

Exercise and the Immune System: Regulation, Integration, and Adaptation

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Pedersen, Bente Klarlund, and Laurie Hoffman-Goetz. Exercise and the Immune System: Regulation, Integration, and Adaptation. *Physiol Rev* 80: 1055–1081, 2000.—Stress-induced immunological reactions to exercise have stimulated much research into stress immunology and neuroimmunology. It is suggested that exercise can be

employed as a model of temporary immunosuppression that occurs after severe physical stress. The exercise-stress model can be easily manipulated experimentally and allows for the study of interactions between the nervous, the endocrine, and the immune systems. This review focuses on mechanisms underlying exercise-induced immune changes such as neuroendocrinological factors including catecholamines, growth hormone, cortisol, β -endorphin, and sex steroids. The contribution of a metabolic link between skeletal muscles and the lymphoid system is also reviewed. The mechanisms of exercise-associated muscle damage and the initiation of the inflammatory cytokine cascade are discussed. Given that exercise modulates the immune system in healthy individuals, considerations of the clinical ramifications of exercise in the prevention of diseases for which the immune system has a role is of importance. Accordingly, drawing on the experimental, clinical, and epidemiological literature, we address the interactions between exercise and infectious diseases as well as exercise and neoplasia within the context of both aging and nutrition.

I. INTRODUCTION

Over the past 15 years a variety of studies have demonstrated that exercise induces considerable physiological change in the immune system. The interactions between exercise stress and the immune system provide a unique opportunity to link basic and clinical physiology and to evaluate the role of underlying stress and immunophysiological mechanisms. It has been suggested that exercise represents a quantifiable model of physical stress (113). Many clinical physical stressors (e.g., surgery, trauma, burn, and sepsis) induce a pattern of hormonal and immunological responses that have similarities to that of exercise. Whereas neural-endocrine-immune interactions have been investigated using a variety of psychological models (176), the exercise model provides a further opportunity to establish these links using a physical stress paradigm. This review extends earlier work on exercise immunology (27, 107, 145, 146, 170, 201, 234, 239, 240) and focuses on underlying endocrine and cytokine mechanisms.

II. ACUTE EXERCISE AND THE CELLULAR IMMUNE SYSTEM

A. Exercise and Lymphocyte Subpopulations

Responses of blood leukocyte subpopulations to an episode of acute exercise are highly stereotyped (Table 1). Neutrophil concentrations increase during and after exercise, whereas lymphocyte concentrations increase during exercise and fall below prevalues after long-duration physical work (182). Several reports describe exercise-induced changes in subsets of blood mononuclear cells (BMNC) (27, 107, 145, 146, 170, 201, 234, 239, 240). Increased lymphocyte concentration is likely due to the recruitment of all lymphocyte subpopulations to the vascular compartment: CD4+ T cells, CD8+ T cells, CD19+ B cells, CD16+ natural killer (NK) cells, and CD56+ NK cells. During exercise, the CD4-to-CD8 ratio decreases, reflecting the greater increase in CD8+ lymphocytes than

CD4+ lymphocytes. CD4+ and CD8+ cells contain both CD45RO+ memory and CD45RA+ virgin or naive cells and "true" naive cells that are identified by the absence of 45RO and the presence of CD62L (14). Data show that the recruitment is primarily of CD45RO+ lymphocytes (83). Recent studies indicate that the concentrations of CD45RO+ and CD45RO-CD62L- increase during exercise, suggesting that memory but not naive lymphocytes are rapidly mobilized to the blood in response to physical exercise (H. Bruunsgaard and B. K. Pedersen, unpublished observations).

To obtain information about lymphocyte turnover in cells recruited during exercise, we recently analyzed telomeric terminal restriction fragment (TRF) length. Telo-

TABLE 1. *Effect of strenuous exercise on the immune system*

	During Exercise	After Exercise
Neutrophil count	↑	↑↑
Monocyte count		↑↑
Lymphocyte count	↑	↓
CD4+ T cell count	↑	↓
CD8+ T cell count	↑	↓
CD19+ B cell count	↑	↓
CD16+56+ NK cell count	↑	↓
Lymphocyte apoptosis	↑	↑
Proliferative response to mitogens	↓	↓
Antibody response in vitro	↓	↓
Saliva IgA	↓	↓
Delayed type hypersensitivity response (skin test)		↓
NK cell activity	↑	↓
Lymphokine activated killer cell activity	↑	↓
C-reactive protein		↑
Neopterin		↑
Plasma concentration of TNF- α	↑	↑
Plasma concentration of IL-1	↑	↑
Plasma concentration of IL-6	↑↑	↑
Plasma concentration of IL-1ra	↑↑	↑
Plasma concentration of IL-10	↑	↑
Plasma concentration of TNF-R	↑	↑
Plasma concentration of MIP-1 β , IL-8		↑

↑, Increase; ↓, decrease; ↑↑, marked increase; TNF- α , tumor necrosis factor- α ; TNF-R, tumor necrosis factor receptors; IL, interleukin; MIP, macrophage inflammatory protein.

meres are the extreme ends of chromosomes that consist of TTAGGG repeats. After each round of cell division, telomeric sequence was lost because of the inability of DNA polymerase to fully replicate the 5'-end of the chromosome. Telomere lengths have been used as a marker for replication history and the proliferation potential of the cells. Cell cultures of CD8+ T cells that have reached replicate senescence after multiple rounds of cell division lack expression of the CD28 costimulatory molecule and have short telomere lengths (63). In response to exercise, lymphocytes lacking the CD28 molecule were mobilized to the circulation, and telomere lengths in CD4+ and CD8+ lymphocytes were significantly shorter compared with cells isolated at rest (Bruunsgaard and Pedersen, unpublished observations).

Thus the initial increase in CD4+ and CD8+ cells after exercise appears not to be due to repopulation by newly generated cells but may be a redistribution of activated cells, in agreement with kinetics of CD4+ lymphocyte repopulation after anti-human immunodeficiency virus (HIV) treatment (147), chemotherapy (96), and CD4+ and CD8+ lymphocyte repopulation after bone marrow transplantation (15). Although the number of all lymphocyte subpopulations increases, the percentage of CD4+ cells declines primarily due to the fact that NK cells increase more than other lymphocyte subpopulations (82, 145), thus contributing to the exercise-induced alterations in *in vitro* immune assays in which a fixed number of BMNC are studied.

B. Exercise and Lymphocyte Proliferation

To function in adaptive immunity, rare antigen-specific lymphocytes must proliferate extensively before they differentiate into functional effector cells of a particular immunogenic specificity. Most studies on lymphocyte proliferation have used polyclonal mitogens, which induce many or all lymphocytes of a given type to proliferate (127). Studies in humans indicate that the lymphocyte responses to the T-cell mitogens phytohemagglutinin (PHA) and concanavalin A (ConA) decline during and for up to several hours after exercise (198); this has also been a consistent finding in animal studies (234) (Table 1). This is at least partly due to the increase in NK cells in circulation and the relative decline of CD4+ cells in *in vitro* assays (82, 145). In contrast, lymphocyte proliferation to the B-cell mitogens pokeweed mitogen (PWM) and lipopolysaccharide (LPS) increases or remains unchanged after exercise (74).

The proliferation response and distribution of BMNC subpopulations in relation to concentric bicycle exercise were studied at 75% of maximal oxygen uptake ($\dot{V}O_{2\max}$) for 1 h (295). In accordance with many other studies, the PHA response declined, the %CD4+ cells declined, and

the %CD16+ cells increased during exercise. To determine whether specific subpopulations of BMNC were responsible for the lower PHA proliferation response during work, BMNC were cultured in the presence of PHA and pulsed with [³H]thymidine, followed by FACS sorting into CD4+ and CD8+ subgroups. The proliferation response per fixed number of BMNC did not change during or after bicycle exercise. However, the proliferation contribution of the CD4+ subgroup (as a percentage of total [³H]thymidine incorporation) declined during bicycle exercise due to the reduced proportion of CD4+ cells (295).

It is important to bear in mind that during exercise more lymphocytes are recruited to the blood, and on a per cell basis, the lymphocyte proliferation response is not actually suppressed. Thus the lower responses to PHA and ConA during exercise simply reflect the proportional changes in lymphocyte subsets and the decline in the percentage of T cells (82, 198, 295). After exercise, the total lymphocyte concentration declines and the proliferation response is unchanged from values obtained before exercise. Consequently, the total *in vivo* lymphocyte function in the blood can be considered as "suppressed" after exercise.

C. Exercise and NK Cells

NK cells are a heterogeneous population that are CD3- and that express characteristic NK cell markers, such as CD16 and CD56 (216). NK cells mediate non-major histocompatibility complex (MHC)-restricted cytotoxicity, with potential resistance to viral infections (308) and cytolysis of some malignant cells (216). The cytolytic activity of NK cells is enhanced by interferon (IFN)- α (217) and interleukin (IL)-2 (216), whereas certain prostaglandins (29) and immune complexes (242) downregulate the function of NK cells. The *in vitro*-generated lymphokine activated killer (LAK) cells have shown a broader range of non-MHC-restricted target cell killing (91). NK and LAK cells, therefore, may play an important role in the first line of defense against acute and chronic virus infections and early recognition of tumor cells and against tumor spread (310).

Exercise of various types, durations, and intensities induce recruitment to the blood of cells expressing characteristic NK cell markers (169, 246). With the use of *in vitro* assays, NK cell activity (lysis per fixed number of BMNC) increases consequent to the increased proportions of cells mediating non-MHC-restricted cytotoxicity (Table 1). During exercise, the NK cell activity on a per NK cell basis is unchanged (209, 229) or reduced (200) depending on exercise intensity.

In an early publication (244), it was shown that NK cells with a high IL-2 response capacity were recruited to the blood during bicycle exercise. When BMNC were

preincubated with cytokines, IFN- α or IL-2, or with the cyclooxygenase inhibitor indomethacin, a significant increase in the NK cell activity was registered at all the time points studied. During exercise, the IL-2-enhanced NK cell activity increased significantly more than the IFN- α -enhanced NK cell activity. When BMNC were incubated with IL-2 for more than 3 days, the LAK cell activity of cells from blood sampled at the end of the exercise period was significantly increased (293). These data support the early findings (244) that during exercise NK cells with a high IL-2 response capacity are recruited to the blood.

