA MA. Allergic contact dermatitis from para-tertiary-butylphenol-formaldehyde resin (PTBP-FR) in athletic tape and leather adhesive. *Contact Dermatitis* 1991;**24**:281–288.
110. GOEBEL MU, MILLS PJ. Acute psychological stress and exercise and changes in peripheral leukocyte adhesion molecule expression. *Psychosom Med* 2000;**62**:664–670.
111. SUZUKI K, YAMADA M, KURAKAKE S, et al. Circulating cytokines and hormones with immunosuppressive neutrophil-priming potentials rise after endurance exercise in humans. *Eur J Appl Physiol* 2000;**81**:281–287.
112. BISHOP NC, BLANNIN AK, WALSH NP, et al. Nutritional aspects of immunosuppression in athletes. *Sports Med* 1999;**28**:151–176.