Exercise, Infection, and Immunity

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Abstract

In this article, emphasis was placed on the relationship between exercise and upper respiratory tract infection (URTI) in humans, experimentally induced infections in animals subjected to varying levels of exertion, and potential changes in the immune system that might explain the altered risk of infection. With regard to induced infections in animals, the influence of any exercise intervention appears to be pathogen specific, and dependent on the species, age, and sex of the animals selected for study, and the type of exercise paradigm. In general, although further research with larger subject pools and improved study designs is needed, published data at this time support a "J" curve relationship between risk of URTI and increasing exercise workloads. For example, individuals exercising moderately may lower their risk of URTI while those undergoing heavy exercise regimens may have higher than normal risk. Although researchers have investigated changes in immune function that might provide a biological rationale for the "J" curve model of infection and exercise, the wide variety of research designs, exercise protocols, subject characteristics, and methodologies combined with the innate complexity of the immune system have made interpretation of published findings equivocal. T and NK cell function, for example, is often reported to be decreased during recovery from high-intensity exercise. However, when adjustments are made for exercise-induced perturbations in blood lymphocyte subsets, any link to decreased host protection is unlikely.

Key Words

Respiratory infection, exertion, immune system, lymphocytes, cortisol, catecholamines

Introduction

In a classic review entitled "The Effect of Muscular Fatigue Upon Resistance", *Baetjer* (5) indicated that in her day (1932), the prevailing view was "that muscular fatigue lowers resistance and is a predisposing factor to infectious diseases, especially with regard to respiratory infections." This viewpoint is still popular today, especially among elite athletes and coaches (29). For example, *Liz McClogan* 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 (95). During the Winter and Summer Olympic Games, it has been regularly reported by clinicians that "upper respiratory infections abound" (40) and that "the most irksome troubles with the athletes were infections" (51).

On the other hand, there is also a common belief among many individuals that regular exercise confers resistance against infection. For example, a 1989 Runner's World subscriber survey revealed that 61% of 700 runners reported fewer colds since beginning to run, while only 4% felt they had experienced more (3).

The US Center for Disease Control and Prevention has estimated that over 425 million upper respiratory tract infections (URTI) occur annually in the United States, resulting in $2.5 billion in lost school and work days, and in medical costs (121). The National Center for Health Statistics reports that acute respiratory conditions (primarily the common cold and influenza) have an annual incidence rate of 90 per 100 persons (1). Understanding the relationship between exercise and infection has potential implications for public health, and for the athlete, it may mean the difference between being able to compete or performing at a subpar level or missing the event altogether because of illness (77,85).

In this article, emphasis will be placed on the relationship between exercise and URTI in humans, experimentally induced infections in animals subjected to varying levels of exertion, and potential changes in the immune system that might explain the altered risk of infection. Several types of infectious diseases affect physically active individuals, often because they perform in an environment in which certain pathogenic microorganisms are particularly widespread, or, due to the type of sports, abrasions or other tissue injury is more likely. Research on the potential for skin infections and other infections in athletes (e.g., from hepatitis B and human immunodeficiency viruses) has been reviewed elsewhere (77,85).

Exercise and Upper Respiratory Tract Infection in Humans

In a review of exercise and infection published in 1932, *Baetjer* complained that comparatively little experimental work had been done to test this relationship scientifically (5). Unfortunately, this is still a problem today, although within the last 10 years a renewed interest among investigators has led to an increasing number of well-designed studies and informative publications.

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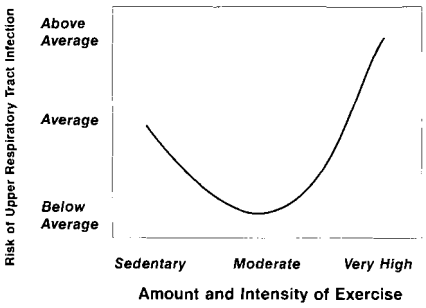

Fig. 1 "J"-shaped model of relationship between varying amounts of exercise and risk of URTI. This model suggests that moderate exercise may lower risk of respiratory infection while excessive amounts may increase the risk.

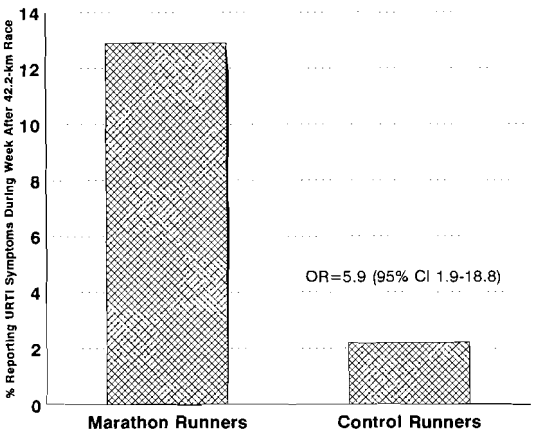

Fig. 2 Self-reported URTI in 2,311 Los Angeles marathon runners during the week following the 1987 Los Angeles Marathon. Data from *Nieman* et al. (81).

