How Physical Exercise Influences the Establishment of Infections

Bente K. Pedersen and *Helle Bruunsgaard*

Copenhagen Muscle Research Centre, Departments of Infectious Diseases, Rigshospitalet,
University of Copenhagen, Copenhagen, Denmark

Contents

Summary

During exercise, leucocytes are recruited to the blood, and if muscle damage occurs the cytokine level is enhanced. After prolonged, intense exercise the number of lymphocytes in the blood is reduced, and the function of natural killer cells is suppressed; furthermore, secretory immunity is impaired. During this time of immunodepression, often referred to as 'the open window', the host may be more susceptible to micro-organisms bypassing the first line of defence. This is of interest to top athletes who perform frequent severe exercise. Clinical observations regarding an increased risk of infections in top athletes are compatible with this model. However, in those performing regular moderate exercise the immune system will often be temporarily enhanced and this will protect these individuals from infections.

During the past few years there has been a growing interest in understanding how exercise influences the immune system. Research into exercise immunology has been stimulated by: (a) reports of increased frequency of upper respiratory tract infections (URTI) among athletes;[1] (b) the finding that in addition to physical exercise several other physical stressors (e.g. surgery, trauma, burn, hypoxia and hyperthermia) induce changes in the cellular immune system;[2] and (c) the possibility that increased levels of some neuroendocrine factors (e.g. catecholamines and growth hormone) may modulate the immune response.[3] This article summarises some of the important findings on exercise and the first line defence mechanisms of the immune system.

1. Short Term Time-Limited Exercise Stress

It is well known that exercise alters the distribution and trafficking of peripheral mononuclear cells.[4] The first English-language publication reporting exercise-induced leucocytosis was by Larrabee in 1902,[5] who described the phenomenon in a small group of marathon runners. Peripheral blood leucocytosis after exercise has been shown to be due to increased concentrations of neutrophils, monocytes and lymphocytes. The neutrophil concentration increases during and after exercise.[4,6] During exercise, natural killer (NK), B and T cells are also recruited to the blood, resulting in an elevated total lymphocyte count. The subpopulation composition of T cells is altered, with the CD4+/CD8+ ratio decreasing because the number of CD8+ T cells increases more than the number of CD4+ cells. After intense exercise, the lymphocyte level decreases below pre-exercise values, and the duration of this suppression depends on the intensity and duration of exercise.[3]

1.1 Natural Killer Cells

NK cells are a heterogeneous population of cells that mediate the killing of a broad range of target cells.[7] They are thought to play an important role in the first line of defence against acute and chronic viral infections and tumour spread.[8]

The modulation of NK cell activity in response to exercise has been investigated extensively.[9-36] During physical exercise, the absolute concentration and the relative fraction of blood mononuclear cells (BMNC) expressing characteristic NK cell markers are markedly enhanced. Simultaneously, the cytotoxic activity of NK cells (the function of NK cells) increases. After intense exercise, NK cell activity is suppressed.[9-36] Among several hypotheses regarding the mechanism behind the postexercise suppression of NK cell activity, one has addressed the possibility that the activity is suppressed by prostaglandins released by the elevated number of monocytes.[29,32]

1.2 Antibody Production

The secretory immune system of mucosal tissues such as the upper respiratory tract is considered to be the first barrier to colonisation by pathogenic micro-organisms which might cause URTI.[37,38] In mucosal secretions immunoglobulin (Ig) A is the major class of immunoglobulins, and the level of IgA in mucosal fluids has been shown to correlate more closely with resistance to URTI than serum antibodies.[39]

