The relationship between heavy exertion, immunity, and infection was approached early in this century by Larrabee (25), who reported a large increase in blood neutrophils among four athletes who ran the 1901 Boston Marathon. Larrabee noted that changes in the white blood cell differential counts paralleled those seen in certain diseased conditions. He also observed that “the exertion had gone far beyond physiological limits, and our results certainly show that where this is the case we may get a considerable leucocytosis of the inflammatory type.” About 30 years later, Baetjer (2), in a review of exercise and infection, indicated that, although the prevailing view was that “muscular fatigue lowers resistance and is a predisposing factor to infectious diseases, especially with regard to respiratory infections”, little experimental work had been done to test this relationship scientifically.

The immune response to heavy exertion has received renewed attention after the publication of several epidemiological studies indicating an increased risk of upper respiratory tract infection (URTI) during the 1- to 2-wk period after marathon and ultramarathon race events (44, 52, 65–67). Also, depending on the pathogen (with some more affected by exercise than others), animal studies have generally supported the finding that one or two periods of exhaustive exercise after inoculation lead to a more frequent appearance of infection and a higher fatality rate (11, 44). It is well established that various measures of physical performance capability are reduced during an infectious episode (73). Several case histories have been published, demonstrating that sudden and unexplained deterioration in athletic performance can be traced to either recent URTI or subclinical viral infections that run a protracted course (44, 73). In some athletes, a viral infection may lead to a debilitating state known as “postviral fatigue syndrome” (35). The symptoms include lethargy, easy fatigability, and myalgia and can persist for several months.

It naturally follows that if athletic host protection is diminished during periods of heavy exertion, some aspect of altered immunity is probably at least in part responsible. In this review, the focus is on the acute immune response to prolonged (>90 min) and intensive (>70% maximal oxygen uptake (V\textsubscript{O\textsubscript{2}\text{max}})) endurance exercise. Other reviews are available, summarizing the immune response to shorter duration exercise and cross-sectional comparisons of immune function in endurance athletes and nonathletes (43, 56, 61). It should be noted that research data on the resting immunity of athletes and nonathletes are limited and present a confusing picture at present (43, 44). For example, the few studies available suggest that the innate immune system responds differentially to the
chronic stress of intensive exercise, with natural killer cell activity (NKCA) tending to be enhanced while neutrophil function is suppressed (21, 47, 51, 62, 69, 80). The adaptive immune system (resting state) in general seems to be largely unaffected by athletic endeavor (3, 47, 84). Further research is needed with larger groups of athletes and nonathletes to allow a more definitive comparison of their immune systems.

In light of the mixed results regarding the effect of chronic intensive training on resting immune function, several authors have postulated that prolonged cardiorespiratory endurance exercise leads to transient but significant changes in immunity and host defense, providing a physiological rationale for the epidemiological data (43, 61, 64). For example, as reviewed in this article, NKCA, various measures of T and B cell function, upper airway neutrophil function, and salivary immunoglobulin A (IgA) concentration, have all been reported to be suppressed for at least several hours during recovery from prolonged, intense endurance exercise. During this "open window" of decreased host protection, it is hypothesized that viruses and bacteria may gain a foothold, increasing the risk of subclinical and clinical infection (24).

Although this is an attractive hypothesis, no one has yet demonstrated conclusively that athletes showing the most extreme immunosuppression are those who contract an infection (26, 31, 69). Exercise immunology is considered a new and burgeoning field of research endeavor, with over 60% of articles in this area published since 1990 (43). Further research should help determine whether the acute immune changes to heavy exertion described in this article have clinical importance. Nonetheless, exercise immunologists in general seem to be largely unaffected by athletic training (25–3 h at an average intensity of 76.4 \( \pm 0.9 \) yr of age, 20.9 \( \pm 2.9 \) marathons run) into my human performance laboratory and had them run for 2.5–3 h at an average intensity of 76.4 \( \pm 0.6 \% \) \( V_O^{2max} \) with multiple blood samples collected before and for up to a day after. Ten nonathletic subjects have rested in the human performance laboratory during testing of the athletes to provide control for diurnal changes, with blood samples collected at the same time as from the athletes. The blood samples have been tested for a wide array of immune measures to determine how the immune system responds to heavy exertion, with the data presented in a series of articles dating back to 1989 (Refs. 6, 41, 45, 46, and unpublished observations by D. C. Nieman, D. A. Henson, E. B. Garner, D. E. Butterworth, B. J. Warren, A. Utter, J. M. Davis, O. R. Fagoaga, and S. L. Nehlsen-Cannarella). The results from these various studies have been amalgamated and are presented in the graphs of this review and contrasted with the findings of others.