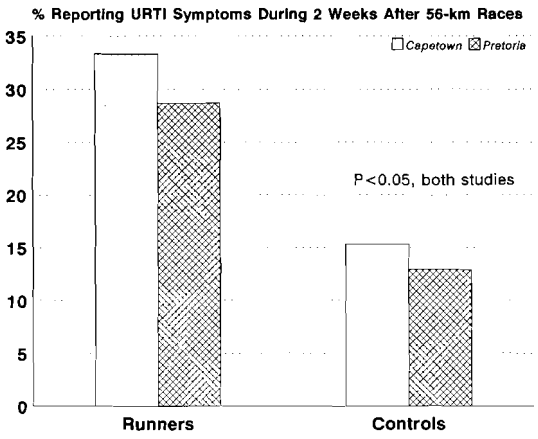

Fig. 3 URTI in runners versus controls during two week periods following 56 km races in Capetown and Pretoria, South Africa. Data from *Peters* (101) and *Peters* and *Bateman* (102).

It has been proposed that the relationship between exercise and URTI may be modeled in the from of a "J" curve (77). (Figure **1**). This model suggests that although the risk of URTI may decrease below that of a sedentary individual when one engages in moderate exercise training, risk may rise above average during periods of excessive amount of high-intensity exercise.

At present, there is more evidence, primarily epidemiological in nature, exploring the relationship between heavy exertion and infection, and the data will be reviewed first followed by a brief section on moderate exercise training and infection. Much more research using larger subject pools and improved research designs is necessary before this model can be wholly accepted or rejected.

Heavy Exertion and URTI: Epidemiological Evidence

Several epidemiological reports suggest that athletes engaging in marathon-type events and/or very heavy training are at increased risk of URTI (81, 101–103). *Nieman* et al. (81) researched the incidence of URTI in a group of 2,311 marathon runners who varied widely in running ability and training habits. Runners retrospectively self-reported demographic, training, and URTI episode and symptom data for the two-month period (January, February) prior to and the one week period immediately following the 1987 Los Angeles Marathon race.

An important finding was that 12.9% of Los Angeles Marathon participants reported an infectious episode during the week following the race in comparison to only 2.2% of similarly experienced runners who had applied but did not participate (for reasons other than sickness). Controlling for important demographic and training data by using logistic regression, it was determined that the odds were 6 to 1 in favor of sickness for the marathon race participants versus the nonparticipating runners (Figure **2**).

Forty percent of the runners reported at least one URTI episode during the two month winter period prior to the marathon race. Controlling for various confounders, it was determined that runners training more than 96 km/wk doubled their odds for sickness compared to those training less than 32 km/wk. Although the lowest odds of sickness were in the less than 32 km/wk group, the odds ratio did not increase significantly until 96 km/wk were exceeded. The researchers concluded that runners may experience increased risk for URTI during heavy training or following a marathon race event.

Other epidemiological data support these findings. *Peters* and *Bateman* (102) studied the incidence of URTI in 150 randomly selected runners who took part in a 56 km Cape Town race in comparison to matched controls who did not run. Symptoms of URTI occured in 33.3% of runners compared with 15.3% of controls during the two week period following the race, and were most common in those who achieved the faster race times. Sore throats and nasal symptoms were most prevalent, and of the total number of symptoms reported by the runners, 80% lasted longer than three days, suggesting an infectious origin.

Two subsequent studies from this group of researchers have confirmed this finding (101, 103). During the two-week period following the 56 km Milo Korkie Ultramarathon in Pretoria, South Africa, 28.7% of the 108 subjects who completed the race reported non-allergy derived URTI symptoms as compared to 12.9% of controls (who were of similar age and with whom they resided or were in frequent contact before the race) (101). The most prevalent symptoms were in the nose and throat, with 39% lasting for more than seven days, but only 4% of subjects reporting fever. Figure **3** summarizes the findings from the Cape Town and Pretoria ultramarathons.

In the most recent report from *Peters* et al. (103), 68 % of runners reported the development of symptoms of URTI within 2 weeks after the 90 km Comrades Ultramarathon. The incidence of URTI was greatest among the runners who trained the hardest coming into the race (85 % versus 45 % of the low- or medium-training status runners). Using a double-blind placebo research design, it was determined that only 33 % of runners taking a 600 mg vitamin C supplement daily for three weeks prior to the race developed URTI symptoms. The authors suggested that because heavy exertion enhances the production of free oxygen radicals, vitamin C, which has antioxidant properties, may be required in increased quantities.

