Review

Potential impact of physical activity and sport on the immune system – a brief review

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Description is given of methods that can evaluate the main functional elements of the immune system. Acute responses to exercise depend on the intensity and duration of the required activity relative to the individual's fitness level. Moderate endurance exercise causes either no change or an enhancement of such indices as total leucocyte count, granulocyte, monocyte, lymphocyte and natural killer cell count, total T cell count, helper:suppresor cell ratio, cell proliferation in response to mitogens, serum immunoglobulin levels, and in vitro immunoglobulin production. However, exhausting exercise tends to produce adverse changes in these same indices, particularly if the physical activity is accompanied by environmental or competitive stress. Moderate, appropriately graded training reduces reactions to any given absolute intensity of exercise. When pursuing a more demanding training regimen, it is important that the exerciser optimize immune responses. If athletic preparation is pursued to the level of staleness and/or muscle damage, it can have substantial negative implications for many aspects of immune function, including resistance to acute infections, HIV infections, ageing, cancer and other conditions influenced by the immune system.

Keywords: exercise, training, leucocytosis, antibodies, immunoglobulins, infection, lymphocytosis, overtraining, staleness

The immune system comprises specific and nonspecific defences against foreign materials (Table 1). Specific mechanisms comprise innate and adaptive or acquired components[1,2]. The innate defence system, always ready for action, includes various cellular elements – natural killer cells and various types of phagocyte (neutrophils, eosinophils, basophils, monocytes and macrophages), together with several important soluble factors: acute phase proteins; complement; lysozymes; and interferons. The adaptive system has the ability to acquire a response to specific antigens. It comprises specific cells (the T and B lymphocytes) and soluble factors (the immunoglobulins).

Methods of evaluating exercise responses of the immune system

The overall effect of exercise on the immune system can be examined by charting a subject's response to innoculations or overall susceptibility to infections. Individual elements of the system can be evaluated by making differential blood counts, testing lytic activity, measuring the extent of cell proliferation or of immunoglobulin synthesis in response to cytokines or external mitogens, and assaying cytokines or cytokine receptor densities (Table 2).

Susceptibility to infections

Susceptibility to infection can be tested by innoculating subjects with a standard dose of a relatively harmless virus such as that for the common cold, but problems arise from rapid mutations of the virus and thus a loss of immunity. It is also possible to look at antibody production following injection of a sterile toxoid such as tetanus or Mérieux Multitest (Mérieux, Lyon, France).

Epidemiologists have linked the incidence of specific infections to bouts of heavy training or strenuous competition, but it is important to remember that exercise can modify the risk of infection through mechanisms other than a change of immune function[3,4]. For example, the activity may cause exposure to contaminated air or water, the function of tracheal cilia may be depressed by the oral inspiration of cold or polluted air, or the chances of illness may be altered by a change in the subject's lifestyle[3].

Differential blood counts

The white cell population comprises polymorphs (neutrophils, basophils and eosinophils), and mononuclear cells (monocytes, lymphocytes and plasmocytes, the last being progeny of B lymphocytes). Various subpopulations can be identified, using monoclonal antibodies (Table 1). Total and differential white cell counts give some indication of the functional status of the immune system, but many other factors modify readings during vigorous exercise.

Table 1. Main elements of the immune system[1,2]

Innate components	Adaptive components
Cellular Natural killer cells (CD 16+, CD56+) Phagocytes (neutrophils, eosinophils, basophils, monocytes, macrophages)	*Cellular* T cells (CD3+, CD4+, CD8+) B cells (CD19+, CD20+, CD22+)
Soluble Acute phase proteins Complement Lysozymes Cytokines (interleukins, interferons, colony-stimulating factor, tumour necrosis factors)	*Soluble* Immunoglobulins IgG, IgA, IgD, IgE, IgM Memory

A partial listing of extraneous influences which may modify peripheral leucocyte counts during vigorous activity includes: (1) a decrease in blood volume; (2) an increase in cardiac output that leads to a demargination of previously sequestered cells; (3) an activation of adrenoreceptors that reduces the attachment of leucocytes to the endothelium for any given level of circulating catecholamines; (4) autonomic nerve activity that leads to a release of catecholamines and cotransmitters; and (5) cortisol secretion that induces a release of granulocytes from bone marrow[1,2].

