# Pearson Edexcel International Advanced Level

# Biology

## Advanced

## Unit 5: Energy, Exercise and Coordination

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Pearson

**Scientific article for use with Question 7**

**The Brain, Exercise and the Immune System**

## Multiple Sclerosis

### Background

1. Multiple sclerosis (MS) is an immune-mediated inflammatory disease that attacks myelinated axons in the central nervous system (CNS), destroying the myelin and the axon in variable degrees. In most cases, the disease follows a relapsing-remitting pattern, with short-term episodes of neurologic deficits that resolve completely or almost completely. A minority of patients experience steadily progressive neurologic deterioration.

2. The cause of MS is not known, but it likely involves a combination of genetic susceptibility and a presumed nongenetic trigger (eg, viral infection, low vitamin D levels) that together result in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS. Geographic variation in the incidence of MS supports the probability that environmental factors are involved in the etiology.

3. MS is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and cerebrospinal fluid examination. Traditionally, MS could not be diagnosed after only a single symptomatic episode, as diagnosis required the occurrence of repeat clinical attacks suggesting the appearance of lesions separated in time and space; however, recent guidelines allow diagnosis of MS even with a first clinical episode as long as ancillary tests support separation of lesions in time or space.

4. A common misconception is that any attack of CNS demyelination means a diagnosis of acute MS. When a patient has a first attack of demyelination, the physician should not rush to diagnose MS, because the differential diagnosis includes a number of other diseases. For example, MS must be distinguished from other neuroinflammatory disorders.

5. Treatment consists of immunomodulatory therapy for the underlying immune disorder and management of symptoms, as well as nonpharmacologic treatments, such as physical and occupational therapy. In the United States, various disease-modifying agents for MS are currently approved for use in relapsing MS.

### Etiology

6. The cause of MS is unknown, but it is likely that multiple factors act in concert to trigger or perpetuate the disease. It has been hypothesized that MS results when an environmental agent or event (eg, viral or bacterial infection, exposure to chemicals, lack of sun exposure) acts in concert with a genetic predisposition to immune dysfunction.

### Genetic and molecular factors

7. The concordance rate for MS among monozygotic twins is only 20–35%, suggesting that genetic factors have only a modest effect. The presence of predisposing non-Mendelian factors (ie, epigenetic modification in 1 twin), along with environmental effects, plays an important role. For first-degree family members (children or siblings) of people affected with MS, the risk of developing the disorder is sevenfold higher than in the general population, but familial excess lifetime risk is only 2.5–5%.

8. Different variants of genes normally found in the general population, commonly referred to as polymorphisms, may lead to different gradations of cellular expression of those genes and therefore of the proteins that they encode. With MS susceptibility, it may be that a polymorphism within the promoter region of a gene involved in immune reactivity generates an exaggerated response (eg, elevated expression of a proinflammatory gene) to a given antigen, leading to uncontrolled immune cell proliferation and autoimmunity.

9. Research on single-nucleotide polymorphisms (SNPs) that confer risk of more severe disease or of developing particular forms of MS will be of great interest to the clinicians treating this complex disorder in the early stages. To date, however, HLA-DRB1 is the only chromosomal locus that has been consistently associated with MS susceptibility. Multiple other polymorphisms that may act in concert to predispose to MS have been described with genome-wide approaches, but their individual contribution to risk is not nearly as high as the risk conferred by the HLA locus.

10. Genes that instead of conferring susceptibility to MS confer relative protection against it are also being investigated, and clues are emerging from within the major histocompatibility complex (MHC) region. For example, it has been suggested that the *HLA-C*05* allele confers protection against MS.)

11. Molecular mimicry has been proposed as an etiologic process in MS. The molecular mimicry hypothesis refers to the possibility that T cells in the peripheral blood may become activated to attack a foreign antigen and then erroneously direct their attack toward brain proteins that share similar epitopes.

**Viral infection**

12. Another hypothesis is that a virus may infect the immune system, activating self-reactive T cells (myelin reactive) that would otherwise remain quiescent. A virus that infects cells of the immune and nervous systems can possibly be reactivated periodically and thus lead to acute exacerbations in MS.

13. Epstein-Barr virus (EBV) infection has been found to become periodically reactivated, but a possible causative role in MS has been difficult to prove. Evidence supporting EBV infection as an etiologic factor includes (1) long-term studies showing a higher association with MS in individuals with early presence of serum antibodies against specific EBV antigens and (2) high expression of EBV antigens within MS plaques.