Leukocyte subsets. Exercise is associated with an extensive perturbation of white blood cell counts, an observation first reported by German researchers in the 1890s [see the 1935 review by Garrey and Bryan (18)]. The change in leukocyte subsets with exercise is dependent on both intensity and duration, with prolonged, high-intensity endurance exercise leading to the greatest degree of cell trafficking (56). As depicted in Fig. 1A, 2.5–3 h of intensive running are associated with a sustained increase in the white blood cell count, peaking ~3 h postrun and returning to normal by the next day. The blood granulocyte count rises strongly (250%) along with monocytes (60%) while lymphocytes egress from the blood compartment (40%). Figure 1B shows that the decrease in blood lymphocytes lasts for at least 6 h, represented by T and natural killer (NK), but not B, cells. Even greater alterations than these have been observed in marathon runners after competitive race events (18, 20, 22, 25, 88). It is interesting that two cells of the innate immune system, neutrophils and NK cells, are most responsive in terms of blood cell count changes to intensive exercise bouts.

Several mechanisms appear to be involved, including exercise-induced changes in stress hormone and cytokine concentrations, body temperature changes, increases in blood flow, and dehydration (24, 44, 64, 68, 74). After prolonged running at high intensity, serum cortisol concentrations are significantly elevated above control levels for several hours, as depicted in Fig. 2A (6, 45, 46, 48). Cortisol has been related to many of the immunosuppressive and cell trafficking changes experienced during recovery (12, 83). Glucocorticoids administered in vivo have been reported to cause neutrophilia, eosinopenia, lymphopenia, and a suppression of both NK and T cell function, all of which occur during recovery from prolonged high-intensity cardiorespiratory exercise (12, 43).

Immediately postendurance run, plasma epinephrine is elevated (Fig. 2B). Although epinephrine is an important hormone in recruiting lymphocytes to the blood compartment after intensive exercise of <90-min duration, its effect is lessened as duration increases and cortisol rises (53, 54, 56, 64, 86). Notice from Fig. 1B that the total lymphocyte count remains essentially unchanged immediately after 2.5–3 h of running. This contrasts with the sharp increase in lymphocyte count that is measured after exercise of <90-min duration (56, 64). It appears that the hormonal milieu after prolonged endurance exercise (Fig. 2, A and B) favors...
cortisol- rather than epinephrine-related effects (44, 57).

Neutrophil and monocyte function. Neutrophils (55–65% of blood leukocytes) and monocytes (3–9%) play an important role in nonspecific or innate immunity. These phagocytes act as first-line-of-defense cells to eliminate infectious agents and are involved in the muscle tissue inflammatory response to exercise-induced injury (16, 68, 91). Neutrophil and monocyte function can be expressed as a measure of the ability to engulf pathogens (phagocytosis), and the facility to kill the pathogens once engulfed (the oxidative burst).

Relatively few studies have been conducted to define the response of these phagocytic cells, especially monocytes, to prolonged intensive exercise (48, 59, 68). Although more research is needed, investigators have observed that while both moderate- and high-intensity exercise are associated with a sustained increase in blood granulocyte and monocyte phagocytosis and degranulation, only moderate exercise (typically ≤60% \( V_{\text{O2max}} \)) tends to enhance oxidative burst activity, whereas high-intensity exercise often has the opposite effect (17, 48, 59, 78, 80, 89).

Notice from Fig. 3, A and B, that both granulocyte and monocyte phagocytosis (of Staphylococcus aureus bacteria) are increased strongly (45 and 75%, respectively) for >6 h in marathoners after 2.5–3 h of intensive running (48). Granulocyte oxidative burst activity, however, shows a small (14%) but significant decrease by 6 h postexercise, with monocyte oxidative burst activity falling 9% (but not significantly).