Analysis is complicated because a large fraction of the total leucocyte count is normally outside the circulation. The numbers and location of noncirculating leucocytes can be tracked by the injection of radiolabelled autologous cells. Noncirculating neutrophils are found in the liver, spleen and lungs, whereas the noncirculating lymphocytes are localized mainly in the liver and spleen. Exhausting running increases the circulating count of immature neutrophils 17-fold, showing that noncirculating cells have been washed into the general circulation. In humans, exercise has little influence on the size of the spleen, and splenectomy also has little influence on the exercise-induced leucocytosis; changes of total leucocyte or lymphocyte count reflect mainly a mobilization of cells from the liver[2].

Lymphocytes carry the main responsibility for cell-mediated immune function. They were classically subdivided into T cells (coded in the thymus in response to both specific allergens and nonspecific mitogens), B cells (maturing in the bone marrow), and null cells. The T cells were originally distinguished because they formed 'rosettes' with sheep red cells; the B cells were identified by a characteristic surface immunoglobulin, and the null cells had neither characteristic.

Differential cell counting has become much easier with the development of automated flow cytometers and fluorochrome-labelled monoclonal antibodies that are specific for each of the various surface antigens (*Table 1*). Cell subpopulations are identified with greater certainty, and the accuracy of counts is much increased because many more cells can be counted. The simplest classification of T cells[1,2] identifies helper cells with a characteristic (CD4) surface antigen, the suppressor cells (with a CD8 surface antigen) and cytotoxic T cells (with both CD3 and CD56 antigens). The helper T cells recognize foreign antigens on the surface of antigen-presenting cells such as monocyte macrophages. The macrophages release the cytokine interleukin-1 as a second local (paracrine) signal to activate helper T cells. The activated helper T cells then produce another lymphokine, interleukin-2 (IL-2). The IL-2 synergizes with interferons to increase T cell activity still further. It also stimulates the helper T cells to secrete another lymphokine (IL-3). This last substance initiates the despatch of a signal to the cytotoxic T cells; they in turn recognize the foreign surface constituents of abnormal or virus-transformed cells, and initiate the destruction of these abnormal cell constituents. The helper T cells also activate the B lymphocytes; these then proliferate and differentiate into plasma cells, with a resultant release of antibodies. The suppressor T cells provide a negative feedback that controls the extent of helper T cell action. The ratio of helper to suppressor cells is critical from the clinical viewpoint; if the ratio drops below 1.5, then immune function is impaired and susceptibility to infections is increased[1,2].

Natural killer (NK) cells are an important subgroup of null cells, serving as a first (innate) line of defence. They recognize and destroy certain tumour cells and some virus-infected cells without the need for prior activation by recognition of abnormal antigens on cell surfaces. However, their activity is increased by various soluble factors such as interleukins (IL-1, IL-2), interferons and growth hormone. Monocyte macrophages and NK cells also migrate selectively to injured muscle, assisting in the repair process. Natural killer cells can be identified and counted using fluorescent antibodies specific to the CD16 and CD56 surface markers. The overall NK

Table 2. Main methods of evaluating immune function[2]

Response to innoculations:
  rhinovirus, tetanus toxoid, Mérieux Multitest
Epidemiology of infections and of related symptoms
Weight of lymphoid organs (animals only)
Differential blood counts
Lysis of radiolabelled tumour cells
Cell proliferation rates (spontaneous, cytokines, mitogens)
Immunoglobulin levels (plasma, saliva)
Immunoglobulin synthesis (plasma, *in vitro*)
Cytokine levels (bioassay, radioimmunoassay, ELISA, mRNA)
Cytokine receptor density

ELISA, enzyme-linked immunosorbent assay; mRNA, messenger RNA

activity can also be assessed by *in vitro* radioactive chromium-release assay, as the NK cells lyse human myeloid tumour cells (K-562) in the absence of cytokine stimulation. An increase in NK activity can reflect either an increase in NK numbers, or an increase in the activity of individual NK cells.

Cell proliferation

If lymphocytes are incubated with tritiated thymidine, the radioactive material becomes incorporated into the DNA of newly formed cells. By measuring their radioactivity in a scintillation counter it is possible to examine how the spontaneous proliferation rate is modified by exercise, training, and nonspecific activators such as antigens, cytokines, hormones and neuropeptides.