Tomasi et al.[40] reported suppressed levels of salivary IgA in cross-country skiers after a race. This finding was confirmed by a 70% decrease in salivary IgA for several hours after 2 hours of intense ergometer cycling.[41] Decreased salivary IgA was found after swimming,[42] and salivary IgA was low for several hours after marathon running.[43] In order to study the mechanism behind the suppression of immunoglobulins, a plaque forming cell (PFC) assay was used. This assay allows the identification of the individual immunoglobulin-secreting cells of blood. Stimulation of cells, *in vitro*, with pokeweed mitogen (PWM), interleukin (IL)-2 or Epstein-Barr virus (EBV) resulted in significantly decreased numbers of IgG-, IgA- and IgM-secreting blood cells both during and 2 hours after exercise, with recovery after 1 day.[44] Purified B cells produce plaques only after

stimulation with EBV and in these cultures no exercise-induced suppression was found. It was found that the suppressed immunoglobulin-production of blood mononuclear cells isolated from the blood, post-exercise, was partly restored by addition of indomethacin to the asssay and by removal of the monocytes. These results indicate that the immunoglobulin-producing cells are not directly influenced by exercise, but by substances e.g. prostaglandins produced by the monocytes.[44]

1.3 Cytokines

The various cells of the immune system communicate by a network of soluble mediators called cytokines, which include interleukins, lymphokines, monokines and interferons. Their coordinated presence is necessary for the growth, differentiation and functional activation of all cells of the immune system.[45] Physical exercise, including eccentric muscle contractions, increases the production of some cytokines. Increased IL-1β in muscle tissue was found for up to 5 days following eccentric exercise.[46] IL-1 activity increased after eccentric exercise in the plasma of untrained subjects.[47] After long distance running, increased concentrations of IL-6 were found in plasma,[48] and others have found increased levels of plasma tumour necrosis factor-α (TNFα).[49] Theoretically, increased production of monokines in response to dynamic exercise could be expected because of an elevated number of monocytes.[3] Furthermore, increased in vitro production of IL-1, IL-6 and TNFα was found in supernatants from lipopolysaccharide-stimulated BMNC isolated from untrained individuals 2 hours after cycling.[50] Several years ago, increased endogenous pyrogen activity in plasma after concentric exercise was shown to occur.[51]

We have recently investigated the effects of aerobic, concentric exercise on plasma levels of IL-1α, IL-1β, IL-6, and TNFα, and the presence of pre-mRNA for these cytokines in BMNC. Moderately trained, healthy young men performed ergometer cycling exercise for 1 hour at 75% of maximum oxygen uptake (VO_{2max}). The levels of plasma IL-6 increased significantly during exercise, but IL-1α, IL-1β and TNFα were not reliably detected in plasma. Pre-mRNA for IL-1α, IL-1β, IL-6 and TNFα could be detected in BMNC, but the amounts did not change in relation to exercise.[52] These results indicate that, although the levels of CD14+ monocytes had increased after exercise, the increased plasma IL-6 noted during exercise may not have been a result of activated monocytes in peripheral blood.

1.4 Exercise of Different Duration and Intensity

It was recently shown that cycling for 1 hour at 25, 50 and 75% of VO_{2max} increased the NK and lymphokine activated killer (LAK) cell activity, whereas the NK cell activity was suppressed only after intense exercise. Furthermore, only intense exercise induced a postexercise monocytosis.[32] In a recent review[2] we concluded from the results obtained from different types of exercise[9-36] that the intensity, rather than the duration, of exercise is responsible for the degree of increment in number of NK cells. On the other hand, the immune system is only suppressed following intense exercise of one hour's duration or more.[2]

1.5 Concentric Versus Eccentric Exercise

Physical exercise consists of concentric, isometric and eccentric muscle contractions, isolated or in combination. In particular, high-intensity eccentric exercise in untrained individuals is associated with muscle damage which is reflected in:

- an increased level of myocellular enzymes in the circulation
- ultrastructural damage in the striation of the muscle cell
- an acute inflammatory response in the muscle, causing oedema, infiltration of inflammatory cells and muscle soreness 24 to 48 hours after exercise (reviewed by Evans et al.)[47]

Differences in the interaction of high-intensity eccentric versus concentric exercise and the immune system are interesting from the point of view that they may serve as a model for, on the one side,

physiological stressors such as surgery, traumatic injury and acute myocardial infarction which involve a component of muscle proteolyse, and on the other side, stressors such as hyperthermia, haemorrhagic shock and hypoxia, which do not.