URTI risk following a race event may depend on the distance, with an increased incidence conspicuous only following marathon or ultramarathon events. For example, *Nieman* et al. (80) were unable to establish any increase in prevalence of URTI in 273 runners during the week following 5 km, 10 km, and 21.1 km events as compared to the week before. URTI incidence was also measured during the two winter-month period prior to the three races, and in this group recreational runners, 25 % of those running 25 or more km/wk (average of 42 km/wk) reported at least one URTI episode, as opposed to 34 % training less than 25 km/wk (average of 12 km/wk) ($p = 0.09$). These findings suggest that, in recreational running, an average weekly distance of 42 versus 12 km is associated with either no change in or even a slight reduction of URTI incidence. Further, they suggest, that racing 5 km to 21.1 km is not related to an increased risk of sickness during the ensuing week.

Linde (61) studied URTI in a group of 44 elite orienteers and 44 nonathletes of the same age, sex, and occupational distribution during a one-year period. The orienteers experienced significantly more URTI episodes during the year in comparison to the control group (2.5 vs 1.7 episodes, respectively). Although one-third of the controls reported no URTI during the year-long study period, this applied to only 10 % of the orienteers. The average duration of symptoms in the group of orienteers was 7.9 days, which was little different from the 6.4 days of the control group. The control group had the expected seasonal variation with the peak incidence in winter and relatively few cases in summer, while the orienteers tended to show a more even distribution throughout the entire year.

Heath et al. (43) followed a cohort of 530 runners who self-reported URTI symptoms daily for one year. The average runner in the study was about 40 years of age, ran 32 km/week, and experienced 1.2 URTI episodes per year. Controlling for various confounding variables using logistic regression, the lowest odds ratio for URTI was found in those running less than 16 km/wk. The odds ratio more than doubled for those running more than 27 km/wk, demonstrating that total running distance for a year is a significant risk factor for URTI among recreational runners, with risk increasing as the running distance rises. Unfortunately, a sedentary control group was not utilized which would have allowed interesting comparisons in URTI symptomatology.

Together, these epidemiological studies suggest that heavy acute or chronic exercise is associated with an increased risk of URTI (44). The risk appears to be especially high during the one or two week period following marathon-type race events. Among runners varying widely in training habits, the risk for URTI is slightly elevated for the highest distance runners, but only when several confounding factors are controlled.

Although there have been other epidemiological reports on the relationship between exercise and URTI published, the methods used in these investigations make it difficult to draw conclusions or make comparisons with other studies (77). For example, *Schouten* et al. (110) conducted a six-month retrospective study of 199 young adults, and concluded that the incidence and duration of URTI was not significantly related to physical activity and fitness levels. However, in this study, no attempt was made to control for potential confounding factors, and the accuracy with which young adults are able to recall the incidence and duration of URTI from the previous six months is questionable. *Strauss* et al. (119) compared incidence of URTI in three different intercollegiate athletic teams (varsity wrestlers, swimmers, and gymnasts) during an eight week period (January, February), and reported no significant differences in incidence among the teams. However, no sedentary control groups were followed for comparison, and total physical activity was not measured. During this winter period, URTI was the leading cause of illness among the athletes, with 86 % diagnosed by a physician to have developed at least one episode.

Osterback and *Qvarnberg* (94) reported no differences in URTI incidence during a one-year period between children engaging in supervised sports (gymnastics, swimming, and icehockey) and those not participating in regular sports training. However, general physical activity was not measured, and as the authors admitted, "the amount of exercise children get by engaging in games and sports among themselves can be quite substantial" (94). In 1960, *Jackson* et al. (49) reported that fatigue resulting from exercise on a treadmill caused an "insignificant increase in the frequency with which colds were observed to follow an infectious challenge." Subjects were challenged with cold viruses in nasal drops of varying dilutions, with symptomatology measured in response to various environmental factors including exercise, lack of sleep, and chilling. However, apart from the statement given above, the investigators did not provide any other information (e. g., the exercise workload), limiting the usefulness of their concluding statement.

Moderate Exertion and URTI

What about the common belief that moderate physical activity is beneficial in decreasing URTI risk? Very few studies have been carried out in this area, and more research is certainly warranted to investigate this interesting question.

At present, there are no published epidemiological reports that have retrospectively or prospectively compared incidence of URTI in large groups of moderately active and sedentary individuals. Several epidemiological studies have compared URTI incidence rates among runners training varying distances, but these studies are more useful for determining whether heavy versus moderate training has a negative effect.

