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## *Position statement part two: maintaining immune health*

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## ***Position Statement***

### ***Part two: Maintaining immune health***

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## **CONSENSUS STATEMENT**

The physical training undertaken by athletes is one of a set of lifestyle or behavioural factors that can influence immune function, health and ultimately exercise performance. Others factors including potential exposure to pathogens, health status, lifestyle behaviours, sleep and recovery, nutrition and psychosocial issues, need to be considered alongside the physical demands of an athlete's training programme.

The general consensus on managing training to maintain immune health is to start with a programme of low to moderate volume and intensity; employ a gradual and periodised increase in training volumes and loads; add variety to limit training monotony and stress; avoid excessively heavy training loads that could lead to exhaustion, illness or injury; include non-specific cross-training to offset staleness; ensure sufficient rest and recovery; and instigate a testing programme for identifying signs of performance deterioration and manifestations of physical stress. Inter-individual variability in immunocompetence, recovery, exercise capacity, non-training stress factors, and stress tolerance likely explains the different vulnerability of athletes to illness. Most athletes should be able to train with high loads provided their programme includes strategies devised to control the overall strain and stress. Athletes, coaches and medical personnel should be alert to periods of increased risk of illness (e.g. intensive training weeks, the taper period prior to competition, and during competition) and pay particular attention to recovery and nutritional strategies.

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Although exercising in environmental extremes (heat, cold, altitude) may increase the stress response to acute exercise and elevate the extent of leukocyte trafficking it does not appear to have marked effects on immune function other than a depression of cell-mediated immunity when training at altitude. The available evidence does not support the contention that athletes training and competing in cold (or hot) conditions experience a greater reduction in immune function compared with thermoneutral conditions. Nevertheless, it remains unknown if athletes who regularly train and compete in cold conditions report more frequent, severe or longer-lasting infections. Research should identify whether the airway inflammation associated with breathing large volumes of cold dry air or polluted air impairs airway defences and whether athletes (and their physicians) wrongly interpret the sore throat symptoms that accompany exercising in cold or polluted air as an infection.

Elite athletes can benefit from immunonutritional support to bolster immunity during periods of physiological stress. Ensuring adequate energy, carbohydrate and protein intake and avoiding deficiencies of micronutrients are key to maintaining immune health. Evidence is accumulating that some nutritional supplements including flavonoids such as quercetin and *Lactobacillus* probiotics can augment some aspects of immune function and reduce illness rates in exercise-stressed athletes. Limited data are non-supportive or mixed for use of N-3 polyunsaturated fatty acids,  $\beta$ -glucans, bovine colostrums, ginseng, echinacea or megadoses of vitamin C by athletes.

Relatively short periods of total sleep deprivation in humans (up to 3 consecutive nights without sleep) do not influence the risk of infection, and the reported increase in natural killer cell activity with this duration of total sleep deprivation would seem to rule out the possibility of an “open-window” for respiratory infections. Very little is known about the effects of more prolonged sleep disruption and repeated sleep disturbances on immune function and infection incidence, although recent studies have highlighted the importance of sleep quantity (total duration of sleep per night) and quality (number of awakenings per night) to protect against the common cold in healthy adults.

Short- or long-term exercise can activate different components of a physiological stress response. Prolonged intense exercise may induce negative health consequences, many of which may be mediated by physiological pathways activated by chronic stress. Psychological stress is likely additive to the effects of physical stress and whereas short exposures to both physical or psychological stress can have a beneficial effect on immune function, chronic exposure to stress exerts detrimental effects on immune function and health. However, regular moderate exercise could be an important factor in ameliorating the negative health effects of chronic stress via the optimization and maintenance of the survival-promoting physiological changes induced by the short-term or acute stress response. Further research on mechanisms mediating the salubrious effects of exercise, and on the relationship between exercise and the psychosocial stress-status of an individual, is likely to be helpful for more fully and widely harnessing the health benefits of exercise.

It is agreed by everyone that prevention of infection is always superior to treatment and this is particularly true in athletes residing in countries with limited medical facilities. Although there is no single method that completely eliminates the risk of contracting an infection, there are several effective ways of reducing the number of infectious episodes incurred over a given period. These means of reducing infection risk include appropriate management of training loads, use of appropriate recovery strategies, good personal hygiene, avoiding contact with large crowds, young children and sick people, good nutrition, getting adequate good quality sleep and limiting other life stresses to a minimum. Part two of the position statement includes sections on: training considerations (David Pyne); nutritional countermeasures to exercise-induced immune perturbations (David Nieman); effects of stress on immune function (Firdaus Dhabhar); sleep disruption and immune function (Roy Shephard); environmental extremes and the immune response to exercise (Neil Walsh and Samuel Oliver) and finally, prevention and treatment of common infections (Stéphane Bermon and Alma Kajeniene).

**Key Words:** exercise; sport; immune; leukocyte; pathogen; infection; training; overtraining; overreaching; adaptation; diet; supplement; stress; in vivo; sleep; environment; treatment; prevention

## TRAINING CONSIDERATIONS

### Background

There is considerable incentive for athletes, coaches, and teams to implement practical strategies that limit the risk of training-related perturbations in immune function. The physical training undertaken by athletes is one of a set of lifestyle or behavioural factors that can influence immune function, health and ultimately exercise performance. Other factors including health status, lifestyle behaviours, pathogen transmission, nutrition and psychosocial issues, need to be considered alongside the physical demands of an athlete's training programme. Guidelines on prescribing training to keep athletes healthy are sought-after in the sporting community.

The challenge of preparing guidelines for prescribing training in the absence of specific experimental studies has been acknowledged (8, 134). There are only a few training studies that have directly examined the relationship between training loads and patterns of illness in highly trained athletes, and the effectiveness of various training and lifestyle interventions – see reviews (85, 171) and the respiratory infections and exercise section in part one of this position statement. It is difficult to study elite athletes in their regular training environment especially during preparations for major competition. Experimental control of training, lifestyle and dietary practices, and other confounders such as time missed with injury can be problematic. Investigators have generally used moderately active individuals, often volunteers in graduate research programmes, as participants in exercise immunology studies. The predominance of short cross-sectional studies of the acute effects of exercise rather than long-term prospective studies of athletes in training over weeks, months or years is another issue (85). The limited number of experimental studies makes it difficult to develop definitive practical guidelines for athletes, coaches, clinicians and team officials.

To overcome the shortage of studies, clinicians and scientists working with athletes need to translate and apply selected findings of studies in related fields. Research areas including clinical immunology, nutritional immunology, sports medicine, exercise physiology, psychoneuroimmunology and sports psychology should yield useful insights. Moderate physical activity may enhance immune function and reduce infection incidence mainly in less fit subjects, and pre-event fitness status can also influence the risk of illness (185). However, results from studies involving sedentary or only moderately active individuals may not easily translate to highly trained athletes. Guidelines for maintaining good health (as discussed later in this part of the position statement) and training will also depend on the experience, skills and knowledge of coaches, athletes, clinicians and scientists.

In most sports it is accepted that there exists a dose-response relationship between training and performance (7). Athletes in endurance sports generally require high training volumes to develop the background necessary for success in high-level competition. Sudden increases in either training volume or intensity, or in combination, may place additional pressure on immune function. Post-exercise immune function dysfunction is most pronounced when the exercise is continuous, prolonged (>1.5 h), of moderate to high intensity (55–75% maximal O<sub>2</sub> uptake), and performed with minimal nutritional support (85) (as discussed in the following section). The risk of developing symptoms of non-functional overreaching (short-term decrements in performance capacity where the athlete is unable to recover fully after sufficient rest) or overtraining (long-term decrements that may take several weeks or months to resolve) (131) can be increased by monotonous training without alternating hard and easy training days, a lack of a complete rest day once per week, increasing loads when the total load is already high, and too many competitions (171). In terms of planning and monitoring, integrated indices of training loads in a multivariate model are likely to be more highly correlated with illness than individual factors such as training load, volume or intensity (72). An imbalance between training loads and recovery is also a major contributor to the onset of fatigue, overtraining and illness (141). A well planned recovery programme is essential if athletes are to stay healthy and be ready to perform at their best.

### **Consensus**

The general consensus on managing training to maintain immune health is to start with a programme of low to moderate volume and intensity; employ a gradual and periodised increase in training volumes and loads; add variety to limit training monotony and stress; avoid excessive training distances that could lead to exhaustion, illness or injury (75); include non-specific cross training to offset staleness; ensure sufficient rest and recovery; and instigate a testing programme for identifying signs of performance deterioration and manifestations of physical stress (85, 171). Inter-individual variability in recovery, exercise capacity, non-training stress factors, and stress tolerance likely explains the differential vulnerability of athletes to illness (172). Most athletes should be able to train with high loads provided their programme includes strategies devised to control the overall strain and stress (Table 1). Athletes should be encouraged to undertake intensive training in

the knowledge that variations in performance and fatigue are symptoms to be expected and respected, and not necessarily problems to overcome (206). Athletes, coaches and medical personnel should be alert to these periods of increased risk of illness (e.g. intensive training weeks, the taper period prior to competition, and during competition) and pay particular attention to recovery and nutritional strategies (151).