The exercise-related effect on NK cells has been studied in relation to whole body exercise concerning concentric exercise (e.g. bicycling) and combinations of concentric and eccentric exercise (e.g. running). The isolated effect of eccentric exercise has only been investigated in exercise involving a small muscle mass.[36] In this study, one-leg exercise increased the percentage of CD16+ cells and NK cell cytotoxic activity per fixed number of BMNC, whereas the NK cell activity per NK cell did not change. In the same study it was shown that the plasma level of neutrophils increased during and after exercise, whereas the level of monocytes increased only during exercise.

The effect of eccentric work on the level and production of cytokines has already been described. We hypothesise that high-intensity eccentric exercise causes a more pronounced increase in the muscle and plasma levels of cytokines involved in acute inflammatory responses (IL-1, TNF and IL-6) during and after exercise than does concentric exercise, because of the more pronounced damage to the muscle. We suggest that the source of the cells responsible for an increased synthesis of cytokines may be macrophages, endothelial cells and fibroblasts in the muscle. Concerning BMNC, we hypothesise that recruitment during physical activity may be due to the same mechanisms (e.g. increases in stress hormones) in eccentric and concentric exercise. Moreover, in eccentric exercise a part of the increased postexercise level of neutrophils and monocytes may reflect inflammation in the muscle. An increased level of cytokines, especially IL-1, in the inflammatory response may play a role in the recruitment and activation of NK cells. Further investigation is necessary to elucidate this.

1.6 Where Do the Cells Come From?

Exercise-related neutrocytosis is thought to be due to movement of neutrophils from marginal pools located intravascularly and from extravascular storage pools. The role of the lung vasculature in neutrophilic granulocyte sequestration has been repeatedly demonstrated.[53,54] In the case of lymphocytes it is less clear where those cells come from. It has been suggested that rapid transfer of lymphocytes into the intravascular compartment of the spleen might contribute to a selective increase in the number of circulating lymphocytes. However, in a recent paper the increase in neutrophils and lymphocytes and their subpopulations was similar in splenectomised patients and controls.[55] Thus, exercise-induced leucocytosis can take place in the absence of the spleen.

1.7 Possible Mechanisms of Action

Physical stress increases the levels of a number of stress hormones in the blood, including catecholamines, growth hormone, β-endorphins, corticotrophin (ACTH) and cortisol. Kappel et al.[21] showed that selective administration of epinephrine (adrenaline) mimicked the exercise-induced effect on BMNC subsets, NK cell activity and lymphocyte function. However, epinephrine infusions caused a smaller increase in neutrophil levels than the exercise-induced increase.[21]

In vivo injection of growth hormone in humans had no effect on BMNC subsets, NK cell activity, cytokine production or lymphocyte function. Growth hormone increased only the neutrophil concentration.[56]

Fiatarone et al.[13] showed that when naloxone was administered *in vivo* to young women who underwent a maximal cycle ergometer test, the rise in NK cell activity was no longer significant. However, the exercise-induced increase in cells expressing the CD16 marker (NK cells) was not significantly altered compared with the group receiving placebo. In another study, healthy young men were given epidural analgesia which blocked the afferent nerve impulses and inhibited increases in β-endorphins and ACTH during exercise. In this way, the exercise-induced increase in NK cell function, the percentage of NK cells and the NK cell concentration were significantly enlarged.[57]

Therefore, blocking the β-endorphin receptor and inhibiting the increase in levels of β-endorphin during exercise exerts differential effects on the immune system (inhibition and augmentation of the exercise-induced rise in NK cell activity, respectively). Only a minor increase in cortisol levels has been described in short term, time-limited exercise stress,[3] and it is unlikely that such modest increments alone can account for the magnitude of exercise-induced immunomodulation. However, this does not preclude an immunomodulatory role for cortisol in long term exercise stress.