Two randomized experimental trials using small numbers of subjects have provided important preliminary data in support of the viewpoint that moderate physical activity may reduce URTI symptomatology. In one randomized, controlled study of 36 women (mean age 35 years), exercise sub-

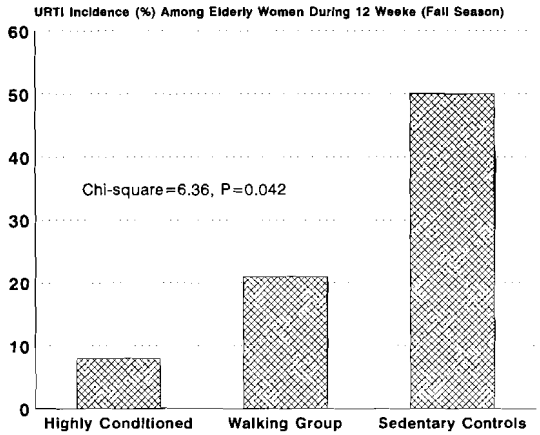

Fig. 4 Incidence of URTI (expressed as a precentage of the group) during a 12-week study period in highly conditioned, walking, and sedentary control groups of elderly women. Data from *Nieman* et al. (79).

jects walked briskly for 45 minutes, five days a week, and experienced one-half the days with URTI symptoms during the 15 wk period compared to that of the sedentary control group (5.1 ± 1.2 vs 10.8 ± 2.3 days, $p = 0.039$) (88).

In a recent study of elderly women, the incidence of the common cold during a 12-week period in fall was measured to be lowest in highly conditioned, lean subjects who exercised moderately each day for about 1.5 hours (8%). Elderly subjects who walked 40 minutes, 5 times/wk had an incidence of 21%, as compared to 50% for the sedentary control group (79) (Figure 4).

Exercise and Experimentally Induced Infections in Animals

Since the beginning of this century, various investigators have studied the effects of varying exercise workloads on the course of experimentally induced infections in laboratory animals (5, 90, 117). In 1932, *Baetjer* reviewed the few studies available at that time, and concluded that "the evidence would seem to indicate that one or two periods of exhaustive muscular exercise following immediately after inoculation of the animal with foreign organisms leads to a more frequent appearance of an infectious disease and induces a greater and more rapid fatality" (5).

However, as recently reviewed by *Cannon* (11) and *Chao* et al. (16), the influence of any exercise intervention appears to be pathogen specific, and dependent on the species, age, and sex of the animals selected for study, and the type of exercise paradigm. For example, *Oppenheimer* and *Spaeth* (90) reported in 1922 that rats forced to run to exhaustion on motorized wheels actually increased their resistance to pre-exercise subcutaneous injections of tetanus toxin and intraperitoneal injections of pneumococcus. *Chao* et al. (16) found that the survival of female BALB/c mice inoculated with the avirulent Me49 strain of *Toxomplasma gondii* and then exercised daily (forced swimming, 45 minutes per session, which is regarded as fatiguing for this animal) for 25 days was unaffected.

On the other hand, there are many reports that the virulence of the coxsackievirus B3 is markedly augmented by intense exercise in mice, including increased replication of the virus in heart muscle cells leading to necrosis and death (9, 36, 46, 105, 122). *Elson* and *Abelmann* (23) have reported that mice swimming one hour a day, five times a week for six weeks suffered greater mortality after inoculation with *Trypanosoma cruzi,* a parasite that causes myocarditis, than did control mice allowed to run spontaneously in activity wheels.

Levinson et al. (58) in 1945, in response to the many anecdotal reports that exhausting exercise had often preceded the onset of poliomyelitis (45), demonstrated in a series of studies with rhesus monkeys that swim exercise to exhaustion (usually 2 to 3 hours) markedly lowered their resistance during the incubation period of experimental poliomyelitis. *Wyatt* (128) has recently suggested that exhausting exercise increases the blood supply to motor neurons serving the muscles, bringing more lymphocytes than normal to the area, amplifying the autoallergic response to the motor neuron antigen of infected cells.

Few investigators have devoted themselves to the question of whether moderate exercise may improve resistance to experimentally induced infections. *Cannon* and *Kluger* (14) randomly assigned 20 mice to cages with activity wheels versus 20 control mice placed in cages without wheels. After 16–18 days, both groups were given intraperitoneal injections of the bacteria *Salmonella typhimurium,* with survival monitored for 7 days. After repeating the same experiment four times, it was established that the survival rate was significantly higher in the exercised (44%) versus sedentary (29%) animals. These researchers have hypothesized that moderate exercise prior to infection of certain pathogens may be beneficial in terms of resistance, while exhaustive exercise, especially following infection, may be detrimental. In concert with this hypothesis, *Anderson* et al. (2) recently reported that an acute bout of intense treadmill exercise by untrained yearling bulls made them more susceptible to experimental pneumonic pasteurellosis *(Pasteurella haemolytica A1)* than bulls who were trained for 24 days on treadmills prior to inoculation.

More research is warranted to establish the effect of varying exercise workloads on respiratory infections in humans. Using the paradigm of *Cohen* et al. (17) in their studies of the relationship between psychological stress and the common cold, human subjects could be housed in hotel rooms and inoculated with specific rhinoviruses intranasally, with symptomatology measured in response to moderate versus exhausting bouts of exercise administered in outdoor sessions. Additionally, elite athletes, moderately-trained and sedentary subjects could be compared cross-sectionally in their response to intranasal injections of rhinoviruses.