More commonly, the rate of cell proliferation is assessed *in vitro*, whole blood or washed peripheral blood mononuclear cells being incubated with nonspecific mitogens like the plant lectins concanavalin A (Con A) or phytohaemagglutinin (PHA). If whole blood samples are used, the responses to PHA are reputedly resistant to oral cortisone, whereas responses to Con A are suppressed by cortisone. These plant-derived mitogens act on receptor sites that differ from the receptors for specific antigens. The lectins induce a nonspecific multiplication of all subsets of T cells that can be used to test the impact of exercise and training upon this type of lymphocyte. The main practical problem with such an assay is that the response varies enormously with mitogen concentration. Tests are thus replicated, using a range of mitogen concentrations in order to find an optimal dose[1,2]. The reproducibility of a given subject's response is further enhanced by a preliminary 12-h fast.

Immunoglobulin synthesis

Changes in plasma or salivary concentrations of immunoglobulins do not necessarily reflect corresponding changes in immunoglobulin synthesis. The concentrations in body fluids can be affected by such factors as receptor binding, haemoconcentration, catabolism, and the migration of protein between the blood and other fluid compartments; salivary concentrations are also influenced by the rate of saliva secretion.

IgG is the most prevalent class of immunoglobulin. It includes antibacterial, antiviral and antitoxic antibodies, together with potent opsonins that enhance phagocytosis. Macroglobulins (IgM) are found not only in the cytoplasm, but also on the surface of B cells in the early stages of their maturation. They are the first group of antibodies to be produced by the plasma cells that develop from activated B cells. Examples include cold agglutinins and haemagglutinins. Other types of immunoglobulin include IgA, IgD and IgE. The ability of the plasmocytes to produce immunoglobulins can be assayed *in vitro*, using antihuman IgG and IgM after incubation of peripheral blood mononuclear cells with a nonspecific mitogen such as pokeweed, which activates both T cells and B cells.

Table 3. Typical responses of immune system to acute exercise[1,2,37]

Leucocyte count	Early increase (during exercise), fall immediately after exercise, final rise
Monocyte count	Increase, during and following exercise
Lymphocyte count	Sometimes increased (both T and B cells) during and following exercise; usually decrease of helper:suppressor cell ratio during and immediately after exercise, with late rise. Increase of cytotoxic cells. Increased expression of IL-2 β-receptors
NK cells	Early increase of NK count and activity. Later, prolonged fall of both count and activity, especially if exercise prolonged and heavy
Cell proliferation rates	Unchanged by moderate exercise, depressed by heavy exercise
Immunoglobulins	Levels in body fluids and *in vitro* synthesis both decreased by exhausting exercise
Soluble factors	C-reactive protein, IL-1 and interferon increased by moderate exercise. IL-2 production and plasma levels decreased immediately, but late rise. Decrease of serum complement if muscle damage

Responses of the immune system to an acute bout of exercise

Although exercise induces quite marked acute responses in many components of the immune system, these responses are normally transient, and it has thus been questioned how far such changes can have an impact upon defence reactions against bacteria, viruses and neoplastic cells[2]. Because analyses are time consuming, many investigators have collected very few blood samples, and if blood sampling is delayed for 30 min after exercise, the study may show only a rebound phenomenon, with the selected measure of immune function actually exceeding pre-exercise levels.

Unfortunately, it is also difficult to generalize (*Table 3*). Responses seem quite variable from day to day and from one person to another. Factors modifying the reactions of the immune system include the intensity of effort that is undertaken relative to the individual's state of training, the duration of exercise (short-term activity mobilizes sequestrated cells, whereas longer bouts of activity lead to their escape into the tissues), and associated competitive and environmental stresses. The reported results also depend on the methods that are used to assess immune function[2].

Leucocytosis and lymphocytosis

Early studies reported simply total white cell or lymphocyte counts. Acute exercise provokes an increase of peripheral venous leucocyte count that is roughly proportional to the intensity and duration of activity. However, if the activity is very prolonged, total leucocyte counts may decrease because monocytes and NK cells are migrating into injured muscle. A delayed leucocytosis may be seen 30 min to 3 h

following strenuous exercise, due to a cortisol-stimulated release of white cells from the bone marrow. The late leucocytosis may persist for several hours after a marathon run, but recovery is usually complete within 6 h of more moderate exercise. Much of the late increase in white cell count is due to granulocytes and especially to neutrophils. The response is most marked in subjects with a high physical working capacity. The eosinophil count is decreased, and there is little change in the basophil count. The functional significance of these responses remains unclear, but nonspecific immunity may be enhanced[2].