2. Training and Fitness Level

Resting levels of NK cell activity were found to be elevated in 29 highly trained elite cyclists compared with sex- and age-matched controls (median VO_{2max} of 72.0 and 54.7 ml/kg/min, respectively).[58,59] The elite cyclists were examined during a period of high (summer) as well as low (winter) training, after 20 hours at rest. At both examinations, NK cell activity was elevated in the trained group. In a study by Nieman et al.,[60] mildly obese premenopausal women performed a 15-week walking exercise training programme (5 × 45-min sessions per week, brisk walking at 60% of maximum HR reserve) and in a study by Crist et al.[61] elderly volunteers performed a 16-week exercise programme (3 × 60 mins/week consisting of at least 20 minutes of aerobic exercise per session at a HR of 50% maximum HR of the HR reserve). Both studies showed that resting levels of NK cell activity increased in response to training.

3. Exercise and Infections

When 2 groups of trained and untrained mice were infected in a resting period with *Salmonella typhimurium*[62] or influenza type A,[63] the trained mice had a higher survival rate than sedentary mice. In contrast, when mice performed intense exercise during the incubation period of an infection with Coxsackie B virus, increased tissue destruction and mortality were found among the exercising animals.[64]

Also, several studies in humans have explored the relationship between exercise and URTI. These are summarised in a recent review by Nieman.[1] These studies were based on self-report and did not include a clinical examination or laboratory workup. An increased frequency of URTI has been reported in a study of 1550 runners who took part in a 56km race, compared with matched controls. Those who ran faster race times reported more symptoms, indicating a dose-response relationship.[65] Nieman et al.[66] reported that the runners who actually ran a marathon reported more symptoms of URTI during the week following the race than similarly experienced runners who entered but did not participate in the race for reasons other than sickness. Heath et al.[67] followed a cohort of 530 runners. Those who ran less than 16km (10 miles) per day, had the lowest odds ratio for respiratory disease, while the odds ratio more than doubled for those running more than 27km (17 miles).

The effects of moderate exercise training were examined in a 15-week study of mildly obese women who were randomly assigned to a walking or a nonexercising group. The women in the exercise group experienced fewer URTI symptoms than their sedentary controls.[60]

On the basis of several reports, including the above mentioned studies, a 'J'-shaped model of the relationship between varying amounts of exercise and the risk of URTI has been suggested.[1] This model suggests that moderate exercise may lower the risk of respiratory infection while excessive amounts may increase the risk.

4. Exercise and Cancer

NK cells are very sensitive to exercise, and these cells are thought to play a role in defence against malignant cells. Hoffman-Goetz[68] has recently reviewed evidence linking exercise, natural immunity and tumour metastasis. In general, there is an inverse relationship between exercise and the development of experimental tumours in animals,[3,58] and epidemiological evidence in humans generally supports this relationship.[69]

The prevalence rates of cancers of the reproductive system (uterus, ovary, cervix and vagina) and breast cancer were determined for 5398 living alumnae, 2622 of whom were former college athletes. For nonathletes/athletes, the relative risk was 2.53 for cancers of the reproductive system and 1.83 for breast cancer.[70] The latter finding was confirmed in a recent study.[71] The association between physical job activity and colon cancer was examined in a 19-year follow-up study of 1.1 million Swedish men.[72] The relative risk of colon cancer in men employed in sedentary occupations was estimated at 1.3. However, in these epidemiological studies the possibility of exercise-induced changes in the immune system as underlying mechanisms was not addressed.

5. Exercise and Training in Patients with Chronic Diseases

In a recent study, patients with rheumatoid arthritis performed an 8-week bicycle exercise programme (30 min interval training, 4 to 5 times a week). No changes were observed in NK cell activity, BMNC proliferation or cytokines.[73] In rats with adjuvant-induced arthritis, exercise did not influence the severity of the disease.[74]

Infection with the HIV type 1 results in progressive and profound immunosuppression. The primary defect is the depletion of CD4+ cells, but depletions and defects in the function of other lymphocyte subpopulations, including NK and LAK cells, and altered cytokine production also occurs.[75-78] HIV seropositive individuals have been shown to possess an impaired ability to mobilise neutrophils, NK cells and LAK cells to the blood in response to short term time-limited exercise stress (bicycling at 75% of $\dot{V}O_{2max}$ for 1 hour).[34] The mechanisms behind this impaired recruitment are unknown, but may be attributed to an altered response to stress, a lower expression of β-receptors on the surface of NK cells and/or a smaller reservoir of cells available for recruitment.