Management of the Athlete During Infection

If an athlete experiences sudden and unexplained deterioration in performance during trained or competition, viral infection should be suspected (77, 106, 107). It is well established that various measures of physical performance capability are reduced during an infectious episode (20, 30, 31, 47). Several case histories have been published demonstrating that sudden and unexplained deterioration in athletic perfor-

mance can in some individuals be traced to either recent URTI or subclinical viral infections that run a protracted course (106, 107). *Daniels* et al (20), for example, concluded that during a mild fever state, there is a marked effect upon the ability and/or willingness of some individuals to perform both cardiorespiratory and musculoskeletal exercise. Other researchers have reported decrements in measurements of muscle strength, including *Friman* et al. (31), who have shown that isometric muscle strength in both the upper and lower extremities is reduced to 85–90% of late convalescent values in patients who were hospitalized with various acute infectious diseases. Although studies consistently show decrements in measurements of exercise performance, the mechanism for these decreases is not completely known. *Friman* et al. (30) have suggested that infection-induced degradation of various performance-related muscle enzymes may be one important factor.

Should athletes exercise when they have a viral infection? Most clinical authorities in this area recommend that if the athlete has symptoms of a common cold with no constitutional involvement, then regular training may be safely resumed a few days after the resolution of symptoms (107). Mild exercise during sickness with a common cold does not appear to be contraindicated but there is insufficient evidence at present to say one way or the other. However, if there are symptoms or signs of systemic involvement (fever, extreme tiredness, muscle aches, swollen lymph glands, etc.), then 2–4 weeks should probably be allowed before resumption of intensive training. *Burch* (8) has urged that there is no method available to predict in advance which individual with an URTI will develop viral myocarditis, cardiomyopathy, or valvulitits, and that the best course of action is to avoid strenuous physical stress for at least two weeks post-infection. *Sharp* (111) cautions that attempting to "sweat it out" can be dangerous if the individual is febrile because it can lead to permanent damage of the myocardium.

These recommendations are speculative, however, and are based on the animal studies reviewed in the previous section and some case reports among humans who died following bouts of vigorous exercise during an acute viral illness (106,107,111). *Phillips* et al. (104), for example, reviewed the clinical and autopsy records of the 19 sudden cardiac deaths that occurred among 1.6 million Air Force recruits during basic training. Strenuous physical exertion was associated with sudden death in 17 of 19 cases, and the most frequent underlying etiology was myocarditis. In view of the fact that viral illness is endemic in barrack-residing recruits, the authors conjectured that exertion may have exacerbated subclinical cases of myocarditis, leading to sudden death in even of eight recruits that had myocarditis. *Drory* et al. (21) in their study of 20 male soldiers in the Israel Defense Forces (1974–1986) who had died suddenly and unexpectedly within 24 hours of strenuous exertion also concluded that febrile disease may have been a cause of death in some of the subjects.

For elite athletes who may be undergoing heavy exercise stress in preparation for competition, several precautions may help them reduce their risk of URTI. Considerable evidence indicates that two other environmental factors, improper nutrition (15) and psychological stress (17,53), 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 overtraining and chronic fatigue, obtain adequate sleep, and space vigorous workouts and race events as far apart as possible (77,85). Immune system function appears to be suppressed during periods of low caloric intake and weight reduction (15,55), so when necessary, the athlete is advised to lose weight slowly during noncompetitive training phases. Regular sleep habits appear to be important in that total sleep time, sleep efficiency, and duration of nonREM sleep have each been correlated with natural killer cell activity (48). Cold viruses are spread by both personal contact and breathing the air near sick people (4,50). 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.

Acute and Chronic Effects of Exercise on the Immune System

It naturally follows that if heavy and fatiguing exertion leads to an increased risk of URTI, various measures of immune function should be negatively affected. And conversely, if moderate exercise decreases URTI risk, there should be some aspect of immune function that is chronically or at least transiently improved.

Despite intense investigation during the last ten years on this issue, however, there is no clear consensus. The wide variety of research designs, exercise protocols, subject characteristics, and methodologies combined with the innate complexity of the immune system have made interpretation of published findings extremely formidable and equivocal.

The Acute Immune Response to Exercise

A growing number of published reports on exercise immunology provide evidence that the immune system is profoundly effected by acute exercise. The clinical significance of these large but transient alterations are disputed, however.