Table 1. Suggested strategies for modifying training and recovery activities to limit the risk of training-induced impairments in immune health.

<b>Training Descriptor</b>	<b>Comment</b>
Frequency	Increase the frequency of shorter training sessions rather than enduring fewer but longer sessions.
Volume	Reduce the overall weekly training volume and/or volume of individual training sessions.
Intensity	Avoid prolonged intensive training sessions or activities. Employ shorter sharper (spike) sessions mixed with lower-intensity work.
Load (volume x intensity)	Systematically manipulate the training volume and/or intensity to manage the degree of training load.
Load increments	Reduce the size of increments in frequency, volume, intensity and load of training e.g. increases of 5-10% per week rather than 15-30%.
Load sequencing – weekly microcycle	Undertake two or three easy-moderate training sessions after each high intensity session rather than the traditional pattern of simply alternating hard – easy sessions.
Load sequencing – multi-week macrocycle	Plan an easier recovery or adaptation week every 2 <sup>nd</sup> or 3 <sup>rd</sup> week rather than using longer 3 – 6 week cycles with increasing loads.
Recovery – session/week	Implement recovery activities immediately after the most intensive or exhaustive training sessions.
Recovery - season	Permit athletes at heightened risk of illness a longer period of passive and active recovery (several weeks) after completion of a season or major competition.

### **Controversies**

Studies are often limited by: using participants with moderate fitness rather than highly trained athletes; poor description or omission of training details; absence of a suitable control group; and, a modest sample size that reduces statistical power. Changes in immune function after exercise are often transient and small in magnitude (106). Although a substantial amount of research has been conduct-

ed, several important questions remain unanswered. Are different guidelines needed for (previously) sedentary individuals, moderately active and highly-trained athletes? How much exercise or training is too much? Should guidelines be general or sports-specific? Which are the best clinical signs and symptoms of overtraining or impending illness (37)? Which diagnostic tests are useful in monitoring immune status (3)? A section in part one of this position statement highlights the strengths and weaknesses of various methods used to assess immune status and the challenges associated with interpreting the clinical significance of results from these tests. What is the relative effectiveness of other tactics such as nutritional countermeasures (see section that follows), sleep (see sleep disruption section in this part of the position statement) and recovery interventions (111, 181)? Given limitations in time, money and resources, coaches are often unable to implement every strategy and a process of prioritising training, recovery and behavioural interventions is necessary.

### **Future directions**

A systematic programme of clinical and experimentally controlled research is needed to formulate evidence-based training guidelines or recommendations to maintain immune health in athletes. Studies are needed with both recreational and elite athletes. Modelling studies of responses to physical training (16) should shed light on the relative influence of training volume, intensity and loads on the immune system. Molecular biology is already yielding some insights for identifying athletes more at risk of illness (36) and should further our understanding of how the immune system responds to various types of training. For a more detailed account of a role for “omics” in exercise immunology, readers are directed to the “omics” section in part one of this position statement. Studies should also address how individual variations in the risk of illness relate to training (172). A combination of field-based diagnostic technology, experimental research, insightful analytical approaches (99), and the clinical/practical experience of physicians and athletes/coaches is likely to be the most effective approach for managing the training and immunity of athletes.

## **NUTRITIONAL COUNTERMEASURES TO EXERCISE-INDUCED IMMUNE PERTURBATIONS**

### **Background**

Nutrition, exercise, mental stress, and other lifestyle factors influence immune function and the risk of certain types of infection such as upper respiratory tract infections (URTI). In contrast to moderate physical activity, prolonged and intensive exertion by athletes causes numerous changes in immunity in multiple body compartments and an increased risk of URTI (150). Elite athletes must train intensively to compete at the highest levels and they can benefit from immunonutritional support to bolster immunity during periods of physiological stress (151). Non-athletes engaging in moderate physical activity programmes do not require nutritional supplements, and can obtain all needed nutrients from a healthy and balanced diet.

Each acute bout of heavy exertion leads to physiological stress and transient but clinically significant changes in immunity and host pathogen defence, with elevations in stress hormones, pro- and anti-inflammatory cytokines, and reactive oxygen species (85, 148). Natural killer cell activity, various measures of T and B cell function, upper airway neutrophil function, salivary IgA concentration, granulocyte oxidative burst activity, skin delayed-type hypersensitivity response, and major histocompatibility complex (MHC) II expression in macrophages are suppressed for at least several hours during recovery from prolonged, intense endurance exercise (as discussed in detail in part one of this position statement). These immune changes occur in several compartments of the immune system and body (e.g., the skin, upper respiratory tract mucosal tissue, lung, blood, muscle, and peritoneal cavity).

During the “open window” of impaired immunity (which may last between three and 72 hours, depending on the immune measure), pathogen resistance is lowered, increasing the risk of subclinical and clinical infection (150). Epidemiological studies indicate that athletes engaging in marathon and ultramarathon race events and/or very heavy training are at increased risk of URTI (150) (as described in the section on respiratory infections and exercise in part one of this position statement). Together, these epidemiological and exercise immunology studies support the viewpoint that heavy exercise workloads increase URTI risk through altered immune function.

### **Consensus**

Various nutritional agents have been tested for their capacity to attenuate immune changes and inflammation following intensive exercise, thus lowering the magnitude of physiologic stress and URTI risk. This strategy is similar to the immunonutritional support provided to patients recovering from trauma and surgery, and to the frail elderly (151). Some question the value of using immunonutritional support for athletes because blocking the transient immune changes, oxidative stress, and inflammation following heavy exertion interferes with important signaling mechanisms for training adaptations (88, 182). Another viewpoint is that efficacious nutritional supplements only partially block exercise-induced immune dysfunction, inflammation, and oxidative stress, analogous to the beneficial use of ice packs to reduce swelling following mild injuries (209, 225). This debate will hopefully spur additional research on the overall value of immunonutritional support for athletes.

Table 2 summarizes published findings on a variety of supplements, with a focus on those investigated by several different research groups on human athletes. Results for most nutritional supplements tested as countermeasures to exercise-induced inflammation, oxidative stress, and immune dysfunction following heavy exertion have been disappointing. Early studies focused on large dose vitamin and/or mineral supplements, and no consistent countermeasure benefit has been observed (41, 42, 87, 157, 158). A series of studies dating back to the mid-1990s have shown that carbohydrate supplement ingestion before and/or during prolonged exercise attenuates increases in blood neutrophil and monocyte counts, stress hormones, and anti-inflammatory cytokines such as interleukin (IL)-6, IL-10, and IL-1ra, but has little effect on decrements in salivary IgA output and T cell

and natural killer cell function (26, 41, 85, 149, 153). Thus, carbohydrate ingestion during heavy exercise has emerged as an effective but partial countermeasure to immune dysfunction, with favourable effects on measures related to stress hormones and inflammation, but with limited effects on markers of innate or adaptive immunity. Glutamine and amino acid supplements are not recommended because the best studies show no benefits when compared to placebo, perhaps due to abundant storage pools within the body that cannot be sufficiently depleted by exercise (85, 86, 113).

### Controversies and future directions

The growing realization that extra vitamins, minerals, and amino acids do not provide countermeasure benefits for healthy and well-fed athletes during heavy train-

Table 2. Summary of rationale and findings for selected immunonutritional supplements.

Immunonutritional Supplement	Proposed Rationale	Recommendation Based On Current Evidence
Vitamin E	Quenches exercise-induced reactive oxygen species (ROS) and augments immunity	Not recommended; may be pro-oxidative with heavy exertion
Vitamin C	Quenches ROS and augments immunity	Not recommended; not consistently different from placebo
Multiple vitamins and minerals	Work together to quench ROS and reduce inflammation	Not recommended; not different from placebo; balanced diet is sufficient
Glutamine	Important immune cell energy substrate that is lowered with prolonged exercise	Not recommended; body stores exceed exercise-lowering effects
Branched chain amino acids (BCAAs)	BCAAs (valine, isoleucine, and leucine) are the major nitrogen source for glutamine synthesis in muscle	Not recommended; data inconclusive, and rationale based on glutamine is faulty
Carbohydrate	Maintains blood glucose during exercise, lowers stress hormones, and thus counters immune dysfunction	Recommended; up to 60 g per hour of heavy exertion helps dampen immune inflammatory responses, but not immune dysfunction
Bovine colostrums	Mix of immune, growth, and hormonal factors improve immune function and the neuroendocrine system, and lower illness risk	Jury still out, with mixed results
Probiotics	Improve intestinal microbial flora, and thereby enhance gut and systemic immune function	Jury still out, with mixed results
N-3 PUFAs (fish oil)	Exerts anti-inflammatory effects post-exercise	Not recommended; no different from placebo
β-glucan	Receptors found on immune cells, and animal data show supplementation improves innate immunity and reduces infection rates	Not recommended; human study with athletes showed no benefits
Herbal supplements (e.g., Ginseng, Echinacea)	Contain bioactive molecules that augment immunity and counter infection	Not recommended; humans studies do not show consistent support within an athletic context
Quercetin	<i>In vitro</i> studies show strong anti-inflammatory, anti-oxidative, and anti-pathogenic effects. Animal data indicate increase in mitochondrial biogenesis and endurance performance, reduction in illness	Recommended, especially when mixed with other flavonoids and nutrients; human studies show strong reduction in illness rates during heavy training and mild stimulation of mitochondrial biogenesis and endurance performance in untrained subjects; anti-inflammatory and anti-oxidative effects when mixed with green tea extract and fish oil