Thus, in patients with chronic diseases such as rheumatoid arthritis and HIV-infection, there have not been reports showing that exercise is harmful to the immune system or worsens disease activity.

6. Conclusions

At rest, trained subjects have slightly elevated nonspecific immunity. During exercise, leucocytes are recruited to the blood and if muscle damage occurs the cytokine level is enhanced. Thus, short term, time-limited exercise stress induces an inflammatory response. Following long term, intense exercise the number of lymphocytes in the blood is suppressed, and the function of NK and B cells is inhibited. During this time of immunodepression, often referred to as 'the open window', the host may be more susceptible to micro-organisms bypassing the first line of defence. This is of interest to top athletes who perform frequent severe exercise without allowing the immune system to recover between each bout. In those performing moderate exercise the immune system is enhanced during exercise, but there is no 'open window' following exercise.

The clinical observations regarding an increased risk of infections in top athletes, but a decreased number of infections in subjects performing regular moderate exercise training, are compatible with this model.

Acknowledgements

References

1. Nieman DC. Exercise, infection, and immunity. Int J Sports Med 1994; 15: S131-41
2. Pedersen BK, Kappel M, Klokker M, et al. The immune system during exposure to extreme physiologic conditions. Int J Sports Med 1994; 15: S116-21
3. Hoffman-Goetz L, Pedersen BK. Exercise and the immune system: a model of the stress response? Immunol Today 1994; 15: 382-7
4. McCarthy DA, Dale MM. The leucocytosis of exercise: a review and model. Sports Med 1988; 5: 282-7
5. Larrabee RC. Leukocytosis after violent exercise. J Med Res 1902; 7: 76-82
6. Pedersen BK. Influence of physical activity on the cellular immune system: mechanisms of action. Int J Sports Med 1991; I Suppl.: 23-9
7. Hercend T, Schmidt RE. Characteristics and uses of natural killer cells. Immunol Today 1988; 9: 291-3

8. Whiteside TL, Herberman RB. Short analytical review: the role of natural killer cells in human diseases. Clin Immunol Immunopathol 1989; 53: 1-23

9. Brahmi Z, Thomas JE, Park M, et al. The effect of acute exercise on natural killer cell activity of trained and sedentary human subjects. J Clin Immunol 1985; 5: 321-8

10. Deuster PA, Curiale AM, Cowan ML, et al. Exercise-induced changes in population of peripheral blood mononuclear cells. Med Sci Sports Exerc 1988; 20: 276-80

11. Edwards AJ, Bacon TH, Elms CA, et al. Changes in the populations of lymphoid cells in human peripheral blood following physical exercise. Clin Exp Immunol 1984; 58: 420-7

12. Espersen GT, Elbæk A, Ernst E, et al. Effect of physical exercise on cytokines and lymphocyte subpopulations in human peripheral blood. APMIS 1990; 98: 395-400

13. Fiatarone MA, Morley JE, Bloom ET, et al. Endogenous opioids and the exercise-induced augmentation of natural killer cell activity. J Lab Clin Med 1988; 112: 544-52

14. Field CJ, Gougeon R, Marliss EB. Circulating mononuclear cell numbers and function during intense exercise and recovery. J Appl Physiol 1991; 71: 1089-97

15. Fry RW, Morton AR, Crawford GPM, et al. Cell numbers and in vitro responses of leucocytes and lymphocyte subpopulations following maximal exercise and interval training sessions of different intensities. Eur J Appl Physiol 1992; 64: 218-27

16. Gabriel H, Schwartz L, Born P, et al. Differential mobilization of leucocyte and lymphocyte subpopulations into the circulation during endurance exercise. Eur J Appl Physiol 1992; 65: 529-34