High-intensity, endurance exercise is associated with a unique biphasic perturbation of the circulating leukocyte count (28,34,35,41,62,82). Immediately post-exercise, total leukocytes increase 50%–100%, represented evenly by lymphocytes and neutrophils with a small contribution from monocytes. Following prolonged endurance exercise such as marathon race events, the increase can be even larger (200–300%) (42,78,84,112). All of the lymphoid tissues appear to contribute cells, with the spleen considered to be of primary importance (100,125). Within 30 minutes of recovery from exercise, however, the lymphocyte count dips 30%–50% below pre-exercise levels, remaining low for 3 to 6 hours. There is no clear consensus regarding the tissue site the blood lymphocytes are transferred to, with some investigators providing evidence that peripheral lymphoid tissues (e.g., the thymus and spleen) are also depleted (27). Eosinophils also vacate the blood in large numbers, while basophils are largely unaffected. Meanwhile, a marked and prolonged neutrophilia can be measured (Figure **5**). Moderate-intensity exercise has been demonstrated to induce a much smaller leukocytosis, lymphocytosis, neutrophilia, and lymphocytopenia (52,76,82,87). The extent and duration of the alterations in leukocyte subset counts are very much dependent on the exercise-induced changes in epinephrine and cortisol which begin to increase strongly when the exercise intensity rises above 60% VO_{2max} (19,32,67,82).

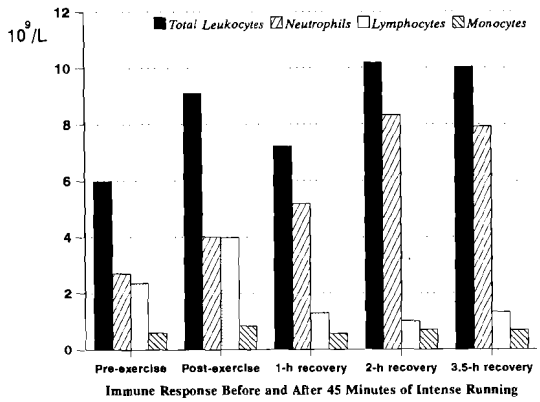

Fig. 5 Changes in circulating concentrations of neutrophils, lymphocytes, and monocytes in response to high-intensity exercise (45 minutes of running at 80 % VO_{2max}). Data from *Nieman* et al. (82).

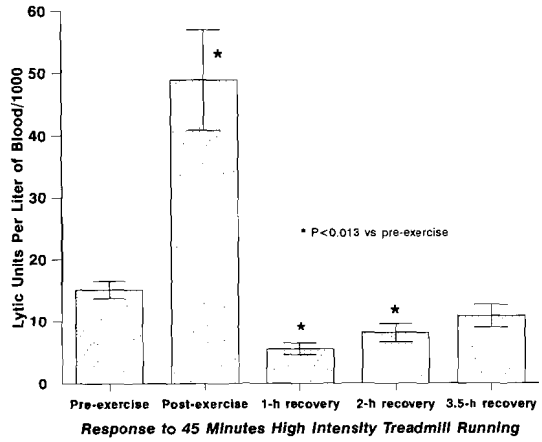

Fig. 6 Effect of high-intensity exercise (45 minutes of running at 80 % VO_{2max}) on the natural killer cell cytotoxic activity of the blood compartment. Data from *Nieman* et al. (83).

Of the three major lymphocyte subpopulations (T, B, and natural killer cells), natural killer (NK) cells are by far most responsive to exercise (34,83). It is typical for NK cells to increase 150 %–300 % within minutes of initiating high-intensity exercise, contributing substantially to the overall lymphocytosis (6,7,34,52,83,98,99). Circulating numbers of T cytotoxic/suppressor cells also increase markedly (50 %–100 %) after high-intensity exercise, while T helper/inducer and B cells are relatively unaffected (34,35,82). However, the effect is transient, and within 30 minutes, lymphocytes from each of the subpopulation groups exit the circulation in large numbers under the influence of cortisol (19).

A common finding immediately following high- but not moderate-intensity exercise is that mitogen-stimulated proliferation of separated mononuclear cells is decreased 35 %–50 %, returning to pre-exercise levels within two hours (28,32,33,37,82,113). The decrease in mitogen response is most likely due to the large exercise-induced increase in NK cells that occurs immediately following sessions of vigorous exercise. Since a constant number of peripheral blood mononuclear cells are utilized in the pre- and post-exercise *in vitro* assays, the large increase in NK cells relative to T cells means that a smaller percentage of cells that respond to mitogens are available (NK cells do not divide in response to mitogens) (82). Thus the drop in T cell function after exercise has been challenged as not being clinically important (32,33,113). However, even though the function of each T cell may be unaltered by intense exercise, the blood and peripheral lymphoid compartments may have less T cells than normal for several hours of recovery from exercise, which may have the same impact on host protection as having fewer soldiers on the front lines of a battlefield. Research to settle this issue is certainly warranted, and may improve our understanding of the acute immune response and its link with epidemiological findings.