After intense exercise of long duration, the concentration of NK cells and NK cytolytic activity declines below preexercise values. Maximal reduction in NK cell concentrations, and hence the lower NK cell activity, occurs 2–4 h after exercise (Table 1).

The percentage of NK cells was suppressed below preexercise values (245) or unchanged compared with preexercise values (169). In accordance with these controversial findings, the postexercise suppression of the NK cell activity has been ascribed to a decreased proportion of NK cells among BMNC. However, it has also been reported that NK cell activity was not lower on a per NK cell basis after moderate exercise; in fact, NK cell activity on a “per cell” basis was elevated postexercise (209). Increases in NK cell activity were accompanied by a corresponding increase in serine-esterase activity (106). Other investigators suggest that reductions in NK cell activity were due to downregulation of the NK cell activity by prostaglandins (245). This hypothesis is based on the observation that indomethacin partly restored postexercise impairment of NK cell function (245) and that the NK cell activity was partly reduced by PGE₁, PGE₂, and PGD₂ (59).

Generally, NK cell activity is increased when measured immediately after or during both moderate and intense exercise of a few minutes. The intensity, more than the duration of exercise, is responsible for the degree of increment in the number of NK cells. If the exercise has lasted for a long period and has been very intense (e.g., a triathlon race), only a modest increase in NK cells is found postexercise (261). NK cell count and the NK cell activity are markedly lower only after intense exercise of at least 1 h duration. The definitive study to map the time course in terms of postexercise NK cell immune impairment has not been done. Initial fitness level or sex do not appear to influence the magnitude of exercise-induced changes in NK cells (26, 148).

D. Antibody Production and Mucosal Immunity

The secretory immune system of mucosal tissues such as the upper respiratory tract is considered by many clinical immunologists to be the first barrier to its colonization by pathogenic microorganisms (172). Although

IgA constitutes only 10–15% of the total immunoglobulin in serum, it is the predominant immunoglobulin class in mucosal secretions, and the level of IgA in mucosal fluids correlates more closely with resistance to upper respiratory tract infections than serum antibodies (165).

Lower concentrations of the salivary IgA have been reported in cross-country skiers after a race (290). This finding was confirmed by a 70% decrease in salivary IgA that persisted for several hours after completion of intense, long-duration ergometer cycling (171). Decreased salivary IgA was found after intense swimming (87, 285), after running (281), and after incremental treadmill running to exhaustion (183) (Table 1). Submaximal exercise had no effect on salivary IgA (118, 183).

The percentage of B cells among BMNC does not change in relation to exercise. This finding suggests that the suppression of immunoglobulin-secreting cells (plaque-forming cells) is not due to changes in numbers of B cells (Table 1). Purified B cells produce plaques only after stimulation with Epstein-Barr virus, and in these cultures no exercise-induced suppression was found. The addition of indomethacin to IL-2-stimulated cultures of BMNC partly reversed the postexercise suppressed B-cell function. Therefore, exercise-induced suppression of the plaque-forming cell response may be mediated by monocytes or their cytokines (292).

E. Exercise and In Vivo Immunological Responses

There are only a few studies that document immune system responses in vivo, in relation to exercise. In vivo impairment of cell-mediated immunity, but not specific antibody production, could be demonstrated after intense exercise of long duration (triathlon race) (31). The cellular immune system was evaluated as a skin test response to seven recall antigens, whereas the humoral immune system was evaluated as the antibody response to pneumococcal polysaccharide vaccine (this vaccine is generally considered to be T cell independent) and tetanus and diphtheria toxoids (both of which are T cell dependent). The skin test response was significantly lower in the group who performed a triathlon race compared with triathlete controls and untrained controls who did not participate in the triathlon (Table 1). No differences in specific antibody titers were found between the groups.

F. Neutrophil Function

Neutrophils represent 50–60% of the total circulating leukocyte pool. These cells are part of the innate immune system, are essential for host defense, and are involved in the pathology of various inflammatory conditions. This latter inflammatory involvement reflects tissue peroxidation resulting from incomplete phagocytosis. One of the

more pronounced features of physical activity on immune parameters is the prolonged neutrocytosis after acute long-term exercise (182).

There are a number of reports showing that exercise triggers a series of changes in the neutrophil population and may affect certain subpopulations differentially. A reduction in the expression of L-selectin (CD62L) immediately after exercise followed by an increase during recovery has been reported (158). There were no concomitant changes in CD11a or CD11b expression. In contrast, however, increased expression of CD11b in response to exercise was found (274). Increased expression of the cell-adhesion molecules after exercise may contribute to neutrophil extravasation into damaged tissue, including skeletal muscle.

With regard to the function of neutrophils, exercise has both short- and long-term effects. The neutrophil response to infection includes adherence, chemotaxis, phagocytosis, oxidative burst, degranulation, and microbial killing. In general, moderate exercise boosts neutrophil functions, including chemotaxis, phagocytosis, and oxidative burst activity. Extreme exercise on the other hand reduces these functions, with the exception of chemotaxis and degranulation which are not affected (27, 218, 275, 277).

G. Repetitive Bouts of Acute Exercise

Little is known about effects of repeated bouts of exercise on the immune system. In the first studies of the effect of repeated bouts of submaximal ergometer exercise on changes in the percentage of BMNC subpopulations, healthy volunteers exercised daily for 1 h at a submaximal intensity of 65% of $\dot{V}O_{2\max}$ (114). The increase in percentage of NK cells to five repetitive bouts of cycling over 5 days (each separated by a rest of 24 h) was not different from that elicited by the first bout (114).

The effect of two bouts of exhaustive cycle ergometer exercise, each lasting 12.9 and 13.2 min, respectively, and separated by 1 h was studied (74). A significant increase in total leukocytes (2-fold), neutrophils (1.9-fold), and lymphocytes (2.3-fold) occurred at the first exercise bout. The concentrations of leukocytes and neutrophils increased to the same level at both experiments, but the concentrations 1 h after the second bout were higher than that 1 h after the first bout of exercise. The concentration of lymphocytes increased less immediately after the second bout.

One hour after the second bout the lymphocyte concentration decreased below prevalues. This reduction was similar to that developed after the first bout of exercise.

Detailed subpopulation changes were investigated after 6 min of "all-out" ergometer rowing over 2 days (2 × 3 bouts) in elite male oarsmen (199). Compared with

levels at rest, the first bout of exercise increased the concentration of leukocytes (2-fold); neutrophils (2-fold); lymphocytes (2-fold); the BMNC subsets CD3+ (2-fold), CD4+ (2-fold), CD8+ (3-fold), CD16+ (8-fold), and CD19+ (2-fold); and the NK cell activity (2-fold). During the last bout, even higher levels were noted for leukocytes (3-fold); neutrophils (3-fold); lymphocytes (4-fold); the BMNC subsets CD4+ (3-fold), CD8+ (5-fold), CD16+ (13-fold), and CD19+ (5-fold); and NK cell activity (4-fold). During the recovery periods all values were at or above the level at rest, and elevated concentrations of leukocytes, neutrophils, lymphocytes, and NK cell activity were also noted on the day after the last bout.

In further studies, healthy male subjects performed three bouts of bicycle exercise lasting 60, 45, and 30 min at 75% of $\dot{V}O_{2\max}$ separated by 2 h of rest (260). The lymphocyte concentration and the PHA-stimulated lymphocyte proliferation declined 2 h after each bout of exercise, whereas the LAK cell activity declined 2 h after the third bout. The concentration of neutrophils continuously increased at the end of each exercise bout and was increased 2 h after the third compared with the first exercise bout. The diversity of results in these studies may reflect the finding that enhancement or reduction of immune responses depends on the intensity of exercise and the duration of rest between exercise session.

H. Leukocyte Trafficking

The movement of neutrophils from marginal pools located intravascularly and from extravascular storage pools contributes to exercise-related neutrocytosis. The role of the lung vasculature in neutrophilic granulocyte sequestration has been demonstrated (247). With respect to the lymphocytosis of exercise, the role of margination is less clear. The spleen may contribute to a lymphocytosis, since it is a major storage pool of lymphocytes, with $\sim 2.5 \times 10^{11}$ cells/day circulating between the blood and the splenic pulpa (225). It has been demonstrated that splanchnic sympathectomy reduces the splenic NK cell activity (142). Splenectomized subjects demonstrate a low lymphocyte count in response to injection of epinephrine (280), and subjects without a spleen show a smaller increase in lymphocyte numbers during exercise (197). However, there are also studies suggesting that the spleen does not play a role in exercise leukocytosis (124).

Based on the available data, we hypothesize the following model of lymphocyte recirculation with exercise. Lymphocytes are recruited to circulation from other tissue pools during exercise. The organs involved include the spleen, the lymph nodes, and the gastrointestinal tract. Because the cells mobilized to the blood have short telomere lengths, it is not likely that these cells are mobilized from the bone marrow or from thymus. The num-

ber of cells that enter the circulation is determined by the intensity of the stimulus. If exercise has been for a prolonged duration and/or of very high intensity, the total concentration of lymphocytes declines. The mechanisms for this probably include the lack of mature cells that can be recruited, as well as the redistribution of lymphocytes from the circulation to organs. In animal models (254), there is some information available about the organs to which these lymphocytes are redistributed after exercise, although the proportion of lymphocyte subsets varies as a function of lymphoid compartments. A recent animal study indicated that redistribution to skeletal muscles did not occur after exercise (64). Whether or not postexercise lymphopenia occurs is therefore dependent on a combination of intensity and duration.