ing has shifted the focus to other types of nutritional components. *In vitro*/cell culture, animal, and epidemiological research indicate that advanced supplements such as probiotics, bovine colostrum,  $\beta$ -glucan, flavonoids and polyphenols such as quercetin, resveratrol, curcumin, and epigallocatechin-3-gallate (EGCG), N-3 polyunsaturated fatty acids (N-3 PUFAs or fish oil), herbal supplements, and unique plant extracts (e.g., green tea extract, blackcurrant extract, tomato extract with lycopene, anthocyanin-rich extract from bilberry, polyphenol-rich pomegranate fruit extract), warrant well-conducted studies with athletes to determine if they are effective countermeasures to exercise-induced immune dysfunction and risk of URTI (6, 124, 144, 152, 155). Limited data are non-supportive or mixed for use of N-3 PUFAs (156), probiotics (221), bovine colostrums (202), ginseng (196), or Echinacea (196) by athletes.

An evolving hypothesis is that the immune system is so diverse that a mixture of these advanced supplements, perhaps within a carbohydrate beverage, will probably perform better than one supplement by itself (6, 156). The “pharma” approach of using large doses of a single molecule is not as effective as a “cocktail” strategy for nutritional supplements.

A secondary hypothesis is that the primary immune target of nutrient supplements should be the nonspecific, innate arm of the immune system to enhance immunosurveillance against a wide variety of pathogens in athletes. If the nutritional supplement improves natural killer cell, macrophage, and granulocyte function before and/or after heavy exertion, then risk of infection is more effectively countered than when the target is the slower moving adaptive immune components (154, 155, 159).

Some nutritional supplements exert impressive effects *in vitro* and in animal-based models, but then fail when studied under double-blinded, placebo-controlled conditions in human athletes. A prime example is  $\beta$ -glucan, a polysaccharide found in the bran of oat and barley cereal grains, the cell wall of baker's yeast, certain types of fungi, and many kinds of mushrooms. Rodent studies indicate that oat  $\beta$ -glucan supplements offset the increased risk of infection associated with exercise stress through augmentation of macrophage and neutrophil function, but these results were not upheld in a study of human cyclists (144, 159).

The physiologic effects of dietary polyphenols such as quercetin, EGCG, curcumin, lycopene, resveratrol, luteolin, and tiliroside are of great current interest to exercise immunologists due to their antioxidative, anti-inflammatory, anti-pathogenic, cardioprotective, anticarcinogenic, and mitochondrial stimulatory activities (151, 152). Several recent quercetin supplementation studies in human athletes have focused on potential influences as a countermeasure to post-exercise inflammation, oxidative stress, and immune dysfunction, in improving endurance performance, and in reducing illness rates following periods of physiologic stress (162). When quercetin supplementation is combined with other polyphenols and food components such as green tea extract, isoquercetin, and fish oil, a substantial reduction in exercise-induced inflammation and oxidative stress occurs in athletes, with chronic augmentation of innate immune function (155). Quercetin

supplementation (1,000 mg/day for two to three weeks) also reduces illness rates in exercise-stressed athletes (154). Animal studies support a role for quercetin as an exercise mimetic for mitochondrial biogenesis, and recent data in untrained human subjects indicate modest enhancement in skeletal muscle mitochondrial density and endurance performance (162). Quercetin has multiple bioactive effects that support athletic endeavour, and research continues to define optimal dosing regimens and adjuvants that amplify these influences (152, 162).

### Summary remarks

Endurance athletes must train hard for competition and are interested in strategies to keep their immune systems robust and to avoid illness despite the physiological stress they experience. The ultimate goal is to provide athletes with a sports drink or supplement bar containing carbohydrate and a cocktail of advanced supplements that will lower infection risk, exert significant and measurable influences on their innate immune systems, and attenuate exercise-induced oxidative stress and inflammation. The athlete can combine this strategy with other approaches that help maintain immunity and health.

## EFFECTS OF STRESS ON IMMUNE FUNCTION – IMPLICATIONS FOR THE EFFECTS OF EXERCISE ON HEALTH

Understanding the psychological, biological, and health effects of exercise in the context of stress and stress physiology is important for several reasons: **First**, the process of exercising induces a physiological stress response and increases circulating concentrations of noradrenaline (norepinephrine), adrenaline (epinephrine), cortisol, and other stress-related factors including cytokines (93, 166). An acute or short-term stress response can have beneficial effects. However, intense prolonged exercise may induce negative health consequences, many of which may be mediated by physiological pathways activated by chronic stress (85). **Secondly**, exercise, when performed under the appropriate conditions, could be a factor in ameliorating the deleterious health effects of chronic stress and increased allostatic load (viz. the physiological cost that results from ongoing adaptive efforts to maintain homeostasis in response to stressors) (128, 223). A novel and important mechanism mediating the salubrious effects of exercise could be through its optimization of the beneficial, survival-promoting effects of the short-term or acute stress response (44). **Thirdly**, the psychosocial stress status of an individual may be important for determining whether a given exercise regimen is salubrious or harmful.

Although the word “stress” generally has negative connotations, stress is a familiar and ubiquitous aspect of life, being a stimulant for some, and a burden for many. Numerous definitions have been proposed for stress, each focusing on aspects of an internal or external challenge/stimulus, on stimulus perception, or on a physiological response to the stimulus (190). An integrated definition proposes that *stress is a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception), that activates physio-*

*logical fight or flight systems in the body (stress response)* (46). The stress response induces the release of the principal stress hormones (noradrenaline, adrenaline, and cortisol/corticosterone) as well as a myriad of neurotransmitters, hormones, peptides, cytokines and other factors. Since virtually every cell in the body expresses receptors for one or more of these factors, all cells and tissues can receive biological signals that alert them regarding the presence of a stressor. The only way that a stressor can affect brain, body, and health is by inducing biological changes through a physiological stress response.

Although stress can be harmful when it is chronic or long lasting (43, 82, 128), a short-term fight-or-flight stress response has salubrious adaptive effects (44, 45, 50). Therefore, the duration of stress is an important factor in determining its effects on immune function and health. *Acute stress* has been defined as stress that lasts for a period of minutes to hours, and *chronic stress* as stress that persists for several hours per day for weeks or months (46). Dysregulation of the circadian cortisol rhythm is one marker that is related to the deleterious effects of chronic stress (46, 192). It is important to note that there are significant individual differences in stress perception, processing, and coping that mediate differences in the intensity and duration of a physiological response to a given stressor (32, 49, 50, 92). It is known that chronic or long-term stressors can have adverse effects on health, many of which may be mediated through immune mechanisms. However, it is important to recognize that a psycho-physiological stress response is one of nature's fundamental survival mechanisms (44). Without a fight-or-flight stress response, a lion has no chance of catching a gazelle, just as the gazelle has no chance of escape. During such short-term stress responses observed in nature, physiological systems act in synchrony to enable survival. Therefore, it was hypothesized that just as the stress response prepares the cardiovascular, musculoskeletal and neuroendocrine systems for fight or flight, under certain conditions, stress may also prepare the immune system for challenges (e.g. wounding or infection) that may be imposed by a stressor (e.g. predator or surgical procedure) (48, 50). Short duration stressors induce a redistribution of immune cells within the body and immune function is significantly enhanced in organs like the skin to which leukocytes traffic during acute stress. Studies have also identified mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function through which acute stressors may enhance innate as well as adaptive immunity.