Investigators have also consistently reported that immediately following high-intensity exercise, NK cell cytotoxic activity (NKCA) is increased by 40 %–100 % before falling 25 %–35 % below pre-exercise levels by 1-hour and 2-hours of recovery (6,7,83,98,99,113). Although most researchers agree that the immediate post-exercise increase in NKCA is due to the recruitment of NK cells into the circulation (83), they tend to disagree on the reasons for the transient NKCA decrease during recovery. Although some reason that the drop in NKCA can be ascribed to numerical shifts in NK cells (63,113), others report that prostaglandins from activated monocytes and neutrophils (96,98,99) or elevated stress hormone levels (6) suppress the ability of NK cells to function appropriately. This issue has not yet been resolved, and will require further investigation. Nonetheless, most researchers would agree that the NKCA of the blood compartment is significantly reduced for several hours after heavy exertion primarily because of the transfer of NK cells to other tissues (83) (Figure 6). Whether this is a reflection of NKCA in other lymphoid compartments remains to be determined, but there is some animal data to support this supposition (83).

Various researchers have investigated the ability of B lymphocytes to produce antibodies following exercise. Following one hour of high-intensity cycle ergometry by untrained individuals, suppression of B lymphocyte function was reported for at least 2 hours because of an inhibitory effect of activated monocytes (124). Other researchers, however, have reported no change in B lymphocyte function after exercise. For example, following two hours of high-intensity cycle ergometry by elite athletes, the *in vitro* production of immunoglobulins by pokeweed-stimulated peripheral blood lymphocytes was not altered (64). Four well-trained runners immunized 30 minutes after a marathon race showed no impairment in ability to produce antibody (*in vivo*, after 14 days) to tetanus toxoid vaccination (24). This occurred despite a significant decrease in T lymphoyte transformation (in response to *in vitro* mitogen stimulation with Con-A) which persisted for several hours following the marathon event. Although activated T cells are important in helping B cells develop into immunoglobulin-secreting plasma cells, the transient nature of the decrease in T lymphocyte transformation following prolonged endurance exercise may mean that the longer term *in vivo* antibody response is unaltered (86).

Secretory IgA is the principal immunoglobulin in the local secretions coating the mucosal surfaces of the nasopharynx, oropharynx, conducting airways, eyes, gut, and bladder (65). Secretory IgA is an important glue-like substance of the mucosal barrier that has been demonstrated to show antibody activity against certain viruses, bacteria, and common al-

lergens, especially in the nasal and oral cavities. Salivary IgA levels in elite athletes have been reported to decrease more than 50% after prolonged, intensive cross country skiing (123) and bicycling (64). Although several studies have shown that salivary IgA concentrations drop after graded maximal exercise or repeated supramaximal exercise (65,70), others claim there is little effect (109,120). The clinical implications of these inconsistent findings are unresolved, and will require following large numbers of heavily exercised subjects for 7–10 days of recovery to establish whether those with low secretory IgA are at increased risk of URTI.

Neutrophils, one of body's best phagocytes, are considered to be a part of the innate functional division of the immune system (as are NK cells), acting as a first line of defense against infectious agents. There is growing evidence that both moderate and intense endurance exercise are associated with a prolonged improvement in the killing capacity of blood neutrophils and peritoneal macrophages (26,39,54, 92,93,108,114). In contrast, immediately following a 20 km race, neutrophils in a nasal lavage taken from 12 male runners were less able to ingest bacteria, an effect which lasted for 3 days (73). Prolonged impairment of lung neutrophil antimicrobial function has also been reported in race horses following a single strenuous event (127). Although blood neutrophils are easier to study, data from these two studies suggest that neutrophils from the respiratory area may respond differently to intense exercise than those from the blood compartment.

Following high-intensity exercise, the immune system becomes involved in the tissue repair process. It has been well established that high-intensity, long-endurance exercise, and eccentric exercise (such as downhill running) are associated with muscle cell damage, local inflammation, and the stereotyped sequence of host defense reactions known as the acute phase response (12,25,115,116,126). Included in this response is a strong activation of both neutrophils and macrophages (10). *Michna* (71,72) has proposed that injured muscle cells release filament fragments whose peptides are capable of being depicted as chemotactic signals for granulocytes and macrophages which aid in the regeneration process. Whether macrophage and neutrophil activation following exercise serves a purpose other than muscle repair (e.g., host protection against viruses and cancer cells) is not yet known at this time. There is some speculation that host protection may be impaired during the time the immune system is involved in tissue repair following heavy exertion, but this has yet to be measured objectively (77,85).

In a recent study by *Sprenger* et al. (118), interferon-γ, tumor necrosis factor-α (TNF), interleukin-1β, and interleukin-6 were elevated in the urine of trained subjects both before (compared to sedentary controls) and after they ran 20 km at a moderate pace (compared to pre-exercise concentrations). Increases in these cytokines occurred despite negligible post-exercise creatine kinase levels, indicating little muscle damage. In that these cytokines are all involved in positively up-regulating the immune response, the authors concluded that moderate physical exercise has a stimulating effect on the immune system, a conclusion which remains to be verified by other investigators. *Kvernmo* et al. (57), for example, found that TNF production in cross-country ski athletes was less than half that of either sedentary or moderately trained subjects, with moderate training conferring no enhancement. The literature on the cytokine response to exercise is difficult to interpret at present (12,22,59,118), with much of the confusion due to the difficulty of measuring detectable levels in the blood compartment. As recounted by *Sprenger* et al. (118), urine samples appear to provide a better indication of the cytokine response to exercise, and further research using this methodology is recommended.