The monocyte count increases substantially during or immediately after exercise, and there is also some increase in the number of lymphocytes at this stage. Some reports have suggested that the response depends on the type of exercise that the subject performs, cycle ergometry giving a larger lymphocytosis than treadmill exercise. Other intertrial differences reflect the timing of blood sampling relative to the bout of exercise. Because of the technical demands of nonautomated cell-counting, early investigations used a relatively small number of blood samples, and the recovery of immune function is often complete within 30 min of ceasing exercise[1,2].

At least two groups of hormones contribute to these changes in cell counts. In the early stages of exercise, catecholamine secretion stimulates the release of lymphocytes from the endothelia of venules, the process of 'demargination'. Later, as exercise continues, cortisol secretion induces an overall leucocytosis, stimulating the release of granulocytes from bone marrow. However, it also inhibits the entry and facilitates the egress of lymphocytes from the circulation. Some of the lymphocytes probably enter muscle tissue along with monocytes and NK cells, facilitating repair processes. Others move to lymphoid tissue, where they have a greater likelihood of encountering macrophages and other antigen-loaded cells.

Lymphocyte subsets

Older studies using nonspecific markers suggested that the proportion of B cells increased with exercise. However, the early investigators were unable to distinguish clearly between B cells and natural killer cells. This is an important source of error when reporting B cell counts, because NK counts are known to increase markedly with exercise, and the detail in such reports must be questioned.

Nevertheless, modern monoclonal antibody techniques show increases in the absolute numbers of both T and B cells immediately following a 15–30-min bout of submaximal exercise. The relative changes in the percentages of T and B cells have varied from one investigation to another, depending on methodology, on the intensity of effort and the fitness of the subjects. In general, there is a small decrease in the proportion of B cells immediately after 30 min of vigorous submaximal treadmill exercise.

The ratio of helper to suppressor cells has a critical influence upon susceptibility to infection. Berk et al.[5] found no change in the overall percentage of T cells

following maximal treadmill exercise. Nevertheless, the helper:suppressor ratio dropped transiently from 1.94 to the unsatisfactory level of 1.36. Werle et al.[6] had essentially similar findings, commenting that strenuous exercise increased the sensitivity of T cell β-adrenoreceptors (by 121% on the helper T cells, and 80% on the suppressor T cells). Some authors have found an increase, and others a decrease in the overall percentage of T cells during exercise, but most investigators have confirmed the early decrease in the helper:suppressor cell ratio[1,2]. Exercise also seems to increase the numbers of cytotoxic T cells. During the later phases of recovery, and continuing for 24 h following exercise, the helper:suppressor cell ratio is elevated, due mainly to a cortisol-induced reduction in the number of suppressor cells[7]; possibly, this may compensate for suppression of natural killer cell activity (see below).

Intercell differences in the number of β-adreno-ceptors, and thus sensitivity to exercise-induced secretion of catecholamines may contribute to the lymphocyte subset changes during and following exercise. B cells have almost three times as many such receptors as T cells, and the T helper cells also have four times as many receptors as the T suppressor cells. There is further a potential for up- or down-regulation of the system, since the density of the lymphocyte β-receptors is modulated by habitual blood levels of catecholamines and cortisol, and also by training.

Natural killer cell numbers and activity

Edwards et al.[8] found that 5 min of stair-running caused an immediate four- to five-fold increase in the number of natural killer cells, and an increase of overall NK activity (based upon chromium release from labelled myeloid tumour cells). Other authors have further documented an early increase of NK cell numbers and/or percentages during moderate bouts of exercise. A catecholamine-mediated decrease of cell margination may contribute to the increased count of NK cells. However, there remains a need to define the intensity and duration of exercise inducing such effects.