### **Effects of acute versus chronic stress on immune cell distribution**

Effective immunoprotection requires rapid redistribution and recruitment of leukocytes into sites of surgery, wounding, infection, or vaccination. Numerous studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood (9, 48, 52, 69, 194). An acute stress-induced redistribution of leukocytes within different body compartments is perhaps one of the most under-appreciated effects of stress (51). Acute stress induces an initial increase followed by a decrease in blood mononuclear leukocyte numbers (48, 187). Stress conditions that result in activation of the sympathetic nervous system induce an increase in circulating leukocyte numbers (both mononuclear and polymorphonuclear cells). These conditions

may occur during the beginning of a stress response, very short duration stress (order of minutes), mild psychological stress, or during exercise. In contrast, stress conditions that result in the activation of the hypothalamic-pituitary-adrenal axis induce a decrease in circulating mononuclear cell (viz. lymphocyte and monocyte) numbers. These conditions often occur during the later stages of a stress response, exposure to long duration acute stressors (order of hours), or during severe stress or prolonged and/or intense exercise. An elegant example comes from Schedlowski et al. who measured changes in blood T cell and natural killer (NK) cell numbers as well as plasma catecholamine and cortisol levels in parachutists 2 hours before, immediately after, and 1 hour after a jump (193). Results showed a significant increase in T cell and NK cell numbers immediately (minutes) after the jump that was followed by a significant decrease an hour later. An early increase in plasma catecholamines preceded early increases in lymphocyte numbers, whereas the more delayed rise in plasma cortisol preceded the later decrease in lymphocyte numbers (193). Importantly, changes in NK cell activity and antibody-dependent cell-mediated cytotoxicity closely paralleled changes in blood NK cell numbers, thus suggesting that changes in leukocyte numbers may be an important mediator of apparent changes in leukocyte “functional activity.” A similar profile of changes in lymphocyte and monocyte numbers has been characterized in patients experiencing surgery stress and has been related to successful postsurgical recovery (187).

Thus, an acute stress response induces biphasic changes in blood leukocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute stress, or exercise, the body’s “soldiers” (leukocytes), exit their “barracks” (spleen, lung, marginated pool and other organs) and enter the “boulevards” (blood vessels and lymphatics). This results in an increase in blood leukocyte numbers, the effect being most prominent for NK cells and polymorphonuclear granulocytes. As the stress response continues, leukocytes exit the blood and take position at potential “battle stations” (such as the skin, lung, gastro-intestinal and urinary-genital tracts, mucosal surfaces, and lymph nodes) in preparation for immune challenges which may be imposed by the actions of the stressor (45, 48, 50). Such a redistribution of leukocytes results in a decrease in blood mononuclear leukocyte numbers. Thus, acute stress induces a redistribution of several leukocyte subsets from the barracks, through the boulevards, and to potential battle stations within the body. It is important to note that in addition to leukocyte redistribution, acute stressors also enhance immune function through additional mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function (215).

In contrast to acute stress, chronic stress induces deleterious changes in leukocyte numbers. First, exposure to chronic stress results in lower resting-state immune cell numbers that would imply a diminished capacity to mount immune responses (46). Secondly, exposure to chronic stress decreases the magnitude of acute stress-induced immune cell redistribution (46). In effect, chronic stress reduces the number of “soldiers” in the body’s army, and reduces the capacity of the remaining leukocytes to mobilize from “boulevards to battle stations” during a fight-or-flight response.

**Acute stress psychophysiology as an endogenous adjuvant**

It has been proposed that a psycho-physiological stress response is nature's fundamental survival mechanism that could be harnessed therapeutically to augment immune function during vaccination, wound healing or infection (54). These adjuvant-like immuno-enhancing effects of acute stress may have evolved because many stressful situations (aggression, accident) result in immune activation (wounding, infection) and vice versa. Interestingly, in modern times, many medical procedures involving immune activation (vaccination, surgery) also induce a stress response. In keeping with the above hypothesis, studies have shown that patients undergoing knee surgery, who show a robust and adaptive immune cell redistribution profile during the acute stress of surgery, also show significantly enhanced recovery (187). Similarly, an elegant series of adjuvant effects of acute mental stress or exercise can enhance vaccine-induced humoral and cell-mediated immunity in human subjects (60, 62) (for review see: (61)). Although acute stress- (or exercise-) induced immunoenhancement may serve to increase immunoprotection during vaccination, infection, or wounding, it may also exacerbate immunopathology if the enhanced immune response is directed against innocuous or self-antigens, or becomes dysregulated following prolonged activation as seen during chronic stress.

Numerous studies have been conducted to elucidate mechanisms mediating acute stress-induced enhancement of immune function. Viswanathan and Dhabhar (216) used a subcutaneously implanted surgical sponge model to elucidate the effects of stress on the kinetics, magnitude, subpopulation, and chemoattractant specificity of leukocyte trafficking to a site of immune activation or surgery. Results showed that an acute stress-induced increase in leukocyte trafficking coupled with specific chemokines and cytokines released during the initiation cascades of inflammation can alter the course of different (innate versus adaptive, early versus late, acute versus chronic) protective or pathological immune responses (216). Since the skin is one target organ to which leukocytes traffic during stress, studies were conducted to examine whether skin immunity is enhanced when immune activation/antigen exposure occurs following a stressful experience. Studies showed that acute stress experienced at the time of novel or primary antigen exposure results in a significant enhancement of the ensuing skin immune response (54). Compared to controls, mice restrained for 2.5 hours before primary immunization with keyhole limpet haemocyanin (KLH) showed a significantly enhanced immune response when re-exposed to KLH nine months later. This immunoenhancement was mediated by an increase in numbers of memory and effector helper T cells in sentinel lymph nodes at the time of primary immunization. Further analyses showed that the early stress-induced increase in T cell memory was followed by a robust increase in infiltrating lymphocyte and macrophage numbers months later at a novel site of antigen re-exposure. Enhanced leukocyte infiltration was driven by increased levels of the Type-1 cytokines, interleukin (IL)-2, interferon- $\gamma$  (IFN- $\gamma$ ) and tumour necrosis factor- $\alpha$  observed at the site of antigen re-exposure. Other investigators have similarly reported stress-induced enhancement of Type-1 cytokine driven cell-mediated immunity (13, 189, 222) and Type-2 cytokine driven humoral immunity (Type-2 cytokines include for example IL-4 and IL-10) (30, 222). Viswanathan et al. (215)

further showed that important interactive components of innate (dendritic cells and macrophages) and adaptive (surveillance T cells) immunity are mediators of the stress-induced enhancement of a primary immune response. Although much work remains to be done, to identify further molecular, cellular, and physiological mechanisms, studies have also identified endocrine and immune mediators of these effects showing that corticosterone and adrenaline are important systemic mediators and IFN- $\gamma$  is an important local mediator of immunoenhancement induced by acute stress (47, 53).

### **Effects of chronic stress on immune function**

The immuno-suppressive and dysregulatory effects of chronic stress have been reviewed extensively (2, 33, 64, 82, 101). Chronic stress is known to dysregulate immune responses (82) by altering the cytokine balance from Type-1 to Type-2 cytokine-driven responses (83) and accelerating immunosenescence (65), and to suppress immunity by decreasing numbers (46), trafficking (46), and function of protective immune cells while increasing regulatory/suppressor T cells (192). Through these effects, chronic stressors are thought to exacerbate pro-inflammatory diseases and increase susceptibility to infections and cancer (44). Exercise and cancer is discussed in detail in part one of the position statement.

### **Importance of relationship between stress and exercise**

Understanding the psychological, physiological, and health effects of exercise in the context of stress and stress physiology is critical for several important reasons: First, the process of exercising invariably induces a physiological stress response and results in higher circulating concentrations of noradrenaline, adrenaline, cortisol, other stress-related factors, and even cytokines (93, 166). Exercise-induced pain, exhaustion, or injury could also induce psychological stress. Moreover, intense prolonged exercise (85) or exercising under extreme environmental conditions (218), may lead to chronic exposure to stress hormones which may make the individual susceptible to the deleterious health effects of chronic stress. Thus, short- or long-term exercise can activate different components of a physiological stress response. The relative concentrations of exercise-induced stress-related hormones, cytokines and other factors induced in the body are likely to depend on a host of factors including the genetic makeup, psycho-physiological health, and fitness of the individual, as well as the type, intensity, duration, and chronicity of exercise. Since immune cells and organs have receptors for, and respond to, the myriad of stress-related physiological factors that are released during exercise, many effects of exercise on the immune system are likely to be mediated by these factors. Secondly, when performed under appropriate conditions, exercise could be a significant factor in ameliorating the deleterious health effects of chronic stress (169, 223). The type, intensity, duration and frequency of exercise and the conditions under which it should be performed in order to effectively reduce the stress burden of different individuals need to be understood and defined clearly. It is likely that one would need different strokes for different folks, i.e., running could serve as a “de-stressor” for some while others would benefit from aerobics, swimming, dancing or yoga. The most desirable results are likely to arise when the physical as well as psychosocial aspects of the exercise are matched with factors such as the fitness, capability, temperament, personality, etc., of the exercis-

ing individual. **Thirdly**, the psychosocial stress status of an individual may affect the relationship between exercise and health positively or negatively. For example, a chronically stressed individual may react differently to the effects of exercise, and may have lower thresholds for exercise-induced wear and tear compared to someone who is not chronically stressed. This is an area of research that is ripe for investigation and is relevant for the well-being of recreational and elite athletes, as well as armed forces and other professions for whom exercise is a critical aspect of training and job-performance.