III. LINKS BETWEEN THE ENDOCRINE, NERVOUS, AND IMMUNE SYSTEMS

The migration and circulation of lymphocytes allow cells of differing specificity, function, and antigen experience to undergo continuous tissue redistribution (223). Despite the diversity of factors that are activated when the integrity of the body is challenged, a stereotypical set of neuroendocrine pathways is critically involved (128). The presence of receptors for endocrine hormones (176) and the anatomic contact between the lymphoid and nervous systems (176) reveal the existence of pathways of communication between the immune system, the nervous system, and the endocrine system (253). The physiological basis for the neural, immune, and hormonal interactions has been extensively reviewed elsewhere (23, 176, 223).

There are several lines of evidence suggesting that various forms of physical stressors can stimulate similar alterations in the immune system (238). Exercise is a quantifiable and reproducible stressor that can be modified experimentally and thus considered as a prototype of stress (113). Acute, intense muscular exercise increases the concentrations of a number of stress hormones in the blood, including epinephrine, norepinephrine, growth hormone, β -endorphins, testosterone, estrogen, and cortisol, whereas the concentration of insulin slightly decreases (84, 151, 306).

In this section we briefly review the evidence for exercise-induced changes in neuroimmune interactions and propose a model for the possible roles of stress hormones in exercise-induced immune changes.

A. Catecholamines

During exercise, epinephrine is released from the adrenal medulla, and norepinephrine is released from the sympathetic nerve terminals. Arterial plasma concentra-

tions of epinephrine and norepinephrine increase almost linearly with duration of dynamic exercise and exponentially with intensity, when it is expressed relative to the individual's $\dot{V}O_{2\max}$ (151).

The expression of β -adrenoceptors on T, B, and NK cells, macrophages, and neutrophils in numerous species provide the molecular basis for these cells to be targets for catecholamine signaling (176). β -Receptors on lymphocytes are linked intracellularly to the adenylyl cyclase system for generation of cAMP as a second messenger (43), and the β -adrenoceptor density appears to change in conjunction with lymphocyte activation and differentiation (1).

The *in vitro* effect of epinephrine on NK cell activity has demonstrated that human NK cell activity was inhibited by the addition of cAMP inducers directly to target and effector cells in a ^{51}Cr -release assay (143). More complex effects were reported when pretreatment of lymphocytes with low concentrations of epinephrine (10^{-7} to 10^{-9} M), followed by removal of the drug, increased NK cell activity (101). Direct addition of epinephrine (10^{-6} M) to the lymphocyte-target cell mixture inhibited the NK cell activity.

When epinephrine was present during preincubation of mononuclear cells as well as in the NK cell assay at epinephrine concentrations obtained during exercise, there were no significant *in vitro* effects of epinephrine on NK cells isolated before, during, or after epinephrine infusion (139). These results suggest that epinephrine may act by redistributing BMNC subsets within the body, rather than directly influencing the activity of the individual NK cells.

The numbers of adrenergic receptors on the individual lymphocyte subpopulations may determine the degree to which the cells are mobilized in response to catecholamines. In accordance with this hypothesis, it has been shown that different subpopulations of BMNC have different numbers of adrenergic receptors (149, 177, 253, 303). NK cells contain the highest number of adrenergic receptors, with CD4+ lymphocytes having the lowest number. B lymphocytes and CD8+ lymphocytes are intermediate between NK cells and CD4+ lymphocytes (177). Dynamic exercise upregulates the β -adrenergic density, but only on NK cells (177). Interestingly, NK cells are more responsive to exercise and other stressors than any other subpopulation. CD4+ cells are less sensitive, and CD8+ cells and B cells are intermediate (113). Thus a correlation exists between numbers of adrenergic receptors on lymphocyte subpopulations and their responsiveness to exercise.

Selective administration of epinephrine to obtain plasma concentrations comparable to those obtained during concentric cycling for 1 h at 75% of $\dot{V}O_{2\max}$ mimicked the exercise-induced effect on BMNC subsets, NK cell activity, LAK cell activity, and the lymphocyte prolifera-

tive response (139, 291, 294). However, epinephrine infusion caused a significantly smaller increase in neutrophil concentrations than that observed after exercise (139, 294).

After administration of propranolol, exercise resulted in practically no increase in lymphocyte concentration (2). The β_1 - and β_2 -receptor blockade, more than β_1 -blockade alone, inhibited head-up tilt-induced lymphocytosis and abolished the stress-induced increase in number of NK cells (154). This finding is in accordance with the fact that primarily β_2 -receptors are expressed on lymphocytes (17). β_2 -Receptor blockade did not abolish the head-up tilt-induced neutrocytosis, which is in agreement with previous findings showing that epinephrine infusion caused smaller increase in neutrophil concentration than the exercise-induced increase (139, 294). The effect of norepinephrine on recruitment of lymphocytes to the blood resembles that of epinephrine (136).

Epinephrine may be responsible for the recruitment of NK cells to the blood during physical exercise and other physical stress forms. The experimental basis includes the findings that 1) epinephrine infusion mimics the exercise-induced effect especially on NK and LAK cells, 2) β -adrenergic receptors are upregulated on NK cells during exercise, and 3) β -adrenergic receptor blockade abolishes lymphocytosis during exercise and the increase in NK cell number during head-up tilt. Additional evidence comes from the observation that β_2 -receptor agonists induce selective detachment of NK cells from endothelial cells (17). Taken together, the findings strongly support the hypothesis that epinephrine strongly contributes to the recruitment of NK cells from the marginating pool in blood vessels, lymph nodes, spleen, and intestines.

B. Growth Hormone

Growth hormone is released from the anterior pituitary in a pulsatile fashion, and irregular time courses for changes in plasma growth hormone have therefore been found. Plasma levels of pituitary hormones increase in response to exercise both with duration and intensity. Growth hormone responses are more related to the peak exercise intensity rather than to duration of exercise or total work output (151).

An intravenous bolus injection of growth hormone at blood concentrations comparable to those observed during exercise had no effect on BMNC subsets, NK cell activity, cytokine production, or lymphocyte function but induced a highly significant neutrocytosis (135). In a hyperthermia stress model, the growth hormone release inhibitor somatostatin abolished the increase in growth hormone as well as the neutrocytosis (137). Based on these observations, we propose that growth hormone

does not have a major role in the exercise-induced recruitment of lymphocytes to circulation. However, epinephrine and growth hormone in combination are probably responsible for the recruitment of neutrophils to the blood during physical stress.

Other pituitary hormones, such as prolactin, have important immune-regulating actions on lymphocytes and thymocytes (19, 192). However, to our knowledge, the impact of acute and prolonged exercise on prolactin and the interaction of exercise with prolactin on lymphocytes have not been characterized.

C. Cortisol

The plasma concentrations of cortisol increase only in relation to exercise of long duration (84). Thus short-term exercise does not increase the cortisol concentration in plasma, and only minor changes in the concentrations of plasma cortisol were described in relation to acute time-limited exercise stress of 1 h (84).

It has been shown that corticosteroids given intravenously to humans cause lymphocytopenia, monocytopenia, eosinopenia, and neutrophilia that reach their maximum 4 h after administration (253). Exogenous glucocorticosteroid administration, especially in supraphysiological doses, induces cell death of immature T and B cells, whereas mature T cells and activated B cells are relatively resistant to cell death (49). In agreement, recent work shows that the percentage of proliferative lymphocytes expressing early markers of apoptosis (annexin V, APO2.7) do not increase immediately after or 2 h after intense exercise despite an increase in blood glucocorticoid levels (116). Incubation of thymocytes and splenocytes with concentrations of corticosterone observed at near-maximal exercise induced profound apoptosis and necrosis after 24 h (115). Recent studies suggest that exercise-associated induction of apoptosis may contribute to lymphocytopenia and reduced immunity after intense exercise (Table 1). A study (178) found electrophoretic evidence of DNA damage in circulating lymphocytes after exercise that was accompanied by flow cytometric measures of apoptosis. Another study (5) reported increased intrathymic and intrasplenic membrane lipid peroxides and lower concentrations of intrathymic and intrasplenic superoxide dismutase and catalase antioxidants immediately after a run to exhaustion in rodents. Taken together, these findings indicate reactive oxygen species-mediated lymphocyte damage (apoptosis) that may mediate reduced immunity postexercise.

Infusion of prednisolone caused a redistribution of circulating cells from blood to the bone marrow, decreased cellular localization to lymph nodes, and impaired lymphocyte crossing of high endothelial venules (50). High doses of corticosteroids inhibit function of NK

cells (232, 236). In vitro studies have shown that pharmacological concentrations of methylprednisolone and hydrocortisone inhibited the NK cell function, partly by an inhibition of the adhesion of effector cells to target cells (104, 235). Unlike catecholamines, however, cortisol exerts its effect with a time lag of several hours. This suggests that cortisol probably does not have a major role in the acute exercise-induced effects. Moreover, after strenuous exercise, a decrease in glucocorticoid sensitivity by lymphocytes occurs due to downregulation of low-affinity high-capacity type II glucocorticoid receptors on lymphocytes (54). We hypothesize that cortisol likely has a role in maintaining the neutrophilia and lymphopenia after prolonged, intense exercise such as a marathon. The impact of cortisol on accumulation of memory and naive T lymphocytes and on release/maturation of thymocytes with exercise has not been studied.

D. β -Endorphin

Normally, under nonstress conditions the circulating level of β -endorphin is extremely low ($1\text{--}100 \times 10^{-12}$ M), although stressors including physical activity increase the level 3–10 times (177). The plasma concentrations of β -endorphin increase in response to prolonged exercise if the intensity is $>50\%$ of $\dot{V}O_{2\text{max}}$ and during maximal exercise if this is performed for a minimum of 3 min. At low work loads, no rise in β -endorphin levels is found despite extremely long exposure time (156).

The results on the effects of β -endorphin on T- and B-cell functions are highly variable (187). On the basis of studies performed in humans, and from infusion studies, β -endorphin inhibits T-cell proliferation (302) but can also inhibit antibody production (188). Both IFN and IL-2 stimulate NK cells to increased cytotoxic activity. If incubated with human BMNC or NK-enriched cell populations, β -endorphin enhances NK activity (180), although this has not been consistently observed (250).