14. Evidence that argues against an etiologic role for EBV infection includes the fact that MS is a highly heterogeneous disease; EBV might help trigger some cases but not others, making associations in populations difficult. In addition, it is possible that EBV reactivation is an effect rather than a cause (ie, instead of viral reactivation being the trigger for MS, reactivation might be an epiphenomenon of a dysregulated immune system).

**Environmental factors**

15. Geography is clearly an important factor in the etiology of MS. The incidence of the disease is lower in the equatorial regions of the world than in the southernmost and northernmost regions. However, a systematic review by Alonso and Hernán found that this latitude gradient became attenuated after 1980, apparently due to an increased incidence of MS in lower latitudes.

16. Apparently, whatever environmental factor is involved must exert its effect in early childhood. If an individual lives in an area with low incidence of MS until age 15 years, that person's risk remains low even if the individual subsequently moves to an area of high incidence.

17. On the other hand, certain ethnic groups (eg, Eskimos), despite living in areas of higher incidence, do not have a high frequency of MS. Therefore, the exact role played by geography versus genetics is not clear.

**Vitamin D levels**

18. Low levels of vitamin D have been proposed as one environmental factor contributing to the development of MS. Vitamin D has a role in regulating immune response, by decreasing production of proinflammatory cytokines and increasing production of anti-inflammatory cytokines; also, high circulating levels of vitamin D appear to be associated with a reduced risk of MS.

19. Thus, lower vitamin D levels due to lower sunlight exposure at higher latitudes may be one reason for the geographic variations in MS incidence, and the protective effect of traditional diets high in vitamin D could help explain why certain areas (eg, Norway) have a lower incidence of MS despite having limited sunlight. This hypothesis would also provide an explanation for the correlation between childhood sun exposure and MS in monozygotic twins discordant for MS.

**Exercise and the Immune System**

**1. Introduction**

20. Epidemiological evidence suggests a link between the intensity of the exercise and the occurrence of infections and diseases. The innate immune system appears to respond to chronic stress of intensive exercise by increased natural killer cell activity and suppressed neutrophil function. The measured effects of exercise on the innate immune system are complex and depend on several factors: the type of exercise, intensity and duration of exercise, the timing of measurement in relation to the exercise session, the dose and type of immune modulator used to stimulate the cell *in vitro* or *in vivo*, and the site of cellular origin. When comparing immune function in trained and non-active persons, the adaptive immune system is largely unaffected by exercise.

21. Physical activity in combination with infections is usually associated with certain medical risks, partly for the person who is infected and partly for the other athletes who may be infected. The risk of infection is greatest in team sports, but also in other sports where athletes have close physical contact before, during and after training and competitions.

**2. The immune system**

22. The immune system is large and complex and has a wide variety of functions. The main role of the immune system is to defend people against germs and microorganisms. Researchers are constantly making new discoveries by studying the immune system. There are several factors which influence or affect the daily functioning of the immune system: age, gender, eating habits, medical status, training and fitness level.

23. Bacteria and viruses can do harm to our body and make us sick. The immune system does a great job in keeping people healthy and preventing infections, but problems with the immune system can still lead to illness and infections. The immune system is separated in two functional divisions: the innate immunity, referred to as the first line of defense, and the acquired immunity, which, when activated, produces a specific reaction and immunological memory to each infectious agent.

24. Regular physical activity and exercise at moderate levels are important factors for disease prevention. Strenuous exercise leads to the activation of several cell lines within the immune system, such as neutrophils, monocytes, and macrophages, which all are capable of producing ROS. During resting conditions, the human body produces ROS to a level which is within the body's capacity to produce antioxidants. During endurance exercise, there is a 15- to 20-fold increase in whole body oxygen consumption, and the oxygen uptake in the active muscles increases 100- to 200-fold. This elevation in oxygen consumption is thought to result in the production of ROS at rates that exceed the body's capacity to detoxify them. Oxidative stress is a result of an imbalance between the production of ROS and the body's ability to detoxify the reactions (producing antioxidants). In the literature, there is disagreement whether or not oxidative stress and subsequent damage associated with exercise is harmful or not. This ambiguity may partly be explained by the methods chosen for the different investigations. Experimental and clinical evidence have linked enhanced production of ROS to certain diseases of the cardiovascular system including hypertension, diabetes and atherosclerosis. Oxidized LDL inhibits endothelial ability to produce nitric oxide (NO). This is unfortunate since NO increases blood flow, allows monocytes to adhere to the endothelium, decreases blood clots and prevents oxidation of LDL. High amount of free radicals promotes the atherosclerosis process by oxidation of LDL. Free radicals react with substances in the cell membrane and damage the cells that line the blood vessels. This means that the fat in the blood can more easily cling to a damaged vessel wall. If there are sufficient antioxidants present, it is believed that the harmful processes in the blood vessels can be slowed down. On the other hand, free radicals are not always harmful, but can serve a useful purpose in the human body. The oxygen radicals are necessary compounds in the maturation process of the cellular structure. Complete elimination of the radicals would not only be impossible, but also harmful.