### **Conclusion**

Exercise and stress are intricately linked. Exercise induces a physiological stress response. Intense and/or prolonged exercise may induce negative health consequences, many of which may be mediated by physiological pathways activated by chronic stress. However, moderate exercise could be an important factor in ameliorating the negative health effects of chronic stress. Moreover, the stress status of an individual could in turn affect the degree and extent of the salubrious effects of exercise. One important mechanism mediating the salubrious effects of exercise could be the optimization and maintenance of the survival-promoting physiological changes induced by the short-term or acute stress response. Further research into the effects of exercise and stress on immune function and health, on mechanisms mediating the salubrious effects of exercise, and on the relationship between exercise and the psychosocial stress-status of an individual, is likely to be helpful for harnessing the health benefits of exercise more fully and widely.

## **SLEEP DISRUPTION AND IMMUNE FUNCTION**

### **Background**

There seems quite a close interaction between immune function and sleep. In laboratory animals the intracerebral infusion of interleukin (IL)-1, interferon- $\gamma$  (IFN- $\gamma$ ) or tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) tends to induce sleep (112, 164), and studies of circulating cytokine levels in patients with excessive daytime sleepiness suggest that these same factors influence human sleep patterns (91, 214). Associations have also been observed between abnormalities of immune function and various forms of sleep disruption of interest to the exercise scientist. Issues include sleep deprivation, shift work, and disturbances of the circadian rhythm associated with global travel. However, it has been difficult to determine whether the observed changes in immune responses reflect a disturbance of sleep per se, disturbances of the circadian periodicity of hormone secretions (114, 145, 213), a general stress response, or a cognitive reaction to loss of sleep.

The following is a brief review of the impact of various types of sleep disturbance upon immune responses, noting the practical significance for the physically active individual.

## Sleep deprivation

Sleep deprivation may be acute (for example, because of the anxiety associated with international competition, or the demands of extended military combat (20)), or chronic (due to pain, or the obstructed breathing associated with severe obesity or airway congestion due to respiratory infection). Although abnormalities of immune function have been described in these various situations, they reflect in part such factors as overall anxiety, very prolonged exercise, and a shortage or excess of food rather than a direct influence of sleep deprivation upon the immune system.

Animal studies have failed to demonstrate consistent immunological responses, perhaps because of problems in enforcing wakefulness in rats and mice. In laboratory studies of humans, some authors have noted alterations of immune function after 4-5 hours of sleep disturbance, but others have not seen changes unless participants remained awake for several days. One study found that keeping healthy volunteers awake between 22:00 and 03:00 led to decreases in both total natural killer (NK) cell activity and activity per NK cell, total lymphokine activated killer cell activity and activity per precursor cell (CD16+56+ cells and CD25+ cells), together with a decrease in concanavalin-stimulated IL-2 production (100). After a night of recovery sleep, NK cell activity was restored, but IL-2 levels remained depressed. By using actigraphy to monitor sleep, a recent study showed decreased NK cell mobilization in response to a cognitive stress test in healthy women who had experienced disrupted sleep (224). Indeed, wrist-mounted actigraph movement monitors may present a simple and inexpensive method to monitor sleep quantity and quality in athletes and soldiers. Sleep deprivation from 23:00 to 03:00 has also been shown to induce markers of inflammation, particularly in women; this is thought to be secondary to an activation of nuclear factor-kappa B, and an up-regulation of pro-inflammatory genes (103). In consequence, increases in lipopolysaccharide-stimulated production of IL-6 and TNF- $\alpha$  have been observed (102), together with increased levels of C-reactive protein (132). CD4+, CD16+, CD56+ and CD57+ lymphocyte counts were decreased after one night without sleep (57), in a manner reminiscent of exposure to other forms of stress (166). More prolonged sleep deprivation leads to increases in leukocyte, granulocyte and monocyte counts and the proportion of lymphocytes in the S phase of the cell cycle (57), with enhanced NK cell activity, interferon production and IL-1 and IL-2 like activity, and increased levels of C-reactive protein (57, 132, 165). However, some authors have found that the increase of NK cell activity is a relatively late phenomenon, seen after 64 h (57) but not 40 h of sleep deprivation (138). Recovery of the various immune parameters follows a similar pattern to the restoration of neuro-behavioural function, suggesting a relationship between immunological change and biological pressures to sleep.

Laboratory studies have also shown small decrements in parameters such as maximal oxygen intake (39) and endurance exercise performance (163) following one or more nights without sleep. One practical consequence is that an individual who attempts to maintain a given submaximal exercise intensity must use a larger fraction of maximal aerobic power, thereby potentially exaggerating normal immune responses to vigorous exercise.

**Shift work**

Shift work is of two main types- an 8-h rotating shift (which requires repeated displacements of the individual's circadian rhythm), and prolonged periods of night work (which increase a person's total exposure to light, often with disruptions of normal social life). Adverse effects seem linked mainly to prolonged periods of night work (40). Such employment is associated with an increased risk of breast, prostate and colon cancers (34, 40). Plainly, the socio-economic, demographic, dietary and lifestyle characteristics of shift workers could contribute to this risk. Exposure to light during the night hours decreases body concentrations of melatonin, thus stimulating the hypothalamic-pituitary-gonadal axis, and causing an increased production of testosterone and/or oestrogen (95, 207). Other investigators have postulated that prolonged night work alters the balance of cytokines that regulate tumour growth. In their view, a chronic decrease in NK cells and cytotoxic, tumour-infiltrating lymphocytes leads to a decreased production of tumour inhibiting cytokines (IL-1, IL-2, IFN- $\gamma$  and TNF- $\alpha$ ) and an increased production of tumour stimulating cytokines such as IL-10 (12, 24, 56, 123).

**Disturbances of circadian rhythm**

Athletes need to adjust their circadian rhythms as a consequence of latitudinal travel. The normal, free-running cycle has a length of 25-27 h. Disturbances are thus greater for an eastward displacement of 6 h (where the circadian clock must be adjusted by moving 18 h forward) than for a corresponding westward journey (where the circadian balance is restored by a 6-h shift). Various determinants of physical performance show a circadian fluctuation (198), and such characteristics may be less than optimal during the daytime until adjustment is complete. However, for many athletes the temporary disturbance of cognitive function is more important than any deterioration of physical performance. Current attempts to speed circadian adjustments are based on pre-travel exposure to bright light at the new hour of waking, immediate adoption of the new schedule of meals and exercise on arrival, and (for some physicians) the ingestion of melatonin (73). Given the known interactions between cytokines and sleepiness, there seems scope for future studies that attempt to speed circadian adaptations by manipulating cytokine levels.

The normal circadian variation of immune responses reflects parallel changes in hormone secretion (213). Total circulating lymphocytes present essentially a mirror image of plasma cortisol concentrations, peaking around 20:00-21:00 when cortisol is at its nadir. Most authors also agree that circulating counts for individual leukocyte subsets are highest during sleep, although the timing of peak concentrations is disputed. Haus et al. (96) and Ritchie et al. (183) reported increased eosinophil, monocyte, lymphocyte, T and B cell counts between 24:00 and 02:00. Others also found the largest numbers of B and NK cells in the early morning (70, 80). On the other hand, Abo et al. (1) and Bertouch et al. (10) found the acrophase for B cells in the evening, with the T cell and the CD4+/CD8+ ratios conforming to a similar pattern (70, 71, 109). Plasma IL-6 concentrations rise with the onset of sleep (176). Plasma IL-1 concentrations peak around midnight, followed by a peaking of IL-2 and a decline of NK cell activity, these various changes apparent-

ly being linked to the onset of slow-wave sleep. Responsiveness to pokeweed mitogen but not phytohaemagglutinin is increased during the sleeping hours (136, 137, 139). The maximum stimulation of cytolytic activity by IFN- $\gamma$  is seen in the early morning, but the inhibitory effect of cortisol peaks at night; moreover, oral melatonin given around 18:00 augments the response to IFN- $\gamma$  (79). There are also circadian variations in serum immunoglobulin concentrations (178) and the *in vitro* production of cytokines in whole blood (98, 168).

### **Clinical significance and future directions**

Stimulation of inflammatory processes in those experiencing chronic sleep disruption may increase the risk of chronic disorders such as atherosclerosis, diabetes mellitus, Crohn's disease, and rheumatoid arthritis (208). Suggestions that immune disturbances increase the risk of cancer in shift workers also merit further exploration.

Sleep deprivation appears to reduce the antibody response to viruses in experimental animals and very prolonged periods of total sleep deprivation (typically about 20 consecutive days without sleep) result in lethal bloodstream infection and mortality in animals (21, 67, 211). However, much shorter periods of total sleep deprivation in humans (e.g. 3 consecutive nights without sleep) do not seem to influence the risk of infection, and the reported increase in NK cell activity with this duration of total sleep deprivation (57) would seem to rule out the possibility of an "open-window" for respiratory infections (147).