After prolonged high-intensity running, substances released from injured muscle cells initiate an inflammatory response (16, 58, 88). Monocytes and neutrophils invade the inflamed area and phagocytose debris. The
increase in granulocyte and monocyte phagocytosis may, therefore, represent a part of the inflammatory response to acute muscle injury. The slight decrease in granulocyte oxidative burst may represent a tendency for reduced killing capacity by blood neutrophils (on a per cell basis) due to stress and overloading (68).

Phagocyte specimens collected from the peripheral blood, however, may react differently than those taken from the respiratory tract. Cells of the innate immune system, unlike T and B lymphocytes, respond to their immediate local environment. Using nasal lavage samples, Müns (37) showed that the capacity of phagocytes to ingest Escherichia coli was significantly suppressed in athletes for >3 days after running a 20-km road race, compared with controls. After a marathon race, nasal mucociliary clearance is significantly slower for nearly a week, compared with that of control subjects (39). These data suggest that host protection in the upper airway passages is suppressed for a prolonged time after endurance running races and may, in part, provide a link between the risk of respiratory infection and athletic endeavor.

The factors that regulate these disparate responses have still not been defined clearly. Neutrophils appear to infiltrate all metabolically active tissues after heavy exercise, including the heart, liver, and skeletal muscle (5). Although cytokines are thought to mediate the immune response, various hormones, including cortisol, growth hormone, prolactin, and thyroxine have been shown to have some regulatory effect on the function of phagocytes (17, 60).

NKCA. NK cells are large granular lymphocytes that can mediate cytolytic reactions against a variety of neoplastic and virally infected cells (27). NK cells also exhibit key noncytolytic functions and can inhibit microbial colonization and growth of certain viruses, bacteria, fungi, and parasites. NKCA is measured with a 4-h $^{51}$Cr release assay where certain types of cancer or virally infected cells are mixed with blood lymphocytes and monocytes. NK cells, which represent ~10–15% of blood lymphocytes, respond quickly and within 4 h can lyse a significant proportion of the $^{51}$Cr-labeled target cells.

The acute response of NKCA to 2.5–3 h of running by 62 marathon runners is depicted in Fig. 4 (Refs. 6, 45, and unpublished observations by D. C. Nieman, D. A. Henson, E. B. Garner, D. E. Butterworth, B. J. Warren, A. Utter, J. M. Davis, O. R. Fagoaga, and S. L. Nehlsen-Cannarella). Notice that, relative to the nonathletic controls, NKCA was significantly higher among the marathoners before the test run. Others have also reported elevated NKCA among endurance athletes compared with sedentary controls (47, 62, 84). After
intensive running, these data show that NKCA is decreased 40–60% for at least 6 h, similar to what has been reported during recovery from prolonged cycling (29) or a triathlon competition (76). This decrease is greater and longer lasting than what has been reported for exercise of >1-h duration (54, 63, 64, 74). Shek et al. (74) have published data suggesting the decrease in NKCA may last for up to a week after heavy exertion, but the lack of resting controls or corroborating evidence from other researchers indicates this may be a spurious finding.

The decrease in NKCA appears to be related to the cortisol-induced redistribution of blood NK lymphocytes from the blood compartment to other tissues (50). In fact, the decrease in NKCA closely parallels the drop in blood NK cell concentration, implying that each NK cell retains normal function (Refs. 45, 74 and unpublished observations by D. C. Nieman, D. A. Henson, E. B. Garner, D. E. Butterworth, B. J. Warren, A. Utter, J. M. Davis, O. R. Fagoaga, and S. L. Nehlsen-Cannarella). It has not yet been determined where the blood NK cells go to and whether the decreased NKCA in the blood compartment represents what is occurring in other lymphoid tissues. There is some evidence that prostaglandins from activated monocytes and neutrophils may also play a role in decreasing NKCA, but thus far this has only been demonstrated after 1 h of cycling (45, 63, 64). No one has yet attempted to link the decrease in NKCA with URTI risk.