Exercise also induces an immediate increase in the proportion of killer cells that are activated. Hanson and Flaherty[9] noted that the cytotoxic activity of NK cells was enhanced both immediately and 24 h after participating in a 12.8-km run. Likewise, Hirsen and Malham[10] reported that antibody-dependent cell-mediated cytotoxicity (ADCC) was increased 30 min after a bout of treadmill exercise, and Mackinnon et al.[11] found a 40% increase of NK activity 1 h after exercise. Unfortunately, the long-term impact of strenuous exercise upon the natural killer cells seems to be less favourable. Berk et al.[12] reported a 31% decrease in NK cell activity 1 h 30 min after an exhausting 3-h marathon run; there was a 50% decrease in the number of cells bearing the NK-specific CD16 antigen, but no change in the number of cells bearing the CD56 antigen, which is common to NK and cytotoxic T cells. Shek and associates[13] and Shinkai et al.[14,15] have also described a prolonged suppression of NK cell activity following a sustained

exercise bout. Shek et al.[13] found that a substantial depression of both NK counts and NK activity persisted for at least a week following a single 90–120 min of exercise at 65% of maximal oxygen intake. However, their important findings have yet to be replicated in other laboratories.

The early increase of cell activity is inhibited by the endorphin inhibitor naloxone, suggesting that endogenous opioids may serve as mediators of the initial stimulation of the natural killer cells. If so, an exercise bout would probably need to be quite vigorous, since moderate activity has little influence upon endorphin secretion. Exercise-induced changes in the concentration of the interleukins and interferons may also alter the surface properties of NK cells, and thus their lytic activity. NK activity is negatively correlated with serum cortisol levels, so that a large surge of cortisol secretion probably contributes to the late suppression of NK activity. Prostaglandins released from monocytes may also contribute to the sustained late reduction of NK cell activity[13]. If so, the adverse impact of prolonged or repeated bouts of heavy exercise might be countered by the administration of indomethacin.

Cell proliferation responses

Responses of the T cells to mitogen stimulation commonly differ from what might be inferred from helper:suppressor cell ratios, so that inferences about the acute effects of exercise upon immune function depend upon the assessment method that is used[16]. A 5-min bout of stair-running, a 30-min bout of submaximal treadmill exercise, and distance running all have little effect on the response of peripheral blood mononuclear cells to mitogens, although an increase in mitogen-induced cell proliferation has been reported after 15 min of cycling or a maximal cycle ergometer test[1,2].

In vitro determinations are usually based upon culturing a fixed number of cells per culture plate. Because exercise induces a lymphocytosis, if proliferation is expressed as a percentage of the total number of lymphocytes examined, a decreased response to mitogen stimulation might be inferred following either brief or more prolonged bouts of exercise, even though the proliferative response per unit volume of blood is increased. Nevertheless, changes in lymphocyte counts do not fully account for the changes in immune responsiveness; for example, Gmünder et al.[17] noted a 70% decrease of the in vitro response to Con A immediately after a marathon run, even though lymphocyte counts were unchanged.

Some studies have used whole blood specimens, and others isolated and washed peripheral blood monocytes[16]. The whole blood approach introduces the complication of humoral factors that could modify the proliferative response, whereas washing may lead to a differential loss of certain subpopulations of cells. In some early studies, another technical problem was a failure to distinguish the different types of mononuclear cell clearly. An apparent decrease of T cell proliferation could arise after exercise, if at this stage a larger proportion of the total lymphocyte count was attributable to nonproliferat-

ing NK cells. However, differences in technique cannot explain all of the discrepancies. For example, Hedfors et al.[18] saw an exercise-induced decrease in responsiveness to mitogens, even when using highly purified lymphocytes.

The time course of any reduction in cell proliferation is not clear-cut. We sampled peripheral blood 5 and 30 min following a 30-min bout of exercise at 80% of maximal oxygen intake, and we saw no significant change of lymphocyte proliferation rates in response to this intensity of activity[7]. Vishnu-Moorthy and Zimmerman[19] also found a normal in vitro responsiveness to PHA 10–15 min after a 32-km race. On the other hand, Eskola et al.[20] noted a 40% suppression of proliferative response to both mitogen and antigen stimulation 30 min after a marathon run, with incomplete recovery at 3 h.

Immunoglobulin synthesis

Hanson and Flaherty[9] observed no change in serum immunoglobulin levels 10 min after a 13-km submaximal run, but concentrations in serum, saliva and nasal secretions have generally decreased following prolonged, exhausting activity, with the recovery process sometimes extending over as long as 4 days. Most authors have inferred a corresponding suppression of immunoglobulin production[1,2].