There is a pressing need to study whether disturbances to sleep quantity (total duration of sleep per night) or quality (number of awakenings per night) may have an adverse effect on immune health of the athlete or soldier. One recent study showed little effect of one night of total sleep deprivation on selected immune indices at rest and after exercise (181). However, very little is known about the effects of more prolonged sleep disruption or repeated sleep disturbances on immune function and infection incidence. One recent landmark study, albeit in healthy adults, showed that those who self-reported poor sleep quantity and/or quality exhibited increased symptoms of the common cold after intra-nasal inoculation with rhinovirus (31). Adults who slept for less than 7 h per night were almost 3-times more likely to develop symptoms of the common cold than those who slept more than 8 h per night. These findings highlight the importance of sleep quantity and quality in protecting humans against upper respiratory tract infections. Athlete and military support staff should consider monitoring sleep quantity and quality using a small, inexpensive and non-invasive movement sensor such as an actigraph. The utility of pharmacological and non-pharmacological interventions to improve sleep quantity and/or quality in those who frequently experience sleep disruption should be investigated alongside objective measures of immune status and infection incidence.

## ENVIRONMENTAL EXTREMES AND THE IMMUNE RESPONSE TO EXERCISE

### Background

Athletes, military personnel, mountaineers and those in physically demanding occupations are often required to reside in, or to perform vigorous physical activity in, adverse environmental conditions. Potential adverse conditions include extremes of heat and humidity, cold, high altitude and air pollutants. Lay people commonly believe that a hot bath or sauna can have therapeutic effects for all manner of ailments and that getting cold and wet increases the incidence of the common cold. Leading exercise immunologists have suggested that physical activity performed in stressful environments poses a greater than normal threat to immune function (199, 201), but this remains controversial (218).

This section summarises what we do and do not know about the immune response to exercise in environmental extremes, outlining some controversies and directions for future research. For a comprehensive review, readers are directed elsewhere (218).

### Heat stress and immune function

#### Consensus

Exercising in hot conditions in which core temperature rises by  $\geq 1^{\circ}\text{C}$  compared with thermoneutral conditions (where core temperature rise is  $< 1^{\circ}\text{C}$ ) augments anticipated increases in circulating stress hormones including catecholamines and cytokines, with associated elevations in circulating leukocyte counts (38, 180). Controlled studies that have clamped the rise in core temperature by undertaking moderate intensity endurance exercise in cool water demonstrate a significant contribution of the rise in core temperature to the development of the leukocytosis and cytokinaemia of exercise (38, 180). However, with the exception of a reduction in stimulated lymphocyte responses after exercise in the heat (197), and in exertional heat illness (EHI) patients (core temperature  $> 40^{\circ}\text{C}$ ) (59), laboratory studies show a limited effect of exercise in the heat on: neutrophil function, monocyte function, natural killer cell activity (NKCA) and mucosal immunity (116-118, 129, 135, 205). Therefore, most of the available evidence does not support the contention that exercising in the heat poses a greater threat to immune function compared with thermoneutral conditions. It is also worth mentioning that individuals exercising in the heat tend to fatigue sooner (compared with performing the same exercise in thermoneutral conditions), so that their exposure to exercise stress in the heat tends to be self-limiting (89).

#### Controversies and future directions

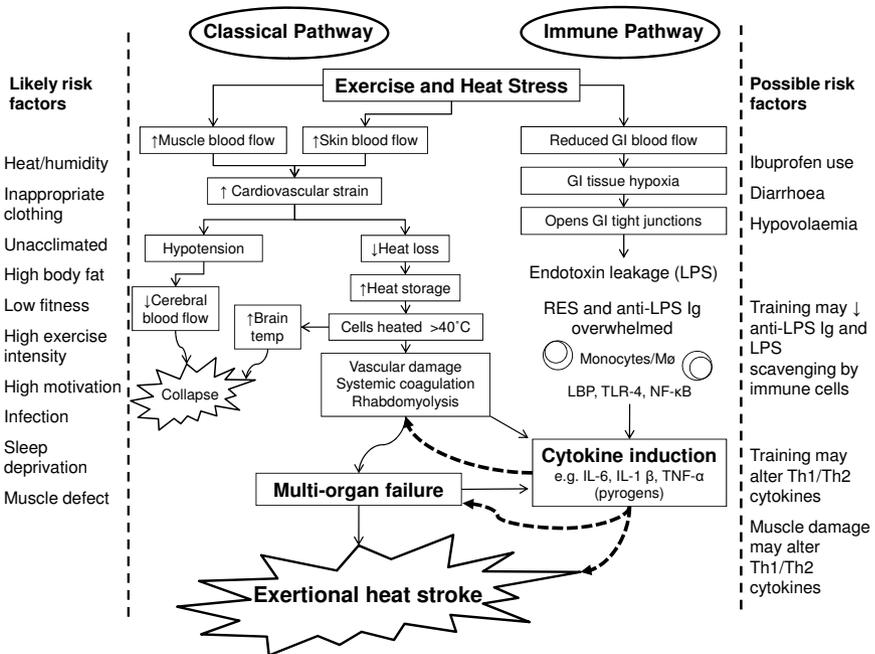
The findings from tightly restricted laboratory studies that have evoked only modest increases in core temperature (peak  $< 39^{\circ}\text{C}$ ) become somewhat redundant when one considers that core temperature often exceeds  $40^{\circ}\text{C}$  in athletes and soldiers whilst exercising in the heat (59, 184). Although field studies provide the opportunity to investigate the effects of severe heat stress on immune function, these studies often lack adequate experimental control. Somewhat surprisingly, clinically significant outcomes such as *in vivo* immune responses and infection

incidence have not been compared between athletes and soldiers training in hot and humid conditions and those training in thermoneutral conditions. In this regard, the next best evidence we have comes from studies showing that whole-body heating with saunas reduces upper respiratory tract infection (URTI) incidence (66) and hot water immersion improves clinical outcomes for cancer patients (105).

Without doubt the most exciting ongoing controversy in this sub-discipline of exercise-immunology centres on whether the immune system is involved in the aetiology of exertional heat stroke (EHS). Unlike the more mild EHI, EHS is a life threatening acute heat illness characterised by hyperthermia (core temperature  $>40^{\circ}\text{C}$ ) and neurological abnormalities that can develop after exposure to high ambient temperature and humidity (142). The putative involvement of immune dysregulation in the aetiology of EHS was first described in the exercise immunology literature by Shephard and Shek (201) and more recently refined by Lim and Mackinnon (120). During exercise-heat stress, gastrointestinal ischaemia can result in damage to the intestinal mucosa and leakage of lipopolysaccharide (LPS) into the portal circulation. The LPS is typically neutralized firstly by the liver and secondly by monocytes and macrophages. However, these defences may become overwhelmed, resulting in increased LPS in the peripheral circulation; the increase in circulating LPS may be exacerbated if immune function is impaired during heavy training (e.g. via decreased anti-LPS antibodies) (15). In turn, a sequence of events ensues involving LPS binding to its binding protein, the transfer of LPS to its receptor complex, toll-like receptor-4, with subsequent nuclear factor-kappa B activation and translation and production of inflammatory mediators including interleukin (IL)- $1\beta$ , tumour necrosis factor alpha (TNF- $\alpha$ ), IL-6 and inducible nitric oxide synthase (195). These events can lead to the systemic inflammatory response syndrome (SIRS), intravascular coagulation and eventually to multi-organ failure. This is an attractive model, particularly for cases of EHS that are otherwise difficult to explain, because the pyrogenic cytokines (e.g. IL- $1\beta$ , and TNF- $\alpha$ ) can alter thermoregulation (IL-1 induces fever) and cause cardiovascular instability resulting in collapse of the athlete or soldier (Figure 1).

Authors often cite support for an involvement of immune dysregulation in the aetiology of EHS from studies showing the following: circulating LPS levels in ultramarathon runners similar to florid sepsis (15); improved heat tolerance in heat-stressed animals treated with corticosteroids and antibiotics to prevent increases in circulating LPS (77, 78); cytokinaemia in EHS patients (17); symptoms of heat stroke in animals receiving IL-1 or TNF- $\alpha$  (122); enhanced survival in heat-stressed animals receiving IL-1 receptor antagonist (27) and important roles for heat shock proteins (e.g. HSP72) in cellular acquired thermal tolerance (126). In addition, recent work in rats shows that experimentally induced inflammation (via intramuscular injection of turpentine) compromises heat tolerance, further supporting a role for immune dysregulation in heat stroke (121).

