INTRODUCTION

Publications on the topic of exercise immunology date from late in the 19th century, but it was not until the mid-1980s that a significant number of investigators worldwide devoted their resources to this area of research endeavor. From 1900 to 1997, just under 900 papers on exercise immunology were published, with 75% of these appearing in the 1990s.

Despite growing attention to the relationship between exercise, the immune system, and host protection, many questions and unexplored issues remain. This article reviews four topics that have received much attention by exercise immunologists and have practical application to athletes:

1. the contrast in immune function between athletes and nonathletes,
2. acute immune changes that occur following prolonged and intensive exercise,
3. the role of nutritional supplements in attenuating exercise-induced changes in immunity,
4. practical recommendations for athletes.
ATHLETES AND NON-ATHLETES: MORE SIMILAR THAN DISPARATE

Among elite athletes and their coaches, a common perception is that heavy exertion lowers resistance and is a predisposing factor to upper respiratory tract infection (URTII) (Nieman, 1997a). In a 1996 survey by the Gatorade Sports Science Institute of 2,700 high school and college coaches and athletic trainers, 89% answered “yes” to the question, “Do you believe overtraining can compromise the immune system and make athletes sick?” (personal communication, Gatorade Sports Science Institute, Barrington, IL). Several studies using epidemiological designs have verified that URTI risk is elevated during periods of heavy training and for 1-2 weeks following competitive endurance race events (Nieman 1997a; Peters-Future, 1997).

Conversely, there is also a common belief among fitness enthusiasts that regular exercise confers resistance against infection. In a survey of 170 non-elite marathon runners (average personal best time of 3 h 25 min) who had been training for and participating in marathons for an average of 12 years, 90% reported that they “rarely get sick” (personal communication, Gatorade Sports Science Institute, Barrington, IL). Studies using similar designs have verified that URTI risk is reduced among fitness enthusiasts (Nieman, 1997a; Peters-Future, 1997).

The innate immune system appears to be largely unaffected by exercise, with natural killer cell activity tending to be enhanced, whereas neutrophil function is suppressed. Even when significant changes in the concentrations and functional activities of immune variables have been observed in athletes, investigators have had little success in linking these changes to a higher incidence of infection and illness. In one report, elite swimmers undertaking intensive training had significantly lower neutrophil oxidative activity at rest than did age- and sex-matched sedentary individuals (Nieman et al., 1990, 1998b). The results indicate that the number of days with URTI was reduced by nearly half in the exercise group.

Do the immune systems of athletes and nonathletes function differently? Although the URTI risk data suggest that disparities should exist, attempts thus far to compare resting immune function in athletes and nonathletes have failed to provide compelling evidence that athletic endeavor is linked to clinically important changes in immunity (Nieman 1997a, 1997b).

In the resting state, the adaptive immune system (i.e., the function of T and B cells that produce specific reactions and immunological memory to each infectious agent when activated) appears to be largely unaffected by intensive and prolonged exercise training. The innate immune system (i.e., immune cells that act as a first line of defense against infectious agents) appears to respond differentially to the chronic stress of intensive exercise, with natural killer cell activity tending to be enhanced, whereas neutrophil function is suppressed.

Two studies indicate that salivary immunoglobulin A (IgA) concentration warrants further research as a marker of potential infection risk in athletes. Mackinnon et al. (1993) demonstrated that elite squash and hockey athletes with low salivary IgA concentrations experienced higher rates of URTI. This was later confirmed in a study of elite swimmers (Gleeson et al., 1996). Salivary IgA levels measured in swimmers before training sessions showed significant correlations with infection rates, and the number of infections observed in the swimmers was predicted by the pre-season and the mean pre-training salivary IgA levels.

In general, when analyzed in resting subjects, the immune systems of athletes and nonathletes appear to be more similar than disparate. Of the various immune function tests that show some change with athletic endeavor, only salivary IgA has emerged as a potential marker of infection risk. Future research should concentrate on this immune measure using large groups of athletes and nonathletes to clarify its potential clinical usefulness.