During naloxone administration, exercise did not induce a significant rise in NK cell activity (72). Employing other physical stress models, it was shown that naloxone in vivo had no effect on head-up tilt-induced recruitment of NK cells to the circulation (153) and no effect on hyperthermia-induced recruitment of NK cells (137). Animal experiments showed that chronic intracerebrovascular infusion of β -endorphin augmented the NK cell activity in vivo and that this effect was abolished by naloxone (132). It was concluded that this was a central effect and opioid receptor mediated, since β -endorphin in the same dose administered peripherally did not influence in vivo NK cell cytotoxicity.

The available data indicate that β -endorphin is not responsible for the immediate recruitment of NK cells to the blood during acute exercise but is likely responsible

for increased NK cell activity during chronic stress. This is based on the observation that NK cells are recruited to the blood immediately after the onset of exercise and even at exercise of very low intensity. The concentrations of β -endorphin increase, however, only at high-intensity and long-duration exercise. These two phenomena make it unlikely that β -endorphin plays a major immunomodulatory role in the immediate recruitment of NK cells to the blood. The hypothesis that β -endorphin is important in maintaining increased NK cell activity during chronic stress is primarily based on animal studies showing that voluntary chronic exercise augments in vivo natural immunity (130).

E. Sex Steroids

Testosterone influences both cellular and humoral components of the immune system. Exposure to dihydrotestosterone (10^{-6} to 10^{-11} M) was associated with reductions in IL-4, IL-5, and IFN- γ production by anti-CD3 activated mouse lymphocytes but had no effect on IL-2 production in vitro (4). Spontaneous IgM and IgG immunoglobulin production by human BMNC was inhibited by exposure to 1 nM testosterone while IL-6 production by monocytes was significantly reduced relative to cultures not incubated with testosterone (133). Other reports document the immune-suppressing effects of testosterone exposure including inhibition of lymphocyte proliferation responses to the T-cell mitogen ConA and changes in CD4/CD8 ratios (92, 18).

Acute, short-term exercise of high intensity increases serum testosterone levels (306). Moderate physical activity increases testosterone concentrations in blood (317). The physiological basis for elevated testosterone with acute exercise may include reduced testosterone clearance (34) and hemoconcentration (311). In contrast, prolonged physical exercise, such as noncompetitive marathon running, reduces serum testosterone concentration (157), possibly by suppressing gonadotropin-releasing hormone secretion (157).

There have been few reports of the interactions among testosterone, acute exercise, and lymphocyte function. Mouse splenocyte but not thymocyte responses to the T-cell mitogen ConA were significantly enhanced, serum testosterone was lower, and the corticosterone levels were higher in swim-exercised, cold-stressed mice (10-min swimming, 15°C) after 1, 3, and 5 days compared with sedentary controls (126). Whether this reduction in testosterone level was due to exercise or to cold exposure (by immediately affecting Leydig cell testosterone production) could not be distinguished in this study.

At high concentrations in vitro (e.g., 400 ng/ml), estrogen induces thymic involution (271), modulates thymosin production (3), and suppresses mixed lymphocyte

proliferation responses (11). At lower concentrations, estrogen exposure *in vitro* has been reported to enhance immunological functions (278). A direct effect of estrogen and diethylstilbestrol on immunocompetent cells has been demonstrated, including inhibition of NK cell cytotoxicity (70). Additional evidence for the immunomodulatory effect of estrogen comes from studies with tamoxifen and other nonsteroid "antiestrogens." Tamoxifen interferes with the expression of C3 receptors on human lymphocytes (9) and increases the secretion of IgG, but not IgM, from PWM-stimulated lymphocytes (10). An older study reported that the effects of estrogen and antiestrogens on lymphocyte proliferative responses may be mediated through modulating CD8+ lymphocytes (224).

Estrogen may influence lymphocyte function through interactions with proinflammatory cytokine elaboration. Administration of estriol, a short-acting estrogen agonist, was associated with significant increases in serum tumor necrosis factor (TNF)- α and IL-6 levels after LPS challenge (318). Estrogen-treated macrophage cultures showed a reduction in IL-6 mRNA and produced significantly less IL-6 than cultures treated with vehicle (319). *In vitro* exposure of rat peritoneal macrophages to 17 β -estradiol stimulated TNF production, whereas higher concentrations reduced TNF- α production (47). In contrast, unstimulated monocytes from women with premature menopause had higher TNF- α levels, and administration of estrogen normalized TNF- α release (226). The influence of estrogen on IL-1 production has also been characterized. Both pretreatment of cultured monocytes and *in vivo* administration of estrogen to women had no effect on spontaneous IL-1 release (282). Similar to the observations regarding exercise and testosterone, physical activity together with energy balance are modulators of the function of the hypothalamic-pituitary-ovarian axis. The effects of physical activity on estrogen vary considerably with age and phase of reproductive life and energy status.

F. A Model of Exercise-Induced Neuroimmune Interaction

On the basis of the above studies, a model is proposed indicating possible roles of these hormones in mediating the exercise-related changes. Epinephrine and to a lesser extent norepinephrine contribute to the acute effects on lymphocyte subpopulations as well as NK and LAK cell activities. The increase in catecholamines and growth hormone mediates the acute effects on neutrophils, whereas cortisol exerts its effects within a time lag of at least 2 h and contributes to the maintenance of lymphopenia and neutrocytosis after prolonged exercise. Testosterone and estrogen may also contribute to the acute exercise-associated reduction in lymphocyte proliferative and NK cell activities. The role of β -endorphin is

not clear, but the evidence suggests that β -endorphin does not contribute to the immediate recruitment of NK cells into the circulation but may play a mechanistic role in chronic or prolonged exercise conditions. Although the classical stress hormones do not seem to be responsible for the exercise-associated increase in cytokines, sex steroid hormones can modulate cytokine effects with exercise. The concentration of insulin slightly decreased in response to exercise, but this decline does not appear to have a mechanistic role (134). Our hypothesis is an extension of the earlier work (182) showing that the immediate leukocytosis during exercise is attributable to elevated catecholamine levels, and the delayed neutrophilia is due to elevated cortisol levels.

IV. EXERCISE AND THE ACUTE PHASE RESPONSE

The local response to an infection or tissue injury involves the production of cytokines that are released at the site of inflammation. These cytokines facilitate an influx of lymphocytes, neutrophils, monocytes, and other cells, and these cells participate in the clearance of the antigen and the healing of the tissue. The local inflammatory response is accompanied by a systemic response known as the acute phase response. This response includes the production of a large number of hepatocyte-derived acute phase proteins, such as C-reactive protein (CRP), α_2 -macroglobulin, and transferrin. Injection of TNF- α , IL-1 β , and IL-6 into laboratory animals or humans (55) will produce most, if not all, aspects of the acute phase response. These cytokines are therefore usually referred to as "inflammatory" or "proinflammatory cytokines," although it may be more reasonable to classify IL-6 as an "inflammation-responsive" cytokine rather than a proinflammatory cytokine since IL-6 does not directly induce inflammation. There are a number of biological inhibitors of the inflammatory cytokines; these include the IL-1 receptor antagonist (IL-1ra), TNF- α receptors, IL-4, and IL-10 (256).

A. Cytokines

The first study suggesting that exercise induced a cytokine response reported that plasma obtained from human subjects after exercise, and injected intraperitoneally into rats, elevated rectal temperature (40). In 1986, two studies were published that indicated that the level of IL-1 increased in response to exercise (38, 67). An increase in IL-6 concentration has been reported immediately after a marathon run, but there was no detectable IL-1 β (215). IL-6 was also shown to be elevated in response to exercise (30, 44, 58, 100, 191, 220–222, 279, 298, 304) (Table 1). Several studies have failed to detect TNF- α

after exercise (258, 275, 298, 300), whereas others report increased plasma TNF- α concentrations (62, 65, 220, 221) (Table 1).

After a marathon race, TNF- α and IL- β increased 2-fold, whereas the concentrations of IL-6 increased 50-fold; this was followed by a marked increase in the concentration of IL-1ra (222). Recent studies show that several cytokines can be detected in plasma during and after strenuous exercise (220–222) (Table 1). Thus strenuous exercise induces an increase in the proinflammatory cytokines TNF- α and IL-1 β and a dramatic increase in the inflammation responsive cytokine IL-6. This release is balanced by the release of cytokine inhibitors [IL-1ra and TNF receptors (TNF-R)] and the anti-inflammatory cytokine IL-10 (221). Also, the concentrations of chemokines, IL-8, and macrophage inhibitory protein (MIP)-1 α and MIP-1 β , are elevated after a marathon (K. Ostrowski and B. K. Pedersen, unpublished observations). These findings suggest that cytokine inhibitors and anti-inflammatory cytokines restrict the magnitude and duration of the inflammatory response to exercise. The presence of multiple cytokines (TNF- α , IL-1 β , IL-6, IL-2 receptors, and IFN- γ) in urine after exercise shows that the expression of a broad spectrum of cytokines in response to exercise is possible (279).

There are several possible explanations for the variable results on proinflammatory and inflammation-responsive cytokines in relation to exercise (241). These include 1) the type of physical activity as well as the intensity and duration of the exercise. Increased cytokine levels have mostly been described after eccentric exercise. Furthermore, the magnitude of increase is probably related to the duration of the exercise, although this remains to be shown in studies comparing cytokine levels in groups of subjects performing exercise at same intensity but at varying durations. 2) The specificity and the sensitivity of the assays is another possible explanation. For example, although IL-1 was believed to be the cytokine responsible for the exercise-induced plasma activities, the possibility exists that other cytokines were measured (7, 38, 40, 67). The latter studies were conducted before the availability of recombinant IL-1 proteins. Furthermore, the thymocyte proliferation bioassay also detects IL-6. Therefore, the possibility exists that the cytokine responsible for the activity measured in the thymocyte bioassay or for the fever-inducing properties of plasma was IL-6 and not IL-1.

Increased cytokine levels have mainly been found after eccentric exercise. Concentric and eccentric exercise were compared at the same relative oxygen uptake (30). Although the catecholamine levels did not differ between the two experiments, the creatine kinase (CK) level increased almost 40-fold 4 days after eccentric exercise.