However attractive an immune model of heat illness appears, there are many inconsistencies and gaps in knowledge that require elucidation. For example,



**Figure 1.** Classical and immune pathways of exertional heat stroke (EHS). GI = gastrointestinal; LPS = lipopolysaccharide; RES = reticuloendothelial system; Ig = immunoglobulin; Mφ = macrophage; LBP = lipopolysaccharide binding protein; TLR-4 = toll-like receptor-4; NF-κB = nuclear factor-kappa B. Solid arrows indicate likely links in pathway; broken arrows indicate unsubstantiated in EHS aetiology.

there exists great variability in circulating LPS and cytokine levels in heat stroke and EHS casualties (15, 17, 23, 218). There is no consensus about the level of circulating LPS associated with clinical manifestations of EHS, although Moore et al. (140) have suggested a threshold of 60 pg.ml<sup>-1</sup>. In light of this, it seems unreasonable that one widely cited paper presents pre-exercise circulating LPS in ultra-distance triathletes of 81 pg.ml<sup>-1</sup>; it would be reasonable to assume that triathletes attend a race without initial clinical manifestations of heat illness (15). Similarly, studies reporting cytokinaemia in heat stroke and EHS patients show large variability in responses between patients and levels that are more often than not below the magnitude seen during SIRS and sepsis (17). Lack of experimental control in field studies and delay in admitting patients to hospital for blood collection add to the confusing picture regarding cytokines and heat stroke pathology. It is quite conceivable that the cytokinaemia of EHS is instrumental in the recovery from EHS, but this idea needs substantiating (119). On a more critical note, studies reporting raised circulating LPS and cytokines in end-stage heat stroke tell us very little about a putative involvement of the immune system in the aetiology of heat stroke. Prospective studies in humans are required to examine the extent of any immune dysregulation prior to collapse (218). An important yet unanswered question is whether the time course of LPS leakage from the gut, the resulting

cytokinaemia, altered thermoregulation and cardiovascular instability during exercise-heat stress coincide with the development of EHS. Human studies have shed some light on this, albeit using an experimental model of endotoxaemia that did not involve exercise-heat stress (133, 212). Infusing  $2 \text{ ng.kg}^{-1}$  *Escherichia coli* endotoxin evoked maximal circulating TNF concentration 60-90 min after infusion and maximal body temperature 180 min after infusion (212). A decrease in blood pressure, which would be expected to contribute to the collapse in an EHS casualty, was not observed until 120 min after endotoxin infusion. Given the time course of these responses, an involvement of immune dysregulation in EHS during relatively short duration exercise (e.g. <60 min) appears less likely. A significant proportion of EHI cases, particularly in military personnel, occur in exercise bouts lasting <60 min (59, 175). The more traditional predisposing factors for EHS (Figure 1) such as high heat load, effort unmatched to fitness and underlying illness (175) alongside a recently proposed muscle defect causing excessive endogenous heat production likely play a prominent role in EHS aetiology (174).

## **Cold stress and immune function**

### **Consensus**

The term 'colds' may come from the popular belief that cold exposure causes URTI (25, 200). To date, there is no conclusive evidence to support a direct effect of prolonged cold exposure on URTI incidence. Reports from a number of Antarctic studies have shown little evidence of URTI among personnel except immediately after the visit of supply ships, when new strains of virus are imported into the community (76, 200), although the extent of cold exposure among study participants may have been relatively small.

Current consensus is that a continuum exists for the effects of passive body cooling on immune function. Very mild decreases in core temperature ( $\sim 0.5^\circ\text{C}$ ) have little or even stimulatory effects on immune function (19, 115) but modest ( $\sim 1^\circ\text{C}$ ) (35) and severe ( $\sim 4^\circ\text{C}$ ) (220) decreases in core temperature have depressive effects on immune function. Compared with exercise in thermoneutral conditions, exercise in cold air conditions is associated with similar, or slightly lower, core temperature and neuro-endocrine activation (217) and similar immune modulation (179, 217, 218).

### **Controversies and future directions**

Although lay people believe that getting cold and wet causes the common cold, this remains controversial because evidence from studies where participants were inoculated intra-nasally with cold viruses after cold exposure does not support such a belief (58). Nevertheless, more recent, novel work indicates that cooling body parts such as the feet increases self-reporting of cold symptoms (104). The authors claim this is due to reflex vasoconstriction in the upper airways and an associated reduction in respiratory defence. To settle this controversy, more experimental work is required that overcomes the limitations of existing studies. For example, published investigations have not mimicked the typical exposure to the common cold (58), have been limited by a small number of participants (58) or did not involve appropriate virology to quantify common cold incidence objectively after cold exposure (104).

To summarise, the limited evidence does not support the contention that athletes training and competing in cold conditions experience a greater reduction in immune function vs. those exercising under thermoneutral conditions. Nevertheless, it remains unknown if athletes who regularly train and compete in cold conditions report more frequent, severe or longer-lasting infections. Research should identify whether the airway inflammation associated with breathing large volumes of cold dry air (81) or polluted air (55) impairs airway defences (both ciliary function and immune responses) and whether athletes wrongly interpret as an URTI the symptoms of sore throat or exercise-induced bronchospasm that accompany exercising in cold or polluted air. As soldiers are often required to spend prolonged periods of activity interspersed with inactivity in cold and wet conditions they are particularly susceptible to hypothermia (core temperature  $\leq 35^{\circ}\text{C}$ ) and associated reductions in immune function. The influence of hypothermia on *in vivo* immune function, wound healing and infection risk warrants further enquiry.

### **Altitude stress and immune function**

#### **Consensus**

Athletes often train, and sometimes compete, at modest altitude (up to 2500 m) whereas mountaineers and occupational groups (e.g. high altitude miners and soldiers) often perform at high altitude (4000 m or higher). Upper respiratory and gastrointestinal tract symptoms are common in lowlanders who travel to high altitude (108, 143, 191, 203) and there are some reports that elite athletes experience increased URTI symptoms during and immediately after training camps at modest altitude (5, 90). Anecdotal reports of impaired wound healing in mountaineers at high altitude (170) are supported by laboratory studies in animals showing that breathing hypoxic air (12%  $\text{O}_2 \approx 4000 \text{ m}$ ) impairs wound healing after intradermal injection with *Escherichia coli* (110). The small number of investigations that have examined immune function in humans working and training at altitude (Table 3) indicate that NKCA and humoral immunity are either unaffected or enhanced (11, 28, 29, 68, 108, 130, 173). In contrast, cell mediated immunity is consistently reported to be impaired at altitude, with studies indicating decreases in CD4+:CD8+ T-lymphocyte ratio (68, 226) and T-lymphocyte proliferation (68, 173). Increased sympathetic nervous activity and hypothalamic–pituitary–adrenal axis activity are thought to play a prominent role in immune modulation at altitude (188).

#### **Controversies and future directions**

Although a small body of evidence supports the commonly held belief that high altitude exposure increases URTI (191, 203) this remains controversial because there exists some overlap in the symptoms of acute mountain sickness and URTI. Given the acknowledged immune alterations with exercise performed at sea level (85) and the additional stress responses to exercise with increasing altitude (127) an appealing hypothesis is that a continuum of responses exists whereby exercise with increasing altitude is associated with a greater degree of immune depression (127, 218). Unfortunately, only limited information from well controlled laboratory and field studies is available in this regard. Relatively little is known about the influence of altitude on innate immune function (Table 3) and the studies to date typically have not employed adequate experimental control (97). It is quite conceivable that other stressors experienced by athletes and mountaineers at alti-

Table 3. Immune function and infection symptoms during sojourns and athletic training in hypoxia. M = male; F = female; SL = sea level; TR = temporary altitude resident; Ig = immunoglobulin; NKCA = natural killer cell activity; URT = upper respiratory tract; LHTL = live high train low; IHT = intermittent hypoxia training, CRP = C-reactive protein. ND = no difference.

Reference	Participants	Hypoxic exposure and activity/training	Immune function and infection symptoms
Chohan et al.(29)	10 altitude natives (M), 8 TR (M) and 31 SL (M).	Natives and TR at 3692m. TR resided at 3692m for 2 years. Activity unknown.	↑ Serum Ig response to inoculation with T-cell dependent vaccine in natives and TR vs. SL.
Chohan and Singh (28)	24 altitude natives (M), 45 TR (M) and 66 SL (M).	Natives and TR at 3692m. TR resided at 3692m for 2 years. Activity unknown.	↑ T-lymphocyte function in natives and TR vs. SL residents.
Meehan et al.(130)	7 (M). No controls.	28 days of progressive decompression to 7620m in a chamber. Minimal activity.	ND in nasal IgA: protein, nasal lysosome: protein, CD4+:CD8+ ratio, lymphocyte function or NKCA.
Biselli et al.(11)	18 TR (M) and 18 SL controls (M).	20 days at 4930m. Activity level unknown.	ND serum Ig [G, A, M] and B-cell response to vaccine (T-cell independent) vs. control.
Bailey et al.(5)	10 elite runners TR and 19 SL controls (12M: 7F).	28 days at 1640m. Training at same relative exercise intensity in both groups.	↑ URT and gastrointestinal symptoms in runners at altitude vs. SL controls.
Pyne et al.(173)	10 elite swimmers TR (5M: 5F) and 8 staff controls (M).	21 days at 2102m. 3 sessions per day for swimmers (~5.5 h/day). Staff <4 h/week.	ND in infections or lymphocyte proliferation between groups. ↓ T-lymphocyte proliferation and ↑ B-cell proliferation vs. pre in both groups.
Hitomi et al.(97)	7 M. No controls.	7 days. IHT 2 h/day at 4500m. Activity unknown.	↑ neutrophil function vs. pre following IHT.
Tiollier et al.(210)	6 LHTL elite cross country (3M: 3F) and 5 elite controls (2M: 3F).	18 days. LHTL 11 h/day for 6 days each at 2500, 3000 and 3500m. Both groups trained at 1200m with matched load (~3h/day). 5 control athletes at 1200m.	ND in saliva [IgA] between groups. ↓saliva [IgA] in LHTL group at 2500 and 3500m vs. pre.
Facco et al.(68)	13 F. No controls.	21 days at 5050m. 1.5 h exercise 3-5 days/week.	ND in NKCA, ↓CD4+:CD8+ ratio and lymphocyte proliferation vs. pre.
Kleessen et al.(108)	7 Mountaineers (5M: 2F). No controls.	47 day altitude expedition where 29 days >5000m.	ND in serum Ig [G, A, M] and total faecal bacteria. ↑ CRP and gram-negative faecal bacteria vs. pre. ↓ Bifidobacteria (anti-microbial capacity) vs. pre.
Zhang et al.(226)	8 LHTL university soccer players (M) and 8 SL controls	28 days. LHTL 10h/day at equivalent of 3000m. Both groups trained at SL.	↑ URT symptoms in LHTL vs. control (2 LHTL with symptoms vs. 0 in control). ↓CD4+:CD8+

tude contribute to the observed alterations in infection incidence and immune function (e.g. raised physical and psychological stress, cold exposure and nutritional restriction).