Figure 2. Elite swimmers (line graph) undertaking intensive training had a significantly lower neutrophil oxidative activity at rest than did age- and sex-matched sedentary individuals (histogram blocks). Function was further suppressed during the period of strenuous training prior to national-level competition. Data (means +SE) from Pyne et al. (1995). Brackets represent mean +SE.

THE ACUTE IMMUNE RESPONSE TO HEAVY EXERTION:
UPDATE ON THE “OPEN WINDOW” THEORY

In light of the mixed results regarding the effect of chronic, intensive training on resting immune function and host protection, several authors have theorized that each bout of prolonged exercise leads to transient but clinically
significant changes in immune function (Hoffman-Goetz & Pedersen, 1994; Nieman, 1997b). During this “open window” of altered immunity (which may last between 3 and 72 hours, depending on the immune measure), viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection.

Although this is an attractive hypothesis, no serious attempt has been made by investigators to establish that athletes showing the most extreme immunosuppression following heavy exertion are those who contract an infection during the following 1-2 weeks. This link must be established before the “open window” theory can be wholly accepted.

Compared to rest, many components of the immune system exhibit change after prolonged, heavy exertion, including the following (Nieman 1997b, 1998):

- High neutrophil and low lymphocyte blood counts, induced by high concentrations of plasma cortisol.
- Increase in blood granulocyte and monocyte phagocytosis (engulfing of infectious agents and of breakdown products of muscle fiber) but a decrease in nasal neutrophil phagocytosis.
- Decrease in granulocyte oxidative-burst activity (killing activity).
- Decrease in nasal mucociliary clearance (swiping movement of cilia).
- Decrease in natural-killer-cell cytotoxic activity (the ability to kill infected cells or cancer cells).
- Decrease in mitogen-induced lymphocyte proliferation (a measure of T cell function).
- Decrease in the delayed-type hypersensitivity skin response (the ability of the immune system to produce hard red lumps after the skin is pricked with antigens).
- Increase in plasma concentrations of pro- and anti-inflammatory cytokines (e.g., interleukin-6 and interleukin-1 receptor antagonist).
- Decrease in ex vivo production of cytokines (interferon-α, interleukin-1, and interleukin-6) in response to mitogens and endotoxin.
- Decrease in nasal and salivary IgA concentration (an important antibody).
- Blunted expression of major histocompatibility complex (MHC) II in macrophages (an important step in recognition of foreign agents by the immune system).

Increase in phagocytic activities of blood granulocytes and monocytes and in blood levels of interleukin-6 suggests a strong pro-inflammatory response to damage of muscle induced by heavy exertion, whereas the rise in cortisol and interleukin-1 receptor antagonist shows that anti-inflammatory forces are also at work. The interleukin response to strenuous exercise is similar to that of sepsis and trauma. The immune system’s involvement in the inflammatory response following heavy exertion has been hypothesized to divert attention and resources away from host protection against URTI (Nehlsen-Cannarella, 1997; Nieman, 1997a).

Taken together, these data suggest that the immune system is suppressed and stressed, albeit transiently, following prolonged endurance exercise. Thus, it makes sense (but still remains unproven) that URTI risk may be increased when the endurance athlete goes through repeated cycles of heavy exertion, has been exposed to novel pathogens, and has experienced other stressors to the immune system, including lack of sleep, severe mental stress, malnutrition, or weight loss.

Several studies have shown that despite altered immunity following prolonged and intensive exercise, the ability of the immune system to mount an antibody response to vaccination over the 2-4 week postexercise period is not affected. In a study by Bruunsgaard et al. (1997), male triathletes, when compared to sedentary controls, had normal antibody production to pneumococcal, tetanus, and diphtheria vaccines following a half-Ironman triathlon competitive event. However, the skin test response to seven recall antigens applied after the race and measured 48 hours later was suppressed when compared to control subjects. (Figure 3). These data suggest that the short-term but complex immunological reaction to the delayed-type hypersensitivity skin test is negatively affected by prolonged and intensive exercise, whereas the longer-term, antibody-titer response to vaccination is not affected. While these data lend support to the “open window” theory, additional research is needed to establish a link with infection risk.