T and B cell function. Determination of the proliferative response of human lymphocytes on stimulation with various mitogens in vitro is a well-established test to evaluate the functional capacity of T and B lymphocytes. Mitogen stimulation of lymphocytes in vitro using optimal and suboptimal doses is believed to mimic events that occur after antigen stimulation of lymphocytes in vivo. When lymphocytes are exposed to a foreign pathogen, their ability to divide and secrete various cytokines is an important component of the adaptive immune system. In the laboratory, researchers expose lymphocytes to various types of mitogens for 3 days and then add [methyl-3H]thymidine during the last 4 h before harvesting. The [methyl-3H]thymidine is incorporated into the DNA of the dividing lymphocytes and then counted by using a liquid-scintillation beta counter.

Figure 5 shows that, compared with resting nonathletic controls, whole blood concanavalin A-induced lymphocyte proliferation (T cell function) falls 30–40% (unadjusted for changes in T cell number) for >3 h after 2.5 h of intensive running (57). Others have reported an even greater decrease after endurance race events (15, 20, 76). The decrease in T cell function is more prolonged than has been described after exercise of <1 h duration (53).

Except for the immediate postrun time point, the decrease in T cell function parallels the drop in blood T cell concentration (Fig. 1B). There is some evidence that plasma cortisol and epinephrine inhibit mitogen-induced lymphocyte proliferation (12, 57, 86). Researchers, however, have not yet been able to differentiate between the direct and indirect effects of these hormones during the exercise recovery time period. Van Tits et al. (86) have suggested that epinephrine has a dual role in impairing T cell responsiveness to mitogens by altering relative and absolute numbers of T cell subsets and by making circulating T cells more responsive to the inhibitory effects of β-adrenergic stimulation.

Bruunsgaard et al. (7) examined the effect of competing in a half-ironman triathlon (mean time 6.5 h) on in vivo cell-mediated immunity through use of a skin test with seven antigens. The delayed-type hypersensitivity (DTH) reaction was suppressed 60% 2 days after the competition in the triathletes, compared with controls, indicating an impairment in this complex immunological process, which involves several different cell types (including T cells) and chemical mediators. This is the first study showing that heavy exertion decreases in vivo cell-mediated immunity.

The major histocompatibility complex (MHC) antigens are essential for reactions of immune recognition (90). Class I MHC antigens play a role in self- and nonself recognition, whereas class II MHC antigens, found on antigen-presenting cells such as macrophages, assist in the process of cell-mediated immune responses. After phagocytosis and antigen processing, small antigenic peptides are bound to MHC II and presented to T lymphocytes, an important step in adaptive immunity. Woods et al. (90) have demonstrated that exhaustive exercise (2–4 h/day for 7 days) significantly suppresses the expression of MHC II in mice macrophages, an effect due in part to elevated cortisol levels. These data imply that heavy exertion can blunt macrophage expression of MHC II, negatively affecting the process of antigen presentation to T lymphocytes and thus their ability to respond to an antigenic challenge (e.g., DTH).

A major function of the immune system is production of soluble components, especially immunoglobulins, a
group of glycoprotein molecules that carry antibody activity, i.e., the property of combining specifically with foreign antigens (55). Antibodies are produced by plasma cells, end-stage B lymphocytes, in response to foreign substances introduced into the body.

A few researchers have measured the ability of the humoral immune system to produce antibodies in response to antigen challenge after heavy exertion. In general, no impairment in antibody production after vaccination has been reported after prolonged and intensive endurance exercise (7, 15, 19, 30). Eskola et al. (15) reported that four elite Finnish runners vaccinated 30 min after a marathon race showed no deficiency in ability to produce antibodies to pneumococcal antigens over a 2-wk period. Brunsgaard et al. (7) found no significant difference between triathletes (after 6.5 h of competition) and controls in ability to produce specific antibodies to pneumococcal antigens and diphtheria and tetanus toxoid. These data suggest that the transient decrease in immune antibody response to pneumococcal antigens is not a general effect (19 untrained controls were capable of mounting an antibody response to pneumococcal antigens over a 2-wk period).