Eskola et al.[20] observed a normal in vitro production of tetanus antibodies 30 min after completing a marathon race. In contrast, Hedfors et al.[18] reported that even 15 min of submaximal exercise was sufficient to decrease the pokeweed-stimulated production of IgG and IgM. More recently, we saw an increase in pokeweed-stimulated IgG production in vitro 5 min after well-trained distance runners had completed a 30-min bout of submaximal treadmill exercise.[7] Such discrepancies reflect differences in the amount of exercise performed, the timing of sampling and the level of training of the subjects; moreover, Hedfors et al.[18] used a whole-blood culture methodology.

Soluble factors

Soluble components of the immune system include C-reactive protein (CRP), interleukins and interferons. Responses to such factors may be altered not only by changes in their absolute concentrations, but also by exercise and training-induced modifications in the type and receptor structure of circulating lymphocytes[1].

Acute local muscular reactions to a bout of severe exercise increase concentrations of CRP, causing macrophages to migrate into the injured tissue. The CRP can in turn activate complement, which reacts with antibodies to form opsonins, substances that enhance macrophage function. Serum complement levels may be decreased after 1 to 2 h of recovery, as cells migrate into damaged tissues and the process of phagocytosis is initiated[1].

Interleukins activate macrophages, T cells and natural killer cells, and are a key step in the chain of events leading to production of immunoglobulins by the B cells. The plasma levels of interleukin-1 are

increased during and following endurance exercise. IL-2 levels fall immediately following strenuous activity, in part because of reduced secretion rates by peripheral blood mononuclear cells[21], and in part because of increased IL-2 receptor activity. However, IL-2 levels are increased 24 h after exercise, apparently as a response of macrophages to muscle damage. Immediately following sustained submaximal exercise, there is a 200% increase in IL-2 β-receptor activity, with a return to normal levels 30 min after exercise; serum IL-2 receptor activity also rises as the cytokine combines with the T-cell receptors[21].

Interferons are produced by certain types of activated T cells, and by cells that have become virally infected. They induce viral resistance in uninfected cells. Plasma α-interferon is apparently increased following exhausting exercise, possibly because the products of muscle injury stimulate interferon release[1].

Status of immune system after endurance training

Cross-sectional comparisons

Cross-sectional comparisons between trained and untrained animals, or endurance athletes and sedentary subjects have the advantage that training has been prolonged, and the individuals concerned have had adequate opportunity to adapt to the physical demands of heavy work. When making such cross-sectional comparisons between the immune responses of endurance athletes and sedentary subjects, it is important to distinguish the relative intensity of any exercise that is performed, to allow for the stresses of concurrent competition and heavy travel schedules, and to ensure adequate recovery from recent training sessions.

In the absence of 'overtraining', the resting immune status of athletes is generally normal (Table 4), although some studies have seen a granulocytosis, a lymphocytosis, an increase in antibody-dependent cytotoxic and NK cell activity, and increases in plasma IL-1 and IL-2 activity. At any given absolute work-rate, the leucocytosis is less in athletes than in sedentary subjects, but if sedentary and athletic groups are both stressed maximally, or at a comparable fraction of maximal effort, the leucocytosis seems comparable in the two groups. There are no essential differences in overall T cell or subset responses to exercise between trained and untrained human subjects. Data on mitogen responsiveness is conflicting[1,2].

Phagocytic activity may be poorer in athletes while they are actively training. Liesen et al.[22] commented that relative to healthy untrained men, athletes who were participating in basic, controlled intensity training showed lower total lymphocyte, T, T helper and NK cell counts, as well as a lower CD4:CD8 ratio in their resting blood samples. Oshida et al.[23] also noted that while exercise invariably decreased the percentage of lymphocytes that were T cells and T helper cells, the percentage of T suppressor cells was markedly increased in trained athletes. However, they observed an increase of NK count, a finding

Table 4. Modifications of immune system induced by endurance training[1,2,37]

Leucocyte count	No change at rest
	Smaller response at given level of exercise
Granulocyte count	No change of resting level
Monocyte count	Decreased phagocytosis if training hard
Lymphocyte count	No change in resting T cells or subsets. (decreased T and T helper cells if training hard, both in rest and exercise)
NK cells	Increased resting NK activity with moderate training, decreased if training hard
	Increased expression of IL-2 β receptors
Cell proliferation rates	Resting proliferation rates increased by training
	Heavy training decreases proliferation during exercise
Immunoglobulins	Increased by moderate training
	Lower resting immunoglobulins if training hard
	Hard training also reduces in vitro synthesis
Soluble factors	Increase of IL-1
	Less suppression of IL-2 production during exercise
	Decrease of complement if training hard

recently duplicated by Rhind et al.[21]. The increase of NK count in athletes also seems linked to an increase in the number of cells carrying markers of the 70–75 kDa β-receptor for IL-2 (but not the p55 IL-2 α-receptor).