No changes were observed in the CK level in relation

to concentric exercise. The IL-6 level increased fivefold in relation to eccentric exercise and was significantly correlated with the CK level in the subsequent days; no changes were found, however, in relation to eccentric exercise. This study indicates that there was an association between increased IL-6 level and muscle damage, but it remains to be shown whether a causal relationship exists. A comparative PCR technique was used to detect mRNA for cytokines in skeletal muscle biopsies and BMNC collected before and after a marathon race (222). Before exercise, mRNA for IL-6 could not be detected in muscle or BMNC, but mRNA for IL-6 was detected in muscle biopsies after exercise; mRNA for IL-6 was not found in BMNC samples. Increased amounts of mRNA IL-1ra were found in BMNC samples after exercise. This study suggests that exercise induces local production of IL-6 in the skeletal muscle and thereafter triggers the production of IL-1ra from circulating BMNC.

Although the role of the LPS endotoxin is undeniable in triggering septic disease, its possible role in exercise is based on only a few studies. When endotoxin crosses gut mucosa and enters into circulation, it triggers a cascade involving TNF- α , IL-1 β , and IL-6. For systemic endotoxemia to occur, the mechanical barrier of the bowel wall, the immunological barrier of the gut-associated lymphatic tissue, and the filtering capacity of the liver must all be overcome.

A study reported that 81% of athletes performing an 81.4-km race had plasma endotoxin concentrations above the upper limit of 0.1 ng/ml, including 2% with plasma levels above 1 ng/ml, a value which is considered to be lethal in humans (28). Interestingly, these authors noticed that the highest endotoxin values were measured in the least fit subjects who completed the race in more than 8 h. This group also found that there was no increase in LPS levels after the 21.1-km run. Increased plasma levels of LPS in athletes who took part in a triathlon competition have been recorded (24). The relationship between mild postexertion illness in 39 cyclists after a 100-mi. ride and endotoxemia found that it was not the cause of postexertion illness and unrelated to rhabdomyolysis (186). The disparity between the studies on runners (28) and cyclists (186) regarding endotoxemia-associated illness is not easily understood. It is, however, possible that gut trauma during running, but not during cycling, may compromise the barrier function of the bowel wall and thereby increase the portal burden of endotoxins.

Although conflicting reports (48, 76, 88, 185, 190) have been published, most authors agree that a monocyte-derived factor is responsible for muscle protein breakdown. Evidence from in vivo experiments indicates that IL-1, TNF- α , and IL-6 contribute to muscle protein catabolism, but in vitro experiments do not support this concept. It is possible that IL-1 and TNF- α require a cofactor or processing (i.e., cleavage), or they are intermediates

that induce an inhibitory factor that acts on the muscle itself. IL-1 β has been found to be increased in muscle up to 5 days after completing exercise (39).

The presence of IL-1 in skeletal muscle several days after the exercise suggests that IL-1 may be involved in prolonged muscle damage or protein breakdown. Branched chain amino acid (BCAA) supplementation reduced net protein degradation without reduction in IL-6, thus suggesting that IL-6 is not closely related to muscle catabolism after prolonged eccentric exercise (262).

Current opinion is that after eccentric exercise myofibers are mechanically damaged and, therefore, an inflammatory and necrotic process occurs. A recent study showed that DNA damage is present in muscle of mice 2 days after spontaneously running for an entire night, but not in sedentary mice (269). These findings suggest that apoptosis is a late manifestation in skeletal muscle damage. Future studies should elucidate whether exercise-induced increased levels of cytokines play a role in the apoptotic process in prolonged muscle damage.

Increased levels of PGE₂ and delayed onset muscle soreness have been found 24 h after eccentric exercise. The time course for PGE₂ and muscle pain indicates a possible relationship. The source of prostaglandin production could be the macrophage, which is the predominant cell at 24 h. What stimulates the PGE₂ release from mononuclear cells? IL-1 α , IL-1 β , and TNF- α have been shown to induce prostaglandin synthesis in endothelial cells, smooth muscle cells, and skeletal muscle (53). Therefore, the production of inflammatory cytokines in response to exercise may stimulate the production of prostaglandins. Further support comes from the high levels of plasma IL-6 found immediately after the completion of an exhaustive exercise bout. Thus the IL-6 production or release precedes neutrophil and macrophage accumulation in the muscle, the increase in PGE₂, the increase in CK, and the sensation of delayed onset muscle soreness.

Interactions between cytokine production and prostaglandins are highly complex. A recent study showed inhibitory effects of PGE₂ on TNF- α and IL-6 production by LPS-stimulated macrophages, with possible autocrine or paracrine feedback involving IL-10 (283). Interpretation of these results suggests that PGE₂ exerts a negative-feedback mechanism on the cytokine response, whereby the inflammatory response in the muscle is limited.

Obviously, there are similarities in the cytokine responses observed in subjects after intense exercise and in patients with trauma and sepsis. In experimental models of meningitis and sepsis, endotoxins induce an increase in TNF- α , followed by an increase in IL-1 β , and considerably later in IL-6 (307). In trauma patients, however, the pattern of cytokine release is different, with elevated IL-6 but not TNF- α (179). Recent work shows that the cytokine response to muscle-damaging exercise is similar to that observed in trauma patients (220, 221).

We suggest a model of the cytokine response in relation to exercise. The mechanical disruption of myofibers initiates local and systemic production of cytokines. The sequential release of cytokines resembles that observed in relation to trauma (i.e., high IL-6 and low TNF- α and IL-1 β) (220). Although high levels of IL-6 have been detected, this IL-6 induces only a modest increase in CRP. The time course for CRP has not been determined (44). Furthermore, many of the other biological effects that occur with trauma induced by proinflammatory cytokines such as myocardium depression, vasodilatation, leukocyte aggregation, and dysfunction of kidneys, livers, lungs, and brain do not develop in response to exercise. Exercise is not characterized by a fully developed systemic proinflammatory response. This lack for systemic response may be due to only a transient cytokine release in response to exercise. Alternatively, this may reflect an adaptation to the cytokine response (e.g., increased ability to induce effective natural occurring inhibitory cytokines and cytokine receptors). Understanding the differences among exercise, trauma, and septic shock in terms of cytokine profiles may have important therapeutic implications.

B. Acute Phase Reactants

In addition to cytokines, serum levels of noncytokine acute phase reactants, including serum amyloid A inducer (SAA), CRP, serum amyloid A, haptoglobin, ceruloplasmin, transferrin, and α_2 -macroglobulin, also change with inflammation (230). Many of these acute phase reactants have essential roles in host defense; for example, ceruloplasmin and transferrin may have antioxidant functions (86). With respect to exercise models, the serum levels of these acute reactants have not been well characterized with the exception of transferrin.

The concentration of serum transferrin, a β_1 -globulin carrier protein of iron which is synthesized in the liver, decreases with inflammation and trauma (255). Transferrin may play a role in nonspecific host defense against bacterial pathogens through the "iron binding" hypothesis (263). However, when samples were corrected for plasma volume shifts, transferrin concentrations did not change immediately after 30, 60, or 120 min after high-intensity swimming or treadmill exercise in athletes (140). In contrast, blood concentration of a related acute phase iron transport molecule, ferritin, was significantly decreased at 5 and 7 days postexercise compared with immediately and 1 day postexercise (120). Iron-binding capacity and percentage of saturation of transferrin did not change after 12 wk of moderate endurance walking/running or cycling exercise in 31 women (25). In rangers participating in an 8-wk United States training course, and who had associated energy deficit of \sim 1,000 kcal/day, there were

no effects on serum transferrin concentrations (214). In contrast, transferrin concentration decreased significantly in male recruits undergoing prolonged physical stress during survival training (93). It is not possible, however, to disentangle the effects of the physical exercise from restricted water and food intake on the levels of serum transferrin that were observed in this study.

CRP concentration was unchanged after either uphill running or 24 h after downhill running (252). However, CRP levels increased in subjects after an intensive training program in elderly subjects (270). Additional research on the impact of exercise on acute phase reactant proteins, other than cytokines, is needed.

C. Cellular Activation in Response to Exercise

Exercise induces numerous changes in the immune system, but it is controversial whether these changes reflect activation of the immune system or altered composition of lymphocyte subpopulations influencing the functional *in vitro* assays (82, 198). Certainly, many of the exercise-induced changes that have been described can be ascribed to changes in the composition of BMNC. For example, the decreased lymphocyte response to PHA is due to the decreased fraction of the CD4⁺ cells, and the increased *in vitro* production of IL-1 from endotoxin-stimulated BMNC is due to increased percentage of monocytes.

However, the increased levels of cytokines in plasma after intense exercise are probably not simply because of a redistribution of monocytes. Increased plasma concentrations of soluble IL-2R, CD8⁺, intercellular adhesion molecule-1 (ICAM-1), CD23, TNF- α -R, and neopterin were recorded in 18 individuals during or after long-duration exercise (289). Exercise has been found to render mouse splenocytes more resistant to the blockade effect of antibodies to LFA-1 (the intercellular adhesion molecule ICAM) (105). These results suggest that there is some immune system activation during intense exercise of long duration. However, in another study, the levels of colony-stimulating factor and neopterin remained unchanged after concentric exercise (276).

Prolonged severe physical exercise has been associated with an initial increase and delayed decrease in circulating immune complexes (60, 61). However, the changes were, although statistically significant, quantitatively small, and the values were only occasionally above the upper limit. Other studies did not indicate these changes (273, 288). The lack of increased concentrations of immune complexes and also the lack of occurrence of C3c and C3d indicate that immune complex-induced complement activation does not occur during concentric exercise (288). Furthermore, the levels of complement receptor type one (CR1) on erythrocytes do not change in

relation to concentric exercise, neither in healthy subjects nor in patients with rheumatoid arthritis (288). A similar time course of changes in myeloperoxidase and C5a and the highly significant relationship between these two variables lend some support to the hypothesis that complement activation contributes to postexercise neutrocytosis in eccentric exercise (35).