In summary, although high altitude exposure has limited effects on humoral immunity, a number of studies have shown decreased cell-mediated immunity at high altitude. There is a need for tightly controlled laboratory and field studies employing exercising normoxia controls, resting hypoxia controls and clinically relevant *in vivo* immune methods to elucidate further the effects of altitude on immune health.

## PREVENTION AND TREATMENT OF COMMON INFECTIONS

### Background

Several studies (84, 160, 161, 167) have suggested that athletes are at increased risk of respiratory tract infections (URTI). For a more detailed account, readers are directed to the section on respiratory infections and exercise in part one of this

position statement. Exercise-induced suppression of some immune functions after intense and/or prolonged exercise and during strenuous training periods may explain the so-called “open window theory” and J-shaped curve paradigm, respectively. Regular sharing of the same training and living facilities within a team may also contribute to this increased frequency or duration of URTI (84). Moreover, the increased exposure to foreign (or new) pathogens while travelling put the athlete at a higher risk of gastrointestinal infections (GI) (14). Thus, acute URTI is the most common reason for presenting to a sports medicine clinic (74, 146), and it is the most common medical condition affecting athletes at both the summer and winter Olympic Games (94, 177).

### **Consensus**

It is agreed by everyone that prevention is always superior to treatment and this is particularly true in athletes residing in countries with limited medical facilities. However, there is no single intervention that completely eliminates the risk of contracting an infection, but there are several effective ways of reducing the number, duration and severity of infectious episodes incurred over a period. Most of the following practical guidelines, driven by common sense, can be understood by everyone who keeps in mind the contagious nature of viruses, bacteria and fungi.

### **Practical guidelines for prevention of infections among athletes**

- Check that your athletes are updated on all vaccines needed at home and for foreign countries should they travel abroad for training and competition.
- Minimize contacts with infected/sick people, young children, animals and potentially contaminated objects.
- Keep at distance from people who are coughing, sneezing or have a “runny nose”, and when appropriate wear or ask them to wear a disposable mask.
- Wash hands regularly, before meals, and after direct contact with potentially contagious people, animals, blood, secretions, public places and bathrooms. Carry alcohol-based gel with you where lavatories are not available or not clean enough.
- Use disposable paper towels and limit hand to mouth/nose contact when suffering from URTI or GI symptoms.
- Do not share drinking bottles, cups, towels, etc.
- While competing or training abroad, prefer cold beverage from sealed bottles, avoid crude vegetables, and meat. Wash and peel fruits before eating.
- Quickly isolate a team member with infection symptoms and move out his/her roommate.
- Protect airways from being directly exposed to very cold and dry air during strenuous exercise, by using a face mask.
- Ensure adequate level of carbohydrate intake before and during strenuous or prolonged exercise in order to limit the extent and severity of the exercise-induced immunodepression phase (see nutritional countermeasures section in this part of the position statement).
- Wear proper out-door clothing and avoid getting cold and wet after exercise.
- Get at least 7 hours sleep per night (31) (see sleep disruption section in this part of the position statement).
- Avoid crash dieting and rapid weight loss.

- Wear flip-flop or thongs when going to the showers, swimming pool and locker rooms in order to avoid dermatological diseases.
- Keep other life stresses to a minimum.

Should infection occur, the athlete and his or her entourage must use some basic guidelines for exercise during infectious episodes (186) before being referred to a physician.

### **Guidelines for exercise during episodes of URTI or GI in athletes**

#### *• First day of illness:*

No strenuous exercise or competitions when experiencing URTI symptoms like sore throat, coughing, runny or congested nose. No exercise when experiencing symptoms like muscle/joint pain and headache, fever and generalized feeling of malaise, diarrhoea or vomiting. Drink plenty of fluids, keep from getting wet and cold, and minimize life-stress.

Consider use of topical therapy with nasal drainage, decongestants and analgesics if feverish. Report illness to a team physician or health care personnel and keep away from other athletes if you are part of a team training or travelling together.

#### *• Second day:*

If body temperature  $>37.5-38^{\circ}\text{C}$ , or increased coughing, diarrhoea or vomiting: no training. If no fever or malaise and no worsening of “above the neck” symptoms: light exercise (pulse  $<120$  bpm) for 30-45 min, indoors during winter and by yourself.

#### *• Third day:*

If fever and URTI or GI symptoms are still present: consult your physician. In GI cases, antibiotics should be taken if unformed stools occur more than four times a day or for fever, blood, pus, or mucus in stools. Quinolones should be avoided whenever possible because of an increased risk of tendinopathy. If no fever or malaise and no worsening of initial symptoms: moderate exercise (pulse  $<150$  bpm) for 45-60 min, preferably indoors and by yourself.

#### *• Fourth day:*

If no symptom relief: do not try to exercise but make an office visit to your doctor. Stool cultures or examination for ova and parasites should generally be reserved for cases that last beyond 10 to 14 days. If first day of improved condition, follow the guidelines below (186):

### **Guidelines for return to exercise after infections**

- Wait one day without fever and with improvement of URTI or GI symptoms before returning to exercise.
- Stop physical exercise and consult your physician if a new episode with fever or worsening of initial symptoms or persistent coughing and exercise-induced breathing problems occur.
- Use the same number of days to step up to normal training as spent off regular training because of illness.
- Observe closely your tolerance to increased exercise intensity and take an extra day off if recovery is incomplete.

- Use proper outdoor clothing and specific cold air protection for airways when exercising in temperatures below  $-10^{\circ}\text{C}$  the first week after URTI.

### **Controversies**

The first one is infectious mononucleosis (IM). Indeed, strenuous physical training performed during the initial or convalescence phase of Epstein Barr virus infection can be associated with increased morbidity, relapse, delayed recovery, and splenic rupture. This last occurrence is rare (0.1% of IM) on the athletic field and rarely fatal now (22). Most splenic ruptures occur between 4 days and 4 weeks after onset and very few occur beyond week 5 (63). Four recent reviews (4, 107, 125, 219) suggested that all spleens that rupture are enlarged, but it is important to note that splenomegaly is found in 50% of IM and that physical examination is quite insensitive to detect an enlarged at-risk spleen reliably. Although return to sport after IM is still a topic of debate, we recommend First, a week without febrile episodes or systemic symptoms and a substantial decrease in serum viral antibody titres and liver enzymes before starting light exercise; Secondly, exclude the possibility of hepatosplenomegaly in an athlete returning to contact sports, by performing abdominal ultrasound or CT scan; Thirdly, observe the tolerance of each training session and its recovery and discontinue the exercise if relapse or worsening while waiting for a consultation with the physician.

The second is about the diagnosis of viral myocarditis, which is the reason for sudden cardiac death in 5-22% of athletes under 35 years of age (see review (18)). For the purpose of prevention it is thus recommended to stop elite sport for 4 weeks after an unspecific infection. As some athletes experience up to six colds or viral (and probably unspecific) infections per year, one can understand why this recommendation is rarely implemented. Thus, it is important to take subtle discomforts seriously and initiate further evaluation when viral infection is strongly suspected particularly in spring and summer (Parvovirus B19, Herpes virus 6, Echovirus, Coxsackie, Poliovirus). Electrocardiogram, laboratory parameters, serologic markers, and echocardiography are helpful in diagnosis of myocarditis, but are not specific. Magnetic resonance imaging of the heart has become an important tool, but is not affordable by all. The cost-benefit ratio of myocarditis diagnosis in athletes remains a matter of controversy.

### **Future directions**

As a high proportion of episodes of respiratory symptoms in athletes have not been associated with identification of a respiratory pathogen (37, 204), other potentially treatable causes of upper respiratory symptoms should be considered, particularly in athletes with recurrent symptoms. A better understanding of this phenomenon could lead to significant changes in the prevention and management of common infections in athletes.

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