Gleeson et al. (19) showed that 20 elite swimmers compared with 19 untrained controls were capable of mounting an antibody response to pneumococcal antigens after exercise (8,88) and others no change (81, 85). IL-1β has been observed in both muscle and urine after exercise (9,81), so it is believed that this cytokine is increased in response to exercise despite being difficult to detect in postexercise plasma (1). Moderate exercise for 1 h or less appears to have little effect on plasma IL-6, IL-1β, or TNF-α concentrations (79).

Despite the difficulties inherent in measuring plasma cytokine concentrations (1, 58), recent studies of subjects exercising intensively for 60 min or more have reported increases in plasma concentrations of IL-6 (58, 81, 85) but a variable IL-1β response, with some reporting an increase (8, 88) and others no change (81, 85). IL-1β has been observed in both muscle and urine after exercise (9,81), so it is believed that this cytokine is increased in response to exercise despite being difficult to detect in postexercise plasma (1). Moderate exercise for 1 h or less appears to have little effect on plasma IL-6, IL-1β, or TNF-α concentrations (79).

Although strenuous and prolonged exercise is felt to affect both proinflammatory and antiinflammatory components, few studies have provided cytokine data from both sides of this control system. Drent et al. (14) collected plasma samples on 19 athletes before and after running for 6 h and reported a 286% increase in IL-6 and a 371% increase in IL-1ra but no change in plasma concentrations of IL-1β or TNF-α. Figure 6 shows the IL-6 and IL-1α response to 2.5 h of intensive running by 30 marathoners (41). IL-6 increased 5.5-fold immediately postrun, falling rapidly to prerun levels by 6 h postrun. IL-1α rose 127% by 1.5 h postrun. No significant change was measured for plasma IL-1β (data not shown). Postrun cortisol (r = 0.70, P < 0.001) and IL-6 levels (r = 0.54, P = 0.003) correlated positively with levels of IL-1α. Overall, the data indicate that both pro- and anti-inflammatory processes are initiated in response to heavy exertion.

Secretory immunity. As reviewed by Mackinnon and Hooper (32), the secretory immune system of the mucosal tissues of the upper respiratory tract is considered the first barrier to colonization by pathogens, with IgA the major effector of host defense. Secretory IgA inhibits attachment and replication of pathogens, preventing their entry into the body.

Data from Müns et al. (38) have shown that IgA concentration in nasal secretions is decreased by nearly 70% for at least 18 h after racing 31 km. Tomasi et al. (82) reported that resting salivary IgA levels in elite
Reserves are depleted and a competition develops for the metabolic needs of the exercising muscles (e.g., when muscle glycogen is depleted, a competition develops for the metabolic needs of the exercising muscles). This competition is facilitated by the demands of the immune cells and the metabolic needs of the exercising muscles. The interplay between these demands is crucial in maintaining homeostasis during exercise.

These are important findings, and Mackinnon et al. (31), in one small study of elite squash and hockey athletes, have demonstrated that low salivary IgA concentrations precede URTI. Lindberg and Berglund (28), however, were unable to show that 14 world-class Swedish canoeists receiving nasal IgA treatment (1 mg/day for 17 days) experienced fewer URTI episodes relative to controls.

Interventions to Alter the Immune Response to Heavy Exertion

Chemical and nutritional interventions have been recommended for athletes to negate potential negative changes in immunity during periods of heavy training (43). There is some preliminary data that various immunomodulator drugs may afford athletes some protection against infection during competitive cycles, but much more research is needed before any of these can be recommended (44, 55).

Indomethacin, which inhibits prostaglandin production, has been administered to athletes before exercise or used in vitro to determine whether the drop in NKCA can be countered (64). Although some success has been reported after 1 h of intensive cycling (63), indomethacin has been found to have no significant effect in countering the steep drop in NKCA after 2.5 h of running (45).

Shephard and Shek (75) have proposed that nutritional status may modulate the interaction between exercise and immune function in several ways. Theories include 1) a more direct competition between the metabolic needs of the immune cells and the demands of the exercising muscles (e.g., when muscle glycogen reserves are depleted and a competition develops for key amino acids); and 2) an alleviation of the potential adverse effects on the immune system of reactive species generated by metabolism or tissue injury (e.g., antioxidant supplementation).