The disparity between the studies (35, 60, 61, 273, 288) may be explained by the fact that only exercise of long duration or exercise involving an eccentric component causes activation of the complement cascade. In support of this hypothesis, downhill running, but not uphill walking, induced increased plasma levels of myeloperoxidase and elastase (36).

V. EFFECT OF CHRONIC EXERCISE ON THE IMMUNE SYSTEM

In contrast to the large number of studies on the immune response to acute exercise, much less is known concerning the effect of physical conditioning or training on immune function. This is largely due to the difficulties in separating fitness effects from the actual physical exercise as well as the long-duration studies that need to be performed. Thus the changes induced by intense physical exercise may last at least 24 h, and even moderate acute exercise induces significant immune changes for several hours. Because it is not easy to persuade athletes to abstain from their normal training program even for just 1 day, it may be difficult to obtain results on true "resting levels." The influence of chronic exercise has been studied in both animal and human models, the latter including both longitudinal as well as cross-sectional studies.

A. Cross-Sectional Human Studies

One indicator of chronic exercise as a life-style factor is to compare resting levels of any immune parameter in untrained controls and in conditioned athletes. Two studies, which have been conducted with competitive male cyclists, controlled for the effects of acute exercise by requiring the subjects not to exercise 20 h before blood sampling. All subjects had been active in sports for a median of 4 yr with mean training volume of 20,000 km/yr. Median NK cell activity was 38.1% in the trained group compared with 30.3% in the untrained group, and the median %CD16⁺ NK cells was 17% in the trained versus 11% in the untrained group (243). In another study, 15 cyclists and 10 controls were examined during a period of high- or low-intensity training. NK cell activity was significantly elevated in the trained group, both during the period of low-intensity training (39.2 vs. 30.9%) and during the period of high-intensity training (55.2 vs. 33.6%) (296). During low-intensity training the increased NK cell activ-

ity in trained subjects was due to an increased percentage of NK cells. During high-intensity training increased NK cell function was not due to simple numerical increases: both trained and untrained subjects had comparable numbers of circulating NK cells. The mechanisms of this enhanced activity might be secondary to differences in NK-cell activation. The results suggested that the NK cells were activated in trained subjects during high-intensity training and that this may lead to an adjustment of the number of CD16+ cells in circulation by some unknown mechanism. In these studies (243, 296), other lymphocyte subpopulations and the lymphocyte proliferative responses did not differ among trained and untrained subjects.

Twenty-two marathon runners who had completed at least 7 marathons were compared with a group of 18 sedentary controls (203). Despite large differences between groups on $\dot{V}O_{2\max}$, percent body fat, and physical activity, only the NK-cell activity among the immune system variables measured emerged as being significantly different among the groups (higher among the marathoners). The NK-cell activity and PHA-stimulated proliferative responses were significantly elevated in a group of highly conditioned elderly women compared with an inactive group (206).

Lymphocyte proliferative responses have been described as decreased (231), elevated (8, 206), or unchanged (202, 203, 219, 243, 296) when comparing athletes and nonathletes. Neutrophil function is either suppressed (164, 251) or not significantly influenced by exercise training (90, 94). Neutrophil function was unchanged in athletes during a low-training period but decreased during periods of high-intensity training (8, 95).

B. Longitudinal Human Studies

The effect of chronic exercise has been studied in longitudinal designs. This approach is advantageous because the studies use randomization, in principle excluding confounding factors. The disadvantage is that the majority of longitudinal studies investigate the effect on the immune system after at most 16 wk of training, whereas the cross-sectional studies reflect many years of training. All studies, however, show significant effects on $\dot{V}O_{2\max}$ as a result of training.

NK-cell activity was not influenced, nor was any other immune parameter, when 30 elderly women were randomized into a 12-wk walking program (206). In contrast, however, the NK-cell activity in elderly women who undertook 16 wk of treadmill exercise was enhanced (51). In another study, 15 wk of walking enhanced the NK-cell activity in moderately obese, previously inactive women (212). When 18 patients with rheumatoid arthritis were allocated to an 8-wk cycling program, chronic exercise

had little effect on the NK-cell activity, lymphocyte proliferative responses, concentrations or proportions of lymphocyte subpopulations, or cytokine production (13).

C. Animal Studies

The influence of 9 wk of chronic exercise on natural cytotoxicity was investigated in male C3H mice (173). Both in vivo cytotoxicity (pulmonary vasculature) and in vitro cytotoxicity (spleen) after voluntary (wheel running) and forced (treadmill running, 15 m/min, 30 min/day) training were examined (173). A sedentary control group and a treadmill control group (5 m/min, 5 min/day) were included. Forced and voluntary chronic exercise enhanced in vivo as well as in vitro cytotoxic activity, but elevated cytotoxicity was not found in either of the control groups. Several studies using training protocols of varying lengths and intensities and of different animal species support these findings of increased resting levels of natural cytotoxicity after voluntary exercise (108, 111, 131, 174, 175).

VI. EXERCISE AND INFECTIONS

Without doubt exercise and training influence the concentration of immunocompetent cells in the circulating pool, the proportional distribution of lymphocyte subpopulations, and the function of these cells. An important question is, however, to what degree are these cellular changes of clinical significance, especially with respect to resistance to infectious diseases.

A. Poliomyelitis

In the 1930s and 1940s, it was demonstrated that polio took a more serious course if patients had exercised during the early stages of the disease. The idea that physical exercise might influence the clinical outcome of poliomyelitis was based on case reports of a great physical exertion before the onset of severe paralysis (e.g., Ref. 166).

It was observed that if the anterior horn cell was engaged in regenerating its neuroaxon (i.e., if the peripheral nerve originating in these cells had been sectioned a few days previously), these anterior cells were refractory to experimental infection with virus (119). On this basis, it was suggested that physical activity at a certain stage of disease might alter the motor neuron physiology in such a way as to influence its susceptibility to infection. The latter observation led to the evaluation of the effect of physical exercise during the preparalytic period (266, 267). In total 100 cases of poliomyelitis were reported, and it was found that physical activity of any kind during

the paralytic stage increased danger of severe paralysis. This observation was confirmed in epidemiological studies (98, 117) and experimental animal studies (117, 163).

B. Myocarditis

One reason why clinicians advise against performing vigorous exercise during acute infections is the potential of supervening myocarditis (79, 80). The effect of exercise in the acute phase of Coxsackie B virus myocarditis has been investigated in several experimental studies (85, 121).

Acute exercise causes increased viral replication, inflammation, and necrosis in the myocardium. Swimming during the initial phase of the infection with murine Coxsackie B₃ virus in 14-day-old mice increased mortality from 5.5 to 50% (85). Many of the affected mice died of congestive heart failure while swimming, with massive cardiac dilatation upon autopsy. Virtually every myocardial fiber showed pathological change as opposed to 25–50% of myocardial involvement when infection was not accompanied by swimming. Concomitantly, viral replication was enhanced by swimming. When swimming was initiated 9 days after virus inoculation (i.e., during phase of waning viral replication), mortality increased only 13.8% over nonexercised controls.

Mice were inoculated with Coxsackie B₃ virus and exercised to exhaustion up to 48 h after inoculation (121). Exercise at the same time as virus inoculation did not influence the myocardial damage, whereas exercise at 48 h after the inoculation increased the myocardial damage to almost 8%. In this study lethality was not influenced by exercise. The exercise-associated increased myocardial inflammation was related to a lower number of cells expressing MHC class II, such as macrophages. Thus the extent of tissue damage in these mice may be related to decreased macrophage mobilization followed by increased destruction of the myocardium, possibly mediated by cytotoxic T cells.

Myocarditis may result in either no symptoms, vague symptoms, or frank symptoms such as chest pain, discomfort, dyspnea, or irregular heart rhythm. The finding that myocarditis can occur without clinical symptoms is in line with the finding of active myocarditis in 1% of unselected autopsies performed during a 10-yr period (89). Sudden death in the acute phase of symptomatic or asymptomatic myocarditis is a well-known phenomenon (141), but sudden unexpected cardiac deaths in young sportsmen, attributable to myocarditis, account for only 10% of the fatalities.

Recently, Swedish orienteering has been struck by an accumulation of sudden deaths. In a case series study, 16 young Swedish orienteers suffered from sudden unexpected cardiac deaths from 1979 to 1992 (309). No sudden

unexpected deaths among young orienteers have occurred since 1992. Histopathological evaluation showed active myocarditis in five cases (309) and right ventricular dysplasia-like alterations in four cases; the remaining seven cases could not be classified into either of the previous groups. Tissue sampling that allowed testing for a variety of microorganisms was performed in only the two recent fatalities. In one of these cases, PCR with the primers directed to the rRNA gene of *Chlamydia pneumoniae* was found in the heart and lungs, but not in specimens from several other organs (309). All cultures and PCR for other microorganisms were negative.

It is not possible to explain the accumulation of deaths among Swedish orienteers. Such a death rate did not occur within other endurance sports in Sweden during the same period of time. *C. pneumoniae* is likely to be the cause of one of the cases who had suffered from prolonged respiratory tract infection before death and in whom active myocarditis was found. *C. pneumoniae* is a common pathogen, which normally causes upper respiratory tract infection (URTI) and eventually pneumonia. One theory is, however, that postexercise immunosuppression allows relatively harmless microorganisms such as Coxsackie B virus and *C. pneumoniae* to invade the host, actively replicate, and spread from the upper respiratory tract to the circulation, the lungs, and the heart. Therefore, relatively harmless microorganisms may have behaved as opportunists in these situations.

C. HIV Infection

The primary immunological defect in individuals infected with HIV is a depletion of the CD4+ T-cell subset (68, 69). However, conjoint effects have been reported on the function of other lymphocyte subpopulations, including the NK and LAK cells and cytokines (297, 299, 301).

In healthy subjects, exercise-induced alterations in the immune system include changes in BMNC, proliferative responses, as well as NK and LAK cell functions (113). A study (300) on acute exercise was designed to determine to what extent HIV-infected individuals were able to mobilize immunocompetent cells to the blood in response to a physical exercise challenge. The study included eight asymptomatic men infected with HIV and eight HIV-seronegative controls, who cycled for 1 h at 75% of $\dot{V}O_{2\max}$. The percentages of CD4+, CD4+45RA+, and CD4+45RO+ cells did not change in response to exercise, whereas the concentration of CD4+ cells increased twofold during exercise.