**3. Antioxidants**

25. An antioxidant is a chemical compound or a substance such as vitamin E, vitamin C, or beta carotene, thought to defend body cells from the destructive effects of oxidation. Antioxidants are important in the context of organic chemistry and biology: all living cells contain a complex system of antioxidant compounds and enzymes which protect the cells from chemical damage due to oxidation. There are many examples of antioxidants: e.g. the intracellular enzymes like superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, catalase, the endogenous molecules like glutathione (GSH), sulfhydryl groups, alpha lipoic acid, Q 10, thioredoxin, the essential nutrients: vitamin C, vitamin E, selenium, N-acetyl cysteine, and the dietary compounds: bioflavonoids, pro-anthocyanin.

26. The task of antioxidants is to protect the cell against the harmful effects of high production of free radicals. A diet containing polyphenol antioxidants from plants is necessary for the health of most mammals. Antioxidants are widely used as ingredients in dietary supplements that are used for health purposes, such as preventing cancer and heart diseases. However, while many laboratory experiments have suggested benefits of antioxidant supplements, several large clinical trials have failed to clearly express an advantage of dietary supplements. Moreover, excess antioxidant supplementation may be harmful.

27. Neutrophils are protected against ROS by SOD, catalase, glutathione peroxidase, and glutathione reductase. The exogenous antioxidants include among others vitamin E ($\alpha$-tocopherol), vitamin C and coenzyme Q. The lipid-soluble $\alpha$-tocopherol is considered the most efficient among the dietary antioxidants, because it contributes to membrane stability and fluidity by preventing lipid peroxidation. Coenzyme Q or ubiquinon is also lipid-soluble, and has the same membrane stabilization effect as vitamin E. Ascorbic acid or vitamin C (water-soluble) is, however, the predominant dietary antioxidant in plasma. The apprehension of increased rates of ROS production during exercise is part of the rationale why many athletes could theoretically profit by

increasing their intake of antioxidant supplements beyond recommended doses. Table 1 shows an overview of the localization and function to the enzymatic antioxidants which protects the cell against oxidative stress.

| enzymatic antioxidants | localisation | function |
|---|---|---|
| Superoxide oxidase | Mitochondria, cytosol | Superoxide anion |
| Glutathione peroxidase | Mitochondria, cytosol, cell membrane | Reduces $H_2O_2$ |
| Catalase | Peroxisomes | Reduces $H_2O_2$ |
| Glutaredoxin | Cytosol | Protects and repair proteins and non-proteins thiols |

**Table 1.** An overview of enzymatic antioxidants and associated free radicals.

28. Non-enzymatic antioxidant reserve is the first line of defense against free radicals. Three non-enzymatic antioxidants are of particular importance. 1) Vitamin E, the major lipid-soluble antioxidant which plays a vital role in protecting membranes from oxidative damage. 2) Vitamin C or ascorbic acid which is a water-soluble antioxidant and can reduce radicals from a variety of sources. It also appears to participate in recycling vitamin E radicals. Interestingly, vitamin C can also function as a pro-oxidant under certain circumstances. 3) Glutathione, which is seen as one of the most important intracellular defense against damage by reactive oxygen species.

29. In addition to these "big three", there are numerous small molecules that function as antioxidants. Examples include bilrubin, uric acid, flavonoids, and carotenoids.

30. The optimal aim is an equal production of free radicals together with equal production of antioxidants. There is broad evidence suggesting that physical exercise affects the generation of ROS in leukocytes which may induce muscle damage and may explain phenomena like decreased physical performance, muscular fatigue, and overtraining. Detrimental influences of free radicals are due to their oxidizing effects on lipids, proteins, nucleic acids, and the extracellular matrix. However, the available data to support the role of ROS in relation to physical exercise are highly inconsistent and partly controversial. These controversies are probably due to the different methodologies used to assess ROS, generally including time-demanding and laborious cell isolation procedures and subsequent cell culturing that most certainly affects the ROS status of these cells in an uncontrolled and unpredictable manner. The type of physical activity studied also varied considerably and probably influenced the results presented.