17. Gabriel H, Urhausen A, Kindermann W. Mobilization of circulating leucocyte and lymphocyte subpopulations during and after short, anaerobic exercise. Eur J Appl Physiol 1992; 65: 164-70

18. Haq A, Al-Hussein K, Lee J, et al. Changes in peripheral blood lymphocyte subsets associated with marathon running. Med Sci Sports Exerc 1993; 25: 186-199

19. Hoffman-Goetz L, MacNeil B, Arumugam Y, et al. Differential effects of exercise and housing condition on murine natural killer cell activity and tumor growth. Int J Sports Med 1992; 13: 167-71

20. Hoffman-Goetz L, Simpson JR, Cipp N, et al. Lymphocyte subset responses to repeated submaximal exercise in men. J Appl Physiol 1990; 68: 1069-74

21. Kappel M, Tvede N, Galbo H, et al. Evidence that the effect of physical exercise on NK cell activity is mediated by epinephrine. J Appl Physiol 1991; 70: 2530-4

22. Keast D, Cameron K, Morton AR. Exercise and the immune response. Sports Med 1988; 5: 248-67

23. Lyngberg K, Tvede N, Halkjær-Kristensen J, et al. Physical exercise modulates the cellular immune system in patients with rheumatoid arthritis. Scand J Med Sci Sports 1991; 1: 167-73

24. MacKinnon LT. Exercise and natural killer cells: what is the relationship? Sports Med 1989; 7: 141-9

25. MacKinnon LT, Chick TW, van As A, et al. Effects of prolonged intense exercise on natural killer cells. Med Sci Sports Exerc 1987; 19: S10

26. Nieman DC, Henson DA, Johnson R, et al. Effects of brief, heavy exertion on circulating lymphocyte subpopulations and proliferative response. Med Sci Sports Exerc 1992; 24: 1339-45

27. Nieman DC, Nehlsen-Cannarella SL, Donohue KM, et al. The effects of acute moderate exercise on leukocyte and lymphocyte subpopulations. Med Sci Sports Exerc 1991; 23: 578-85

28. Pedersen BK, Tvede N, Hansen FR, et al. Modulation of natural killer cell activity in peripheral blood by physical exercise. Scand J Immunol 1988; 26: 673-8

29. Pedersen BK, Tvede N, Klarlund K, et al. Indomethacin in vitro and in vivo abolishes postexercise suppression of natural killer cell activity in peripheral blood. Int J Sports Med 1990; 11: 127-31

30. Shinkai S, Shore S, Shek PN, et al. Acute exercise and immune function. Int J Sports Med 1992; 13: 452-61

31. Targan S, Britvan L, Dorey F. Activation of human NKCC by moderate exercise increased frequency of NK cells with enhanced capability of effector-target lytic interactions. Clin Exp Immunol 1981; 45: 352-60

32. Tvede N, Kappel M, Halkjær-Kristensen J, et al. The effect of light, moderate and severe exercise on lymphocyte subsets, natural and lymphokine activated killer cells, lymphocyte proliferative response and interleukin 2 production. Int J Sports Med 1993; 14: 275-82

33. Tvede N, Pedersen BK, Hansen FR, et al. Effect of physical exercise on blood mononuclear cell subpopulations and in vitro proliferative responses. Scand J Immunol 1989; 29: 382-9

34. Ullum H, Palmø J, Halkjær-Kristensen J, et al. The effect of acute exercise on lymphocyte subsets, natural killer cells, proliferative response and cytokines in HIV seropositive persons. J AIDS 1994; 7: 1122-33

35. Nielsen HB, Hanel B, Loft S, et al. Restricted pulmonary diffusion capacity after exercise is not an ARDS-like injury. J Sport Sciences 1995; 13: 109-13

36. Palmø J, Asp S, Daugaard J, et al. Effect of eccentric exercise on natural killer cell activity. J Appl Physiol. In press