The level of CD4+ cells in the circulation has prognostic value for predicting the development of acquired immunodeficiency syndrome (AIDS) (268). However, increases in the concentration of CD4+ cells (the CD4 count) and CD4 percentage in response to treatment may not always reflect a better prognosis (155).

Interestingly, HIV-seropositive subjects were shown to possess an impaired ability to mobilize neutrophils and cells mediating NK cell activity. Furthermore, only seronegative persons showed increased LAK cell activity in the blood in response to exercise, whereas HIV-seropositive subjects did not (300).

The mechanisms behind the defective recruitment of cells to the blood are not fully understood but may include 1) an impaired stress hormone response (e.g., the increase in catecholamines and growth hormone during physical exercise may be lower in HIV-seropositive subjects), 2) low expression of β -receptors on the surface of NK cells, or 3) HIV-seropositive persons may simply have a smaller reservoir of cells available for recruitment (57).

There are only a few controlled studies on the effect of chronic exercise on the immune system in HIV-seropositive subjects. Despite significant increases in neuromuscular strength and cardiorespiratory fitness, there were no significant effects on the CD4 cell numbers or other lymphocyte subpopulations (257). Similar observations have been found in a number of other studies (21, 159, 168, 257). Lack of details about subject dropout is a limitation in several reports (e.g., Ref. 159). However, other studies reported 1 of 5 (29%; Ref. 21), 4 of 23 (17%; Ref. 257), and 19 of 25 (76%; Ref. 168) dropouts. Clinical deterioration in some patients may be a cause of the high dropout rates reported in training studies including seropositive patients. This would be a major source of bias and error.

Some of the studies have shown an insignificant increase in CD4+ T cells in patients that train. On the basis of these results, it has been concluded that training increases the CD4+ T cells in HIV-seropositive patients (160). This is a very important conclusion since it could lead to the acceptance of physical training as a treatment of HIV infection. However, no study has to our knowledge been able to show any significant effect of training on the CD4+ cell numbers in HIV-infected patients. There is a lack of studies on the effect of training on viral load as measured by plasma HIV RNA and β_2 -microglobulin. Furthermore, there are no data showing a beneficial effect of training on resting levels of lymphocyte proliferation and cytotoxic functions in HIV-seropositive individuals.

D. Upper Respiratory Tract and Other Infections

In the past decade there have been several comprehensive reviews of exercise and infections (37, 79, 213). In this section we briefly highlight those studies that extend our understanding of exercise effects on resistance to infections. In 1922 it was reported that 80% of sedentary guinea pigs ($n = 12/15$) died after exposure to type I pneumococcus, whereas animals given acute exercise before inoculation showed only a 20% fatality rate ($n = 3/15$)

(196). In contrast, swim exercise during the incubation period of *Toxoplasma gondii* did not significantly alter the disease outcome in mice (46).

Mice trained on running wheels and then injected with *Salmonella typhimurium* had a significantly higher survival rate than sedentary mice, and this was related to increased levels of IL-1 (41). Comparable results in trained mice that were infected by influenza virus at rest had a lower mortality rate (122). A 4-wk training program in rats with gradually increasing swimming time before infection with pneumococcus caused no protection from lethality; the catabolic response was less pronounced (123).

From these experimental studies it is clear that effects of exercise stress on disease lethality varies with the type and time that it is performed. In general, exercise or training before infection has either no effect or decreases morbidity and mortality. Exercise during the incubation period of the infection appears to have either no effect or increase the severity of infection.

In contrast to the limited experimental evidence, there are several epidemiological studies on exercise and URTI. These studies are based on self-reported symptoms rather than clinical verification. In general, increased number of URTI symptoms have been reported in the days after strenuous exercise (e.g., a marathon race) (99, 148, 207, 208), whereas moderate training has been claimed to reduce the number of symptoms (206, 212). However, in neither strenuous nor moderate exercise have these symptoms been causally linked to exercise-induced changes in immune function.

VII. EXERCISE AND CANCER

Physical activity is a primary strategy that has received little attention in cancer control, but an increasing number of epidemiological studies address the question of a possible influence of physical activity in occupation or during leisure time on the risk of cancer. In this section, we consider the possibility of whether exercise-associated changes in immune function contribute to risk modification for breast cancer specifically. It is beyond the scope of this review to consider physical activity mechanisms in all cancers.

The epidemiological evidence concerning breast cancer in women and the protective effect of physical activity have been reviewed elsewhere (77, 109, 110).

In line with previous reviews, we find that it is premature to make strong conclusions about the role of exercise in preventing breast cancer. However, regarding breast cancer, most studies showed either a protective effect of exercise (20, 103, 305, 316) or some evidence of borderline significance (78, 81), whereas few studies have shown no significant effect and no trend (284, 227) or a

trend toward increased incidence of breast cancer in physically active women (56).

The role of endogenous estrogens in the development of breast cancer has been under extensive scientific interest. Strenuous physical exercise decreases the estrogen level and is associated with delay in the onset of menses, and an increase in the number of anovulatory cycles. Exercise may thereby ultimately alter the lifetime exposure to estrogens.

It is not known if natural immune changes associated with exercise and training may have biological relevance for the development of breast cancer. It has been shown that exogenous β -estradiol increases tumor metastasis and natural immune suppression in mice. Adoptive transfer of normal spleen cells enhanced the NK cell activity and increased the resistance of estradiol-treated mice to tumor metastasis (97).

In animal studies, after 8 wk of forced treadmill exercise or voluntary wheel running, female BALB/c mice received an intravenous injection of MMT line 66 tumor cells; animals were then randomized into continuation of activity, cessation of activity, initiation of activity, and maintenance of sedentary condition for 3 wk (112). The LAK cell activity measured in vitro was enhanced in the trained compared with the sedentary animals. However, endurance training did not alter the development of tumor metastasis.

The MTT66 is a highly aggressive tumor cell line that is only partially LAK sensitive, and because IL-2 was not administered in vivo, the lack of significance was not surprising. Interestingly, it was found that tumor multiplicity was lower in animals trained (and then rested) before tumor inoculation than in animals that either continued exercise during tumor metastasis or that were sedentary throughout the study (110, 112).

In two other studies (173, 175), trained mice had higher in vitro NK cell activity, greater lung clearance of radiolabeled CIRAS tumor cells, and lower absolute tumor incidence. With the use of the beige mutant mouse (deficient in NK cells), exercise training resulted in greater clearance of the CIRAS fibrosarcoma cell line than mice who remained sedentary (125).

Exercise has been shown to enhance in vitro macrophage antitumor cytotoxicity (52, 312–314), but the number of metastases of a mouse mammary adenocarcinoma did not differ between control mice that were exercised 3 days before tumor injection and 14 days after (312–314).

In a recent review (110), it was concluded that for tumors that are insensitive to natural immune control, and for those that are highly aggressive, exercise may have little or even negative consequences. Thus the underlying mechanisms regarding influence of exercise training on breast cancer are likely to include tumor characteristics, host characteristics, exercise characteristics, and timing of exercise.

The theory that cancer may arise in a host under conditions of reduced immune capacity was first put forward in 1959 (287) and later developed in the theory of immune surveillance (33). Although this hypothesis in its original form has been abandoned, the role of the immune system in the neoplastic process was supported by observations in experimental animals (32). More recent animal data, however, have indicated that the immune system is involved primarily in malignancies of viral origin (150).

This is in accordance with the finding of increased incidence of specific cancers in patients with AIDS. These cancers are non-Hodgkin's lymphoma, Kaposi's sarcoma, anal cancer, and cervical cancer, which have all been shown to be of viral origin (162). Nevertheless, reports of patients with immune impairment caused by immunosuppressive treatment, as seen after kidney transplantation, show an excess of cancer where a viral etiology is not known (22). However, there is no reason to believe that the list of cancers caused by an infection is now complete. In recent years microorganisms have been linked to a couple of new cancers. Thus herpes virus type 8 has been identified as the cause of Kaposi's sarcoma (45), and gastric infection with *Helicobacter pylori* has been identified as a risk factor for gastric cancer (286).

With regard to the acute exercise effects on the immune response, it has been shown that natural immunity is enhanced during moderate exercise. However, the numbers and function of cells mediating cytotoxic activity against virus-infected and tumor target cells are suppressed after intense, long-term exercise (27, 75, 113, 246).

In accordance with the immune surveillance theory, it is therefore to be expected that moderate exercise protects against malignancy whereas exhaustive exercise is linked to increased cancer risk. To date there are limited data to support this theory. In a case control study (315), the risks of non-Hodgkin's lymphoma were only marginally higher in women as a function of greater levels of occupational physical activity; however, occupational physical activity measures did not capture high-intensity work and hence the findings may be biased to the null.

VIII. EXERCISE AND AGING

Given the shift in population demographics showing increased numbers of elderly individuals in most western countries, and their involvement in physical activities, it is important to know how the elderly respond to the stress imposed by exercise. This is important not only from a mechanistic point but also for public health reasons.

A. Aging, Acute Exercise, and Immune Function

Although few studies have been performed to date, recent evidence suggests that the ability of the immune

system in older individuals to respond to the stress imposed from a single bout of exercise is maintained with age. The effect of a single bout of exercise on immune function in young (23 ± 2 yr) and elderly (69 ± 4 yr) subjects showed that in response to exercise the young subjects had a decrease in PHA proliferative capacity (181). Both young and old subjects had an increase in the NK activity in response to exercise (51, 73). IL-1 β and TNF- α secretion can be increased the morning after exercise without any current changes in mononuclear cell numbers, indicating that the monocytes are activated in relation to eccentric exercise (42).

B. Aging, Chronic Exercise, and Immune Function

The effect of 12 wk of walking (5 days/wk at 60% heart rate reserve) was tested, and no effect on NK activity and T-cell function in previously sedentary elderly women (73 ± 1 yr) was found (206). T-cell function and NK activity were greater in a group of highly conditioned female endurance competitors (73 ± 2 yr) compared with age-matched sedentary controls (181, 272).