Tomasi et al.[24] found lower resting salivary IgA levels in élite cross-country skiers than in controls, although this may have reflected incomplete recovery from previous exercise. Readings were further decreased by 2–3 h of exhausting skiing, although interpretation of this data is complicated by alterations in the volume of saliva secreted. Some other authors have also noted low serum immunoglobulin levels in élite performers, but most authors have found either no change or even an increase of immunoglobulin readings in response to more moderate training, particularly if care has been taken to allow for the training-induced expansion of plasma volume.

Nieman et al.[25] observed that complement levels during and following exercise were lower in marathoners than in age-matched controls. They speculated that the demands of repeated distance running may have overloaded the liver's ability to synthesize complement, although alterations of blood volume, the catabolism of amino acids such as glutamine in response to glycogen depletion, and immediate repair reactions in damaged muscle could also have contributed to this finding. Athletes also have lower serum levels of C-reactive protein than controls, probably because of the chain of events induced by muscle injury.

Longitudinal training studies

The response to deliberate training depends on the intensity, frequency and duration of the applied regimen, and on the initial condition of the indi-

vidual. A number of reports concern training that has been pushed almost to the point of overtraining.

After training, T cells may account for a larger percentage of the total lymphocytes, but the ratio of helper to suppressor cells is decreased. If training has been heavy, the number of NK cells may also decrease because they migrate to injured tissues, or are converted into T cells. However, Crist et al.[26] found that NK cell activity was increased in a geriatric population after they had completed a light training programme.

Resting mitogen-induced lymphocyte proliferation tends to be increased by training, although there must be an adequate recovery interval after the final bout of exercise if this response is to be observed. Thus, Hoffman-Goetz et al.[27, 28] observed a decreased response to mitogens at the immediate end of a training programme, but an increased response after 72 h of recovery.

Training typically attenuates the overall lymphocytosis that accompanies exhausting exercise in a sedentary individual. Rhind et al.[21] found that 12 weeks of moderate training attenuated the exercise-induced decrease of in vitro IL-2 production, and increased the expression of IL-2 β-receptors. However, exhausting training has a depressant action in both animals and humans. In animals such as the rat and the mouse, the mass of the thymus decreases, and splenic lymphocytes become less responsive to mitogen stimulation, perhaps due to an alteration in the relative proportions of T and B cells, and perhaps due also to the action of T suppressor cells or macrophage-secreted prostaglandin $E_2^{1, 2}$. Likewise, human data show that after heavy training, a bout of submaximal exercise usually decreases the lymphocyte response to mitogens[29], although proliferation may be increased in athletes who are abusing anabolic steroids.

Moderate training apparently increases resting plasma IgA levels. On the other hand, heavy training reduces resting levels of IgG and IgM, and mitogen-stimulated IgG synthesis. IgG, IgA and IgM are also low immediately before and during major competitions[1].

Interaction with other stressors

If an athlete's diet is inadequate to meet the demands of exercise, then a lack of amino acids such as glutamine may adversely affect the growth of immune cells[30]. Athletic competition may also be perceived as stressful, either in itself, or because it causes exposure to other forms of stress, environmental and psychological. The stress-induced secretion of cortisol can suppress certain aspects of immune function. Finally, prolonged exercise may in itself stimulate the release of cortisol; although this is a normal metabolic control mechanism, it has parallel implications for immune function.

Systemic infections modify the immune responses to exercise. They may also cause a direct deterioration of physical performance, and this can be stressful for an athlete. An intensity of exercise that is not stressful to a healthy individual can become both physically and psychologically stressful when it is coupled with a developing infection. When evaluating supposed training-induced responses, it is thus important to consider superimposed stresses, and how these have changed as subjects become habituated to a given laboratory or competitive environment.

Clinical implications

In conclusion, a few clinical implications of the exercise-induced changes in immune function will be briefly noted.

