Pearson Edexcel International Advanced Level

Biology

Advanced

Unit 5: Energy, Exercise and Coordination

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Scientific Article for use with Question 7

Paper Reference

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Scientific article for use with Question 7.

Aspects of Aging and Disease

1. Aging is difficult to define but is perhaps most widely understood to be a decrease in the ability to survive. As people age, they are less able to perform strenuous physical activities which were relatively easy when they were younger. With aging comes a decline in the function of most organs in the body, making elderly people more susceptible to disease. Indeed, most major diseases of the developed world, such as coronary heart disease, cancer and diabetes type 2 are age-related. With aging comes senescence, that is, a decline in the functions of almost all parts of the body and at all levels of organisation, from cells to organ systems. Senescence changes may be responsible for some diseases of old age or may increase susceptibility to certain diseases. Thus elderly people make up a large proportion of patients in hospitals and in most countries a higher proportion of the health budget is devoted to the care and treatment of the elderly.

2. The average length of life of individuals in a population is known as the life expectancy. Life expectancy has increased over the last 100 years in the UK from 46 years in 1893 to 78 years in 2004. This increase has been due to developments in modern medicine, as well as to improvements in public health care, nutrition and housing. The increase in life expectancy has resulted in an enormous expansion of the elderly population in all industrialized countries, though this is less marked in developing countries. However, although the life expectancy has increased over the last 100 years, the human life span, that is, the maximum age that can be attained by members of a particular species, has not. Humans can live up to the age of about 120 years, but such longevity is exceptional. Humans live longer than other mammals: an elephant, for example has a life span of 70 years, while that of a mouse is a mere three years. While the life span of a species is inherent, humans are able, to a certain extent, to increase their life expectancy by controlling their environment.

3. The deleterious effects of the aging processes are numerous and diverse. They affect cells, tissues, organs and systems.

4. Cellular functions decline in efficiency with advancing age. For example, the abilities of mitochondria to survive hypoxic insult and perform oxidative phosphorylation, the synthesis of structural, enzyme and receptor proteins, the abilities of cells to take up nutrients and repair chromosomal damage all decline with age. Aged cells also have irregular and abnormally shaped organelles, particularly nuclei, Golgi apparatus and endoplasmic reticulum and accumulate waste products.

5. All tissues are affected with age. For example, muscle mass is subject to a condition known as muscle atrophy due to a reduction in size of muscle groups and to losses of individual muscle fibres. This results in a decreased capacity for work. Other factors, such as cardiovascular, respiratory and joint functions, also influence muscle strength. If the elderly are disabled by disease, for example, arthritis, mobility may also be restricted and muscles will atrophy unless specific exercises are undertaken.

6. Age-related changes to organs include a decrease in the size and activity of several major organs. There is a decrease, for example, both in size and elasticity of the lungs, resulting in a reduced gas exchange capacity. In general, the function of the lungs is still sufficient for most activities although the capacity for strenuous activity will be reduced due to a decline in cardiovascular function.

7. The brain loses weight with age, reducing from a typical mass of 1.4 kg at 20 years of age to about 1.3 kg at the age of 60. The loss is due to changes in the composition that include an enlargement of the ventricles and a widening of the surface channels. Nerve cells are also lost and amyloid protein may be deposited. An accumulation of the pigment lipofuscin also occurs in certain neurons. These changes are believed to be responsible for a lengthening in reaction times, a decline in problem-solving and learning abilities and an impairment of memory.

8. Changes to the skin are among the most easily recognized effects of aging. Indeed, many people use the appearance of skin and hair to assess the age of an individual. These changes include wrinkling, changes in skin pigmentation and greying and loss of hair. Skin wrinkling is caused by changes to collagen, with increased cross-linking and a reduction in elasticity. The follicles producing grey hair lack the pigment-forming melanocytes. There is a large variation in hair loss that is not surprising given the many genetic and hormonal influences involved.

9. Skin wounds heal more slowly in older individuals. Studies have compared healing of ischemic (reduced blood flow) and fully vascularized wounds in young and old rats. The fully vascularized wounds healed equally well in both populations whereas ischemic wounds took