**ROLE OF NUTRITIONAL SUPPLEMENTS IN ATTENUATING EXERCISE-INDUCED IMMUNOSUPPRESSION**

Although endurance athletes may be at increased risk for URTIs during heavy training cycles, they must exercise intensively to compete successfully. Athletes appear less interested in reducing training workloads and more receptive to ingesting nutrient supplements that have the potential to counter exercise-induced immunosuppression.

Investigators have measured the influence of nutritional supplements, primarily zinc, vitamin C, glutamine, and carbohydrate, on the immune response to intense and prolonged exercise (Shephard & Shek, 1995). Several double-blind placebo-controlled studies of South African ultramarathon runners have demonstrated an association between vitamin C supplementation (about 600 mg/day for 3 weeks) and fewer reports of URTI symptoms (Peters-Futre, 1997). This has not been replicated, however, by other research teams, and the method of reporting URTI symptoms resulted in unrealistically high incidence rates. A double-blind, placebo-controlled study
was unable to establish that vitamin C supplementation (1,000 mg/day for 8 days) had any significant effect in altering the immune response to 2.5 hours of intensive running (Nieman et al., 1997b).

Glutamine, a nonessential amino acid, has attracted much attention from investigators (Mackinnon et al., 1996). Glutamine and glucose are important fuels along with glucose for lymphocytes and monocytes, and decreased amounts of these nutrients have a direct effect in lowering proliferation rates of lymphocytes. Reduced plasma glutamine levels have been observed in response to various stressors, including prolonged exercise. Whether exercise-induced reductions in plasma glutamine levels are linked to impaired immunity and host protection against viruses in athletes is still unsettled, but most studies have not favored such a relationship.

The most impressive results have been reported in the carbohydrate supplementation studies (Nieman, 1998). Earlier research had established that a reduction in blood glucose levels, an attenuated rise in plasma levels of cortisol and growth hormone, fewer perturbations in blood immune-cell counts, lower granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response. Overall, the hormonal and immune responses to carbohydrate compared to placebo ingestion suggest that physiologic stress was diminished. Some immune variables were affected slightly by carbohydrate ingestion (for example, granulocyte and monocyte function), while others were strongly influenced (e.g., plasma cytokine concentrations and blood cell counts).

The clinical significance of these carbohydrate-induced effects on the endocrine and immune systems awaits further research. At this point, the data indicate that athletes ingesting carbohydrate beverages before, during, and after prolonged and intensive exercise should experience lowered physiologic stress. Research to determine whether carbohydrate ingestion will improve host protection against viruses in endurance athletes during periods of intensified training or following competitive endurance events is warranted.

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Although public health recommendations must be considered tentative, the data on the relationship between moderate exercise and lowered risk of URTI are consistent with guidelines urging the general public to engage in near-daily brisk walking. There is reason to believe that endurance athletes engaging in normal training cycles also experience a reduced URTI risk.

For athletes undergoing intensified training or engaging in long-endurance race events, the risk of immune suppression and sickness is increased. Several lifestyle practices may help serve as countermeasures. Considerable evidence indicates that improper nutrition and psychological stress can compound the negative influence that heavy exertion has on the immune system. Based on current understanding, the athlete is urged to eat a well-balanced diet, keep other life stresses to a minimum, avoid over-training and chronic fatigue, obtain adequate sleep, and space vigorous workouts and race events as far apart as possible. The new research data on carbohydrate supplementation suggest that drinking carbohydrate beverages before, during, and after prolonged and intensive training bouts or competitive race events may lessen physiologic stress to the immune system.

Immune system function appears to be suppressed during periods of low caloric intake and weight reduction, so when necessary, the athlete is advised to lose weight slowly during noncompetitive training phases. Cold viruses are spread by both personal contact and breathing the air near sick people. Therefore, if at all possible, athletes should avoid being around sick people before and after important events. If the athlete is competing during the winter months, a flu shot is recommended.