37. Tomasi TB, Trudeau FB, Crewinski D, et al. Immune parameters in athletes before and after strenuous exercise. J Clin Imunol 1982; 2: 173-8

38. Mackinnon LT, Hooper S. Mucosal secretory immune system responses to exercise of varying intensity and during overtraining. Int J Sports Med 1994; 15: S179-83

39. Liew FY, Russell SM, Appleyard G, et al. Cross-protection in mice infected with influenza A virus by the respiratory route is correlated with local IgA antibody rather than serum antibody or cytotoxic T cell reactivity. Eur J Immunol 1984; 14: 350-6

40. Tomasi F, Trudeau D, Czerqinski D, et al. Immune parameters in athletes before and after strenuous exercise. J Clin Immunol 1982; 2: 173-8

41. MacKinnon LT, Chick A, van As A, et al. The effect of exercise on secretory and natural immunity. Adv Exp Med Biol 1987; 216A: 869-76

42. Tharp GD, Barnes MW. Reduction of salivary immunoglobulin levels by swim training. Eur J Appl Physiol 1990; 60: 61-4

43. Muns G, Liesen H, Riedel H, et al. Influence of long-distance running on IgA in nasal secretion and saliva. Deutsch Zeitschr Sportsmed 1989; 40: 94-9

44. Tvede N, Heilmann C, Halkjær-Kristensen J, et al. Mechanisms of B-lymphocyte suppression induced by acute physical exercise. J Clin Lab Immunol 1989; 30: 169-73

45. Northoff H, Weinstock C, Berg A. The cytokine response to strenuous exercise. Int J Sports Med 1994; 15: S167-71

46. Cannon JG, Fielding RA, Fiatarone MA, et al. Increased interleukin 1 beta in human skeletal muscle after exercise. Am J Physiol 1989; 26: R451-5

47. Evans WJ, Meredith CN, Cannon JG. Metabolic changes following eccentric exercise in trained and untrained men. J Appl Physiol 1986; 61: 1864-8

48. Northoff H, Berg A. Immunologic mediators as parameters of the reaction to strenuous exercise. Int J Sports Med 1991; 12: S9-15

49. Espersen GT, Elbaek A, Ernst E, et al. Effect of physical exercise on cytokines and lymphocyte subpopulations in human peripheral blood. APMIS 1990; 98: 395-400

50. Haahr PM, Fomsgaard A, Tvede N, et al. Effect of physical exercise on the in vitro production of IL-1, IL-6, TNF-α, IL-2 and IFN-γ. Int J Sports Med 1991; 12: 223-7

51. Cannon JG, Kluger MJ. Endogenous pyrogen activity in human plasma after exercise. Science 1983; 220: 617-9

52. Ullum H, Haahr PM, Diamant M, et al. Bicycle exercise enhances plasma IL-6, but does not change pre-mRNA for IL-1α, IL-1ß, IL-6 or TNF-α in blood mononuclear cells. J Appl Physiol 1994; 77 (1): 93-7

53. Muir AL, Cruz M, Martin BA, et al. Leucocyte kinetics in the human lung: role of exercise and catecholamines. J Appl Physiol 1984; 57: 711-9

54. Peters AM, Allsop P, Stuttle AWJ, et al. Granulocyte margination in the human lung and its response to strenuous exercise. Clin Sci 1992; 82: 237-44

55. Iversen PO, Arvesen BL, Benestad HB. No mandatory role for the spleen in the exercise-induced leucocytosis in man. Clin Sci 1994; 86: 505-10

56. Kappel M, Hansen MB, Diamant M, et al. Effects of an acute bolus growth hormone infusion on the human immune system. Horm Metab Res, 1993; 11: 593-602

57. Klokker M, Kjaer M, Secher NM, et al. Natural killer cell response to exercise in humans: effect of hypoxia and epidural anesthesia. J Appl Physiol 1995; 78: 709-16

58. Pedersen BK, Tvede N, Christensen LD, et al. Natural killer cell activity in peripheral blood of highly trained and untrained persons. Int J Sports Med 1989; 10: 129-31