## 4. Physical activity and antioxidant supplementation

31. A very important question in this context is whether exercise-induced oxidative stress is associated with an increased risk of diseases. The great disparities as to whether ROS production increases or decreases after physical exercise should be considered when comparing different studies of antioxidant supplementation and exercise-induced oxidative stress; likewise the differences in antioxidant dosages used, the biological potency of different forms of the same antioxidant and the different manufacturers' products. The main explanations for the inconsistencies of the effect of antioxidant supplementation on oxidative stress seems to be due to the different assay techniques used to measure in vitro neutrophil ROS production, the exercise mode, and the fitness levels of participants.

32. The human body has an elaborate antioxidant system that depends on the endogenous production of antioxidant compounds like enzymes, as well as the dietary intake of antioxidant vitamins and minerals. Still, there is not enough knowledge at present as to whether the body's natural antioxidant defense system is sufficient to counteract the induced increase of free radicals during physical exercise or if additional supplements are needed.

33. Until now, the majority of investigations address the effects of exercise on markers of oxidative stress, and not the occurrence of disease. However, most research points to a beneficial effect of regular moderate-to-vigorous physical activity on disease prevention.

## 5. Effect of exercise on immunity

### 5.1. The J-curve

34. Although the consensus is lacking in some areas, there is sufficient agreement to make some conclusions about the effects of exercise on the immune system. Numerous publications before 1994 resulted in assumption that a J-shaped relationship best described the relationship between infection sensitivity and exercise intensity. The hypothesis is based on cross-section analysis of a mixed cohort of marathon runners, sedentary men and women as well as longitudinal studies on athletes and non-athletes that showed increased immunity with increased exercise training. However, one study observed a lower risk for upper respiratory tract infections (URTI) in over-trained compared with well-trained athletes. Interpretations of the results of such studies need to be made with care.

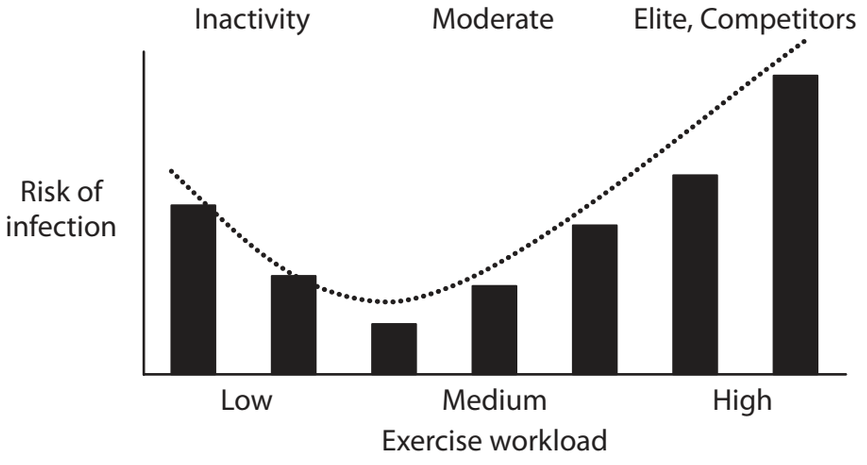


**Figure 1.** The risk of infection in relation to physical activity. Nieman et al.,1994.

### 5.2. The S-curve

35. With regard to induced infections in animals, the influence of any exercise intervention appears to be pathogen specific, and dependent on the species, age, and sex of the animals selected for study, and the type of exercise paradigm. Individuals exercising moderately may lower their risk of upper respiratory tract infections (URTI) while those undergoing heavy exercise regimens may have higher than normal risk. When including elite athletes in the J-curve model, the curve is suggested to be S-shaped (Figure 2).