C. Animal Studies

Acute exercise produced a significant stimulation of antibody-dependent cellular cytotoxic capacity only in aged animals, whereas there was no difference in NK cell activity with regard to both young and old animals (71). Old Fischer 344 rats had a poorer antibody response than young animals; however, exercise training did not influence the antibody production to specific antigen (12). An age-related decline in rats for both unstimulated and mitogen-stimulated lymphocyte proliferation and in IL-2 synthesis has also been recorded (228).

Mitogen-induced proliferation and IL-2 production were found to decrease significantly with age in both trained and untrained animals (189). Training significantly reduced proliferation and IL-2 production in younger animals (167, 189). However, the proliferative response and the IL-2 production were found to increase in response to training in the old animals compared with the age-matched controls. The NK cell activity declined significantly with age, and training did not alter this response.

Thus immunocompetent cells are mobilized to the circulation in the elderly during an acute bout of exercise. The ability of the immune system to respond to a single bout of exercise seems to be maintained in the elderly, but there is little information about the function and phenotype of the cells that are mobilized in response to exercise in old versus young individuals. It is not possible to conclude whether an endurance training program alters age-related declines in immune function. The major reason for this uncertainty is related to the scarcity of

data addressing the issue of exercise and immune function in the elderly. There is especially a lack of human studies. The available amount of data suggest that although age-related decline in immune function can be retarded, the greatest effect will be seen only in very highly conditioned subjects (27).

IX. EXERCISE, METABOLISM, AND IMMUNE FUNCTION

The mechanisms underlying exercise-associated immune changes are multifactorial and include multiple neuroendocrinological factors. Alterations in metabolism and metabolic factors contribute to exercise-associated changes in immune function. Reductions in plasma glutamine concentrations due to muscular exercise have been hypothesized to influence lymphocyte function (195). Altered plasma glucose has also been implicated in decreasing stress hormone levels and thereby influencing immune function (213). Furthermore, as a consequence of the catecholamine- and growth hormone-induced immediate changes in leukocyte subsets, the relative proportion of these subsets changes, and activated leukocyte subpopulations may be mobilized to the blood. Free oxygen radicals and prostaglandin released by the elevated number of neutrophils and monocytes may influence the function of lymphocytes and contribute to the impaired function of the later cells. Thus nutritional supplementation with glutamine, carbohydrate, antioxidants, or prostaglandin inhibitors may in principle influence exercise-associated immune function.

A. Glutamine

It has generally been accepted that cells of the immune system obtain their energy by metabolism of glucose. However, it has been established that glutamine is also an important fuel for lymphocytes and macrophages (195). Several lines of evidence suggest that glutamine is used at a very high rate by these cells, even when they are quiescent (194). It has been proposed that the glutamine pathway in lymphocytes may be under external regulation, due partly to the supply of glutamine itself (194).

Skeletal muscle is the major tissue involved in glutamine production and known to release glutamine into the bloodstream at a high rate. It has been suggested that the skeletal muscle plays a vital role in maintenance of the key process of glutamine utilization in the immune cells. Consequently, the activity of the skeletal muscle may directly influence the immune system. According to the "glutamine hypothesis," under intense physical stress, such as exercise, the demands on muscle and other organs for glutamine are such that the lymphoid system may be forced into a glutamine debt. Thus factors that directly

or indirectly influence glutamine synthesis or release could theoretically influence the function of lymphocytes and monocytes (193, 194). After intense long-term exercise and other physical stress disorders, the glutamine concentration in plasma declines (66, 144, 161, 233), and low glutamine levels have been reported to be associated with overtraining (264, 265).

Although there is evidence that glutamine has an important role in lymphocyte function *in vitro*, recent placebo-controlled glutamine intervention studies (259, 260) found that glutamine supplementation after the exercise abolished the postexercise decline in plasma glutamine without influencing postexercise immune impairment. Thus there is little experimental support to the hypothesis that postexercise decline in immune function is caused by a decrease in the plasma glutamine concentration.

B. Glucose

Given the link between stress hormones and immune responses to prolonged and intensive exercise (237), carbohydrate compared with placebo ingestion should maintain plasma glucose concentrations, attenuate increases in stress hormones, and thereby diminish changes in immunity. This hypothesis has been tested in a number of studies (184, 191, 205, 210, 211) using double-blind, placebo-controlled randomized designs. Carbohydrate beverage ingestion before, during, and after 2.5 h of exercise was associated with higher plasma glucose levels, an attenuated cortisol and growth hormone response, fewer perturbations in blood immune cell counts, lower granulocyte and monocyte phagocytosis and oxidative burst activity, and a diminished pro- and anti-inflammatory cytokine response. However, carbohydrate ingestion has not been shown to abolish postexercise immune impairment, and the clinical significance remains to be determined.

C. Lipids

It has been suggested that if the *n-6/n-3* ratio is shifted in favor of *n-6*, this will result in increased production of prostaglandin (PGE) and cellular immune suppression. Thus, during stress conditions, *n-3* fatty acids may counteract latent immunosuppression. Under the condition of hypermetabolism, *n-3* fatty acids therefore potentially act to reduce the incidence of new infections. In animal experiments it was shown that the stress response following application of endotoxin, IL-1, or TNF was reduced when the animals were pretreated with *n-3* fatty acids (fish oil) (129).

The possible interaction between intense acute exercise, immune function, and polyunsaturated fatty acids

(PUFA) was examined in inbred female C57Bl/6 mice (16). The animals received either a natural ingredient diet or a diet supplemented with various oils such as beef tallow, safflower, fish oil, or linseed oil for an 8-wk period. In the group receiving 18:3 (*n-3*) linseed oil, it was shown that linseed oil abolished postexercise immunosuppression of the IgM plaque-forming cell response.

Thus the effect of linseed oil may be ascribed to a link between a diet rich in *n-3* PUFA and abolishment of prostaglandin-related immunosuppression. In support of this hypothesis, it has been shown that when the PGE₂ production was inhibited by the prostaglandin inhibitor indomethacin, exercise-induced suppression of the NK cell activity and B-cell function was partly abolished (245, 292). The possibility that *n-3* fatty acids may diminish the exercise-induced cytokine response has not been investigated.

D. Antioxidants

Antioxidants may in theory neutralize the reactive species that are produced by neutrophilic leukocytes during phagocytosis and as part as normal cellular respiration (6, 102). There is limited evidence of the role of exogenous antioxidants (vitamin C, vitamin E) in modulating immune function in exercise and virtually no evidence on endogenous antioxidants. With the use of a double-blind placebo design, the effect of vitamin C on the incidence of URTI during the 2-wk period after an ultramarathon has been evaluated (249). Vitamin C was reported to reduce the number of symptoms of URTI when supplementation began 3 wk before the race. The same group (248) found that vitamin A supplementation had no effect on the incidence of self-reported symptoms in marathoners. Vitamin C supplementation (204) had no effect on lymphocyte function and stress hormone levels.

Multiple endocrine and metabolic factors are involved in the exercise-induced immune changes (237). Furthermore, altered temperature and oxygen desaturation may play a mechanistic role (138, 152). Therefore, in our opinion, it is unlikely that a single nutrient supplement will have physiologically relevant effects on exercise-induced immune modulation.

X. CONCLUSION

In the last decade, there has been a remarkable increase in the number of descriptive studies on exercise and the immune system. The available evidence shows that exercise has important modulatory effects on immune dynamics and possibly on immune function. These effects are mediated by diverse factors including exercise-induced release of proinflammatory cytokines, classical stress hormones, and hemodynamic effects leading

to cell redistribution. The nature of the interactions is complex, with modification in expression of cell adhesion molecules, selective recruitment of mature but not naive lymphocytes, and alterations in apoptosis and in mitotic potential to identify but a few of these mechanisms. As molecular techniques are incorporated into studies of exercise immunology, greater understanding of the pathways of cell activation and regulation should be forthcoming.

XI. FUTURE PERSPECTIVES

For the past decade, there have been many studies describing a variety of immune system consequences of endurance and resistance exercise. The focus of future work in exercise immunology should move beyond descriptive, phenomenological studies to studies of underlying neural, hormonal, cytokine, and biochemical mechanisms for the observed effects. For instance, acute exercise is accompanied by the generation of highly reactive oxygen species (ROS) that may contribute to lymphocyte damage, lymphocytopenia, and altered immunity. The source of the ROS may be activated neutrophils arising from inflammatory events in damaged muscle or may occur from other pathways. Evaluation of exercise-associated hormone- and cytokine-receptor binding to lymphocytes with opening up of calcium gates and phospholipase degradation of membrane phospholipids might be considered as a source of ROS. Alternatively, consideration of the biochemistry of xanthine oxidase reactions through exercise-induced ATP degradation or of mitochondrial uncoupling due to exercise-induced hyperthermia is also a pathway to consider in the generation of ROS and subsequent lymphocyte damage.

Unusual models to test the eccentric exercise-muscle damage hypothesis are another direction to consider in exercise immunology. Use of genetically modified mice, such as the Rag2-deficient mouse, may be useful in partitioning the neutrophil events in damaged muscle from later inflammatory changes arising from activated lymphocytes and macrophages. The use of mutant and transgenic rodents will be essential to determine mechanisms for the inflammatory changes with exercise and the natural course of resolution of these events.

Molecular biological techniques are being introduced into exercise immunology. These methods may allow us to identify the source of cells producing the high amounts of cytokines in response to muscle contractions and to identify the role of these in repair and muscle growth. It is also time to move from small-scale studies evaluating the effect of exercise on surrogate immune markers to go for large-scale studies evaluating the effect of moderate physical exercise on clinical outcome in various groups, including the elderly and patients with immune disorders or malignant diseases.

We thank Professor Bengt Saltin, The Copenhagen Muscle Research Centre, for critical review of the manuscript.

Preparation of this manuscript was supported in part by Danish Research Foundation Grant 514 and by research grants from the Natural Sciences and Engineering Research Council of Canada.

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