In general, there is no convincing data at this time that exercise-induced changes in the lymphocyte proliferative response to mitogens *in vitro,* natural killer cell cytotoxic activity, B cell function, or neutrophil/macrophage function explain the increased risk of URTI suggested by epidemiological data. Researchers disagree on the mechanistic interpretation of their findings, and none have provided follow-up data of large numbers of subjects to determine if various changes in immunity translate to altered host protection. Further research is needed to settle these issues, and to determine if the large but transient perturbations in leucocyte cell concentrations in both blood and peripheral lymphoid tissue (which often underlie reported *in vitro* functional alterations) are important from a clinical viewpoint.

Immune Response to Chronic Exercise

Several studies have made cross-sectional comparisons of the immune systems of athletes and non-athletes (38,56,59,67,79,89,91,97), or followed sedentary individuals as they initiate exercise programs, comparing pre- and post-exercise training immune measures relative to control groups (75,79,88). Most of these studies have failed to demonstrate any important effects of regular exercise training on circulating concentrations of total leukocytes or their various subpopulations. Most researchers have also reported that trained athletes have resting serum immunoglobulin levels within the normal reference range and similar to those of sedentary controls (86).

Several studies on animals and humans, however, have shown significant improvements in NKCA with exercise training (18,56,66,79,88,97). In a randomized controlled study of 36 sedentary women, subjects in the exercise group walked 45 minutes/session, 5 times/wk, for 15 continuous weeks, and after six weeks experienced a 57% increase in NKCA relative to the control group (88). In a randomized controlled study of mice, 9 weeks of moderate training were associated with significantly higher NKCA (66). NKCA was found to be 47% higher in physically active versus inactive Japanese men (56). Trained elderly women have been reported to have significantly higher NKCA than their sedentary peers (18,79) (Figure 7). Investigators from Denmark have measured higher NKCA in elite cyclers relative to untrained subjects (97). The mechanism underlying the higher NKCA in trained individuals has not yet been established. In one study with elderly female subjects, multiple regression analysis revealed that leanness (low body fat) was the most important predictor of high NKCA in old age (79).

Of the various components of the immune system, T cells are most sensitive to the effects of ageing. A common finding among researchers is that the elderly when compared to young subjects exhibit a 45%–65% decrease in the ability of T lymphocytes to proliferate in response to mitogens (69,79). In a recent study comparing T cell function in highly conditioned and sedentary elderly women (mean age, 73 years),

Fig. 7 Natural killer cell cytotoxic activity and PHA-induced lymphocyte proliferative response in highly conditioned versus sedentary elderly females. Data from *Nieman* et al. (79).

a 56% higher level was measured for the highly conditioned subjects (79) (Figure 7). Animal data are supportive of this interesting finding. In one study, 15 weeks of treadmill running at 75% VO_{max}, 5 days per week for 60 minutes by old rats caused a dramatic increase in splenic T cell function such that levels equivalent to untrained young rats were attained (74).

Mitogen-stimulated lymphocyte proliferation does not appear to be altered substantially with exercise training in young adult subjects (67). The literature is mixed on the effect of exercise training on neutrophil killing capacity, with investigators reporting lower (114), higher (91), or similar (39, 59) function when comparing elite athletes and untrained controls. Serum complement and salivary but not serum immunoglobulin have been reported to be lower in athletes versus nonathletes (86,89).

Although studies on humans have produced conflicting data on the chronic effect of exercise on immunity, results from animal studies have rather consistently supported the viewpoint that heavy chronic exertion is related to negative changes in immune function (60,68).

Conclusions

Although further research is needed, present epidemiological findings suggest that heavy exertion is associated with an increased URTI risk, while moderate activity lowers this risk. Although animal studies using a wide variety of experimentally induced pathogens tend to support this supposition, results are so dependent on the research design, exercise mode, type of pathogen, and other factors that it is difficult to arrive at a clear consensus.

Other than the potential effect of chronic training on NKCA, there is little agreement in the literature as to consistent changes in immune function. Although the immune system is affected profoundly by acute exercise bouts, interpretation of the findings is heavily based on the intensity and duration of the exercise bout, and the type of immune measurements and assays used. Most investigators have demonstrated that exercise stimulates phagocytic function of blood neutrophils and peripheral macrophages, but it is uncertain whether this is related more to an involvement of the immune system in the acute phase response rather than enhanced host protection from pathogens. Lymphocyte function is often reported to be transiently decreased following high-intensity exercise, but researchers disagree on whether the changes reflect alterations in circulating numbers of lymphocytes or real immune suppression. Further research is warranted to establish the clinical importance of exercise-induced changes in immune function, and whether a physiological rationale can be provided in support of preliminary epidemiologic findings.

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