A few studies have been conducted investigating the role of nutritional supplementation in the immune and infection response to intense and prolonged exercise, including zinc (77), glutamine (10, 33, 42, 70, 71), and vitamin C (49, 66, 67).

Glutamine, a nonessential amino acid, has attracted the most attention. Glutamine is an important fuel along with glucose for lymphocytes and monocytes, and decreased amounts have a direct effect in lowering proliferation rates of lymphocytes (42, 70). Reduced plasma glutamine levels have been observed in response to various stressors, including prolonged exercise (10, 42, 71). Whether reduced plasma glutamine levels relate to impaired immunity and URTI risk in athletes is still unanswered. Mackinnon and Hooper (33) were unable to show that URTI incidence was related to changes in plasma glutamine concentration during intensified training in elite swimmers. Castell et al. (10) have reported a reduction in incidence of URTI in athletes using fluids containing glutamine.

In a study by Peters et al. (66), 68% of runners reported the development of symptoms of URTI within 2 wk after the 90-km Comrades Ultramarathon. The incidence of URTI was greatest among the runners who trained the hardest coming into the race (85 vs. 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 3 wk before 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 (66, 67). This is an interesting finding, and further research will help to determine whether this finding also applies to runners racing shorter distances (for example, a typical marathon of 42.2 km). It should be noted that one double-blind placebo-controlled study was unable to establish that vitamin C supplementation (1,000 mg/day for 8 days) had any significant effect in altering the immune response to 2.5 h of intensive running (49).

A double-blind placebo randomized study was designed to investigate the effect of carbohydrate fluid (6% carbohydrate beverage, Gatorade) ingestion on the immune response to 2.5 h of running (Refs. 41, 48, and unpublished observations by D. C. Nieman, D. A. Henson, E. B. Garner, D. E. Butterworth, B. J. Warren, A. Utter, J. M. Davis, O. R. Fagoaga, and S. L. Nehlsen-Cannarella). In prior research, carbohydrate vs. water ingestion during prolonged endurance exercise had been associated with an attenuated cortisol and epinephrine response through its effect on the blood glucose concentration (36, 40). Drinking the carbohydrate beverage before, during (1 l/h), and after 2.5 h of running attenuated the rise in both cortisol and the neutrophil-to-lymphocyte ratio (48). The immediate postrun blood glucose level was significantly higher in...
the carbohydrate vs. placebo group and was negatively correlated with cortisol (r = −0.67, P < 0.001). Trafficking of most leukocyte and lymphocyte subsets was lessened in accordance with the lower cortisol levels in the carbohydrate subjects (48). Carbohydrate intake also blunted the rise in IL-6 and IL-1ra (41). These data suggest that carbohydrate ingestion before, during, and after prolonged endurance exercise may help to lessen the stress on the immune system and attenuate cytokine levels in the inflammatory cascade.

Summary

Hoffman-Goetz and Pedersen (24) have proposed that the immunological responses to acute exercise can be viewed as a subset of stress immunology. Other physical and mental stressors such as space travel, thermal and traumatic injury, surgery, acute myocardial infarction, prolonged depression or anxiety, and hemorrhagic shock have all been associated with immunosuppression. Thus it makes sense that physical exercise when performed at stressful levels may be related to the same outcome.

In this review, emphasis was placed on the acute immune response to prolonged and intensive endurance exercise. Although some findings are not as well studied as others, heavy exertion has been associated with the following changes in immunity (which last at least several hours).

1. Decrease in NK cell cytotoxic activity.
2. Decrease in nasal neutrophil phagocytosis.
3. Decrease in granulocyte oxidative burst activity.
4. Decrease in nasal mucociliary clearance.
5. Decrease in IL-6 and IL-1ra.
6. Decrease in in vivo cell-mediated immunity, but normal vaccination response following intense, long-term exercise.

REFERENCES


45. Pedersen, B. K., N. Tvede, K. Klarlund, L. D. Christensen, F. R. Hansen, H. Galbo, A. Kharazmi, and J. Halkjær-Kristensen. Indomethacin in vitro and in vivo abolishes post-