Detection of overtraining

There have been hopes that an alteration of resting immune parameters, or a disturbed immune response to exercise might provide an early warning that an athlete was undertaking too heavy a conditioning programme, and was becoming overtrained. The issue is difficult to investigate experimentally, since athletes cannot ethically be asked to push themselves to the level of injury. Verde et al.[31] noted that when a group of distance runners who were already training hard deliberately increased their average training volume by a stressful 38% for a period of 3 weeks, the resting mitogen-stimulated lymphocyte proliferation tended to increase. The ratio of helper to suppressor cells decreased (although, probably because they did not reach the threshold of overtraining, the ratio remained above the critical 1.5 level), and pokeweed mitogen induced less synthesis of immunoglobulins than normally. Moreover, 30 min of submaximal exercise (which previously had not modified cell proliferation) now induced an 18% suppression of lymphocyte proliferation, and the exercise-related stimulation of immunoglobulin synthesis no longer occurred. Nevertheless, all of these changes were small and rather variable. The authors thus concluded that simple psychological tests would probably offer not only a simpler, but also a more effective method of detecting staleness in an athlete[31].

Risk of infection

Viral infections pose a major threat to the international competitor. Animal experiments and clinical studies have each linked excessive physical activity to an increased risk of such infections[3, 32, 33], with the attendant dangers of a viral myocarditis[3]. Verde et al.[31] commented that two of ten distance runners developed an acute rhinoviral infection in response to 3 weeks of a deliberate increase in training schedules, and they linked this finding to evidence of immunosuppression. Likewise, Nieman et al.[34] found that the odds of developing a respiratory infection were doubled in runners who were training more than 97 km per week, relative to those who were running less than 32 km per week. Participation in a major marathon event increased the odds of infection almost six-fold relative to the experience of other runners who did not participate[33].

On the other hand, moderate exercise apparently increases the resistance of human volunteers to some diseases[3].

Risk of cancer

Given the role of the natural killer cells in the destruction of tumour cells, excessive exercise and training might be thought to have an adverse effect upon an athlete's risk of developing some type of cancer.

A number of early animal experiments suggested that moderate exercise enhanced the resistance of animals to experimental tumours. Human studies also suggest that moderate, occupational and/or leisure activity protects against certain types of cancer[35]. In the case of colonic cancer, the mechanism is probably an alteration of colon transit time, rather than an exercise-induced alteration of immune function[34]. There may also be a small alteration of reproductive cancers in active women, but this change seems linked to reduced body fat and lower oestrogen levels, rather than enhanced immune function[34].

IL-2 has recently been used experimentally in the treatment of certain types of cancer. Excessive doses of interleukins cause major complications, and a training programme may play a valuable role in developing IL-2 receptors, thus reducing the dose of cytokine that is needed in treatment[24].

Ageing

Ageing is associated with a progressive deterioration in immune function, and with the development of various autoimmune disorders. It might thus be supposed that moderate exercise would be protective, and that excessive exercise might hasten such problems. There is currently little evidence that habitual exercise slows the inherent rate of ageing[36], but there have been occasional disturbing animal studies suggesting that inherent aging proceeds most slowly in animals that combine physical inactivity with a restricted diet.

AIDS

Some data suggest that moderate exercise can induce a useful stimulation of immune function in the early phase of HIV infection[37], with increases of CD4 cells, an improved helper:suppressor cell ratio, and a conservation of lean tissue. However, if sport participation is to be considered in a therapeutic perspective, then the dose of exercise becomes critical to achievement of the desired outcome.

Transplant rejections

A final potential area of clinical interest, as yet unexplored, is the possibility that moderate training could modulate the rate of rejection of various tissue transplants, providing a more natural control of immune function than the long-term administration of immunosuppressant drugs.

Summary

The evidence presented in this brief review suggests that whereas a moderate dose of endurance exercise has a beneficial effect upon human immune responses, more intense and more stressful exercise can have a persistent adverse effect. Most of the changes resulting from a single bout of moderate exercise are fairly short-lived, but a prolonged single bout of exercise or training for an event such as a marathon race can cause a more prolonged suppression of NK activity, leaving the athlete with an immediate susceptibility to viral infections, and a potential for adverse changes in other more long-term manifestations of impaired immune function. The likelihood that any given bout of exercise will have an adverse impact on immune function depends on the *relative* intensity of effort that is demanded. Regular training can shift the threshold for adverse reactions upwards. Nevertheless, given the importance of the immune system to many aspects of health, we need to know much more about the dose of exercise that will optimize human responses and avoid long-term negative consequences.

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