Possible indicators of overtraining include immunosuppression with loss of motivation for training and competition, depression, poor performance, and muscle soreness. However, at this time, there are no practical markers of immunosuppression (other than infection) that coaches and clinicians can use to indicate that the athlete is overtrained.

Further research is needed to establish the relationship of carbohydrate supplementation to changes in both immune function and host protection against URTI pathogens.
SUMMARY
There is growing evidence that prolonged intensive exercise is associated with altered immune function and an increased risk of URTI. Attempts have been made to alter these negative changes through nutritional means, with carbohydrate supplementation offering the most promising results thus far.

References


Can Too Much Exercise Increase the Risk for Sickness?

Among elite athletes and their coaches, a common perception is that heavy exertion lowers resistance to colds. For example, Liz McColgan, one of the best female runners in Scotland, blamed overtraining, “which led to a cold and two subsequent illnesses,” as the major reason for her poor performance in the 1992 World Cross Country Championships. Uta Pippig, winner of the 1994 Boston Marathon, caught a cold the week before the race after training 140 miles each week for 10 weeks at high altitude. Claimed Pippig, “When you are on such a high level, you can so quickly fall off.”

Alberto Salazar, once one of the best marathon runners in the world, reported that while training for the 1984 Olympic Marathon, he caught 12 colds in 12 months. “My immune system was totally shot,” he recalls. “I caught everything. I felt like I should have been living in a bubble.”

There are limited numbers of studies on illnesses among endurance athletes to establish whether the perception is true. The few epidemiological studies suggest marathoners may have an increased risk of illness during heavy training and following the race. Experimental studies support this, showing depression of immune function 3-72 h past heavy exercise.

Athletes must train hard to prepare for competition. Although this increases the risk for infection if the training becomes too intensive, there are several practical recommendations the athlete can follow to minimize the impact of other stressors on the immune system:

— Keep other life stresses to a minimum. Mental stress in and of itself has been linked to an increased risk of upper respiratory tract infection.
— Eat a well-balanced diet to keep vitamin and mineral pools in the body at optimal levels. Although there is insufficient evidence to recommend nutrient supplements, ultramarathon runners may benefit by taking vitamin C supplements before ultramarathon races (600 mg/day for at least 1 week). Vitamin C may help reduce oxidative damage to important immune cells.
— Avoid overtraining and chronic fatigue.
— Obtain adequate sleep on a regular schedule. Sleep disruption has been linked to suppressed immunity.
— Avoid rapid weight loss, which has also been linked to negative immune change.
— Avoid putting hands to the eyes and nose (which is a primary route of introducing viruses into the body). Before important race events, avoid sick people and large crowds when possible.
— For athletes competing during the winter months, flu shots are recommended.
— Use carbohydrate beverages before, during, and after marathon-type race events or unusually heavy training bouts. This may lower the impact of stress hormones on the immune system.

Rest or Exercise When Sick?

Athletes and fitness enthusiasts are often uncertain of whether they should exercise or rest during sickness. It is well established that the ability to perform optimally is reduced during sickness. Also, several case histories have shown that sudden and unexplained downturns in athletic performance can sometimes be traced to a recent bout of sickness. In some athletes, exercising when sick can lead to a severely debilitating state known as “post-viral fatigue syndrome.” The symptoms can persist for several months and include weakness, inability to train hard, easy fatigability, frequent infections, and depression.

Concerning exercising when sick, most clinical authorities in the area of exercise immunology recommend:

— If one has symptoms of the common cold (e.g., runny nose and sore throat without fever or general body aches and pains), intensive exercise training may be safely resumed a few days after the resolution of symptoms.
— Mild-to-moderate exercise (e.g., walking) when sick with the common cold does not appear to be harmful. In two studies using nasal sprays of a rhinovirus leading to common cold symptoms, subjects were able to engage in exercise during the course of the illness without any negative effects on severity of symptoms or performance capability.
— With symptoms of fever, extreme tiredness, muscle aches, and swollen lymph glands, 2-4 weeks of rest should probably be allowed before resumption of intensive training.