59. Tvede N, Steensberg J, Baslund B, et al. Cellular immunity in highly-trained elite racing cyclists and controls during periods of training with high and low intensity. Scand J Sports Med 1991; 1: 163-6

60. Nieman DC, Nehlsen-Cannarella SL, Markoff PA, et al. The effects of moderate exercise training on natural killer cells and acute upper respiratory tract infections. Int J Sports Med 1990; 11: 467-73

61. Crist DM, Mackinnon LT, Thompson RF, et al. Physical exercise increases natural cellular-mediated tumour cytotoxicity in elderly women. Gerontology 1989; 35: 66-71

62. Cannon JG, Kluger MJ. Exercise enhances survival rate in mice infected with Salmonella typhimurium. Proc Soc Exp Biol Med 1984; 175: 518-21

63. Ilback NG, Friman G, Beisel WR, et al. Modifying effects of exercise and clinical course and biochemical response of the myocardium in influenza and rularemia: augmentation of the virulence of murine coxsackie-virus B-3 myocardiopathy by exercise. Infect Immun 1984; 45: 498-504

64. Gatmaitan BG, Chason JL, Lerner AM. Augmentation of the virulence murine coxsackie-virus B-3 myocardiopathy by exercise. J Exp Med 1970; 131: 1121-36

65. Peters E, Bateman E. Ultramarathon running and upper respiratory tract infections: an epidemiological study. S Afr Med J 1983; 64: 583-4

66. Nieman DC, Johanssen Lee JW, et al. Infectious episodes in runners before and after the Los Angeles Marathon. J Sports Med Phys Fitness 1990; 30: 316-28

67. Heath GW, Ford ES, Craven TE, et al. Exercise and the incidence of upper respiratory tract infections. Med Sci Sports Exerc 1991; 23 (2): 152-7

68. Hoffman-Goetz L. Exercise, natural immunity, and tumor metastasis. Med Sci Sports Exerc 1994; 26 (2): 157-63

69. Sternfeld B. Cancer and the protective effect of physical activity: the epidemiological evidence. Med Sci Sports Exerc 1992; 24: 1195-209

70. Frisch RE, Wyshak G, Albright NL, et al. Lower prevalence of breast cancer and cancers of the reproductive system among former college athletes compared to non-athletes. Br J Cancer 1985; 52: 885-91

71. Bernstein L, Henderson BE, Hanisch R, et al. Physical exercise and reduced risk of breast cancer in young women. J Natl Cancer Inst 1994; 21: 1371-2

72. Gerhardsson M, Norell S, Kiviranta H, et al. Sedentary jobs and colon cancer. Am J Epidemiol 1986; 123: 775-80

73. Baslund B, Lyngberg K, Andersen V, et al. The effect of eight weeks bicycle training on the immune system of patients with rheumatoid arthritis. J Appl Physiol 1993; 75: 1691-5

74. Ferry A, Le Page C, Rieu M. Sex as a determining factor in the effect of exercise on in vivo autoimmune response adjuvant arthritis. J Appl Physiol 1994; 76: 1172-5

75. Rosenberg ZF, Fauci AS. Immunopathogenic mechanisms of HIV expression: cytokine induction of HIV expression. Immunol Today 1990; 11: 176-80

76. Fauci AS. Immunologic abnormalities in the acquired immunodeficiency syndrome (AIDS). Clin Res 1984; 32: 491-9

77. Brenner BG, Dascal A, Margolese RG, et al. Natural killer cell function in patients with acquired immunodeficiency syndrome and related diseases. J Leukoc Biol 1989; 46: 75-83

78. Brenner BG, Gryllis C, Wainberg MA. Role of antibody-dependent cellular cytotoxicity and lymphokine-activated killer cells in AIDS and related diseases. J Leukoc Biol 1991; 50: 628-40

Correspondence and reprints: Dr *Bente Klarlund Pedersen*, Department of Infectious Diseases, M 7721, Rigshospitalet, Tagensvej 20, DK-2200 Copenhagen N, Denmark.