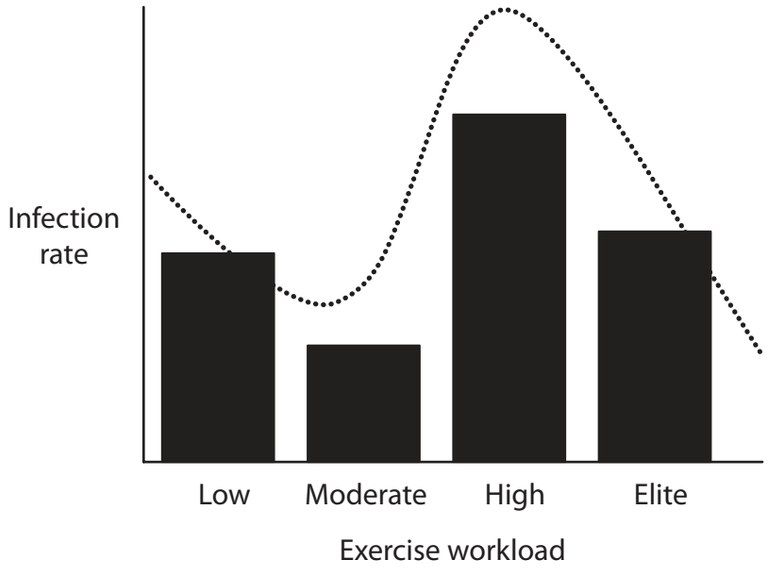


**Figure 2.** S-shaped relationship between training load and infection rate. Malm et al., 2006.

**6. The open window theory**

36. The J-curve relationship has been established among scientists, coaches, and athletes. However, the immunological mechanism behind the proposed increased vulnerability to upper respiratory tract infections (URTI) after strenuous physical exercise is not yet described. The phenomenon is commonly referred to as the "open window" for pathogen entrance. The "open window" theory means that there is an 'open window' of altered immunity (which may last between 3 and 72 hours), in which the risk of clinical infection after exercise is excessive. This means that running a marathon or simply engaging in a prolonged bout of running, increases your risk of contracting an upper-respiratory system infection. Fitch reported that Summer Games athletes who undertake endurance training have a much higher prevalence of asthma compared to their counterparts that have little or no endurance training. Years of endurance training seems to incite airway injury and inflammation. Such inflammation varies across sports and the mechanical changes and dehydration within the airways, in combination with levels of noxious agents like airborne pollutions, irritants or allergens may all have an effect.

37. It is well known that exhausting exercise can result in excessive inflammatory reactions and immune suppression, leading to clinical consequences that slow healing and recovery from injury and/or increase your risk of disease and/or infection. Comparing the immune responses to surgical trauma and stressful bouts of physical activity, there are several parallels; activation of neutrophils and macrophages, which accumulate free radicals, local release of proinflammatory cytokines, and activation of the complement, coagulation and fibrinolytic cascades. Both physical and psychological stress have been regarded as potent suppressors of the immune system, which leaves us with many unanswered questions about whether or not physical exercise is beneficial or harmful for the immune system.

38. One of the most studied aspects of exercise and the immune system is the changes in leukocyte numbers in circulating blood. The largest changes occur in the number of granulocytes (mainly neutrophils). The mechanisms that cause leukocytosis can be several: an increased release of leukocytes from bone marrow storage pools, a decreased margination of leukocytes onto vessel walls, a decreased extravasation of leukocytes from the vessels into tissues, or an increase in number of precursor cells in the marrow. During exercise, the main source of circulatory neutrophils are primary (bone marrow) and secondary (spleen, lymph nodes, gut) lymphoid tissues, as well as marginated neutrophils from the endothelial wall of peripheral veins. Fry et al.,

observed that neutrophil number increases proportionally with exercise intensity following interval running over a range of intensities. Exercise intensity, duration and/or the fitness level of the individual may all play a role in regards to the degree of leukocytosis occurring. One way to cure physical stress for the immune system is to increase the total number of leukocytes for fighting the infection and for normalizing the homeostasis. The argument that exercise induces an inflammation like response is also supported by the fact that the raised level of cytokines result in the increased secretion of adrenocorticotrophic hormone (ACTH), which induces the enhancement of systemic cortisol level. Monocytes and thrombocytes are responsible for the initiation of exercise induced acute phase reaction.

**7. Physical activity – A stimulator and an inhibitor to the immune system**

39. Primarily physical activity stimulates the immune system and strengthens the infection defense. There are indications that untrained people who start exercising regularly get a progressively stronger immune system and become less susceptible to infections. Intensive endurance training or competition which last for at least one hour stimulates the immune system sharply in the beginning, but a few hours after exercise/competition, a weakened immune system results. This means that the immune system in the hours after hard exercise/competition has a weakened ability to fight against bacteria and viruses and the susceptibility to infection is temporarily increased. This effect is seen in both untrained and trained individuals. How long this period lasts for is partly dependent of the intensity and duration of the exercise, and is very individual. The "open period" can last from a few hours up to a day. If such a long-term activity session happens too frequently, it can cause prolonged susceptibility to infections and increased risk of complications if an infection is acquired. Planning of training/activity/competition and rest periods is therefore very important and should be done on an individual basis.

**References and Acknowledgements**

http://emedicine.medscape.com/article/1146199-overview#showall

http://www.intechopen.com/books/current-issues-in-sports-and-exercise-medicine/exercise-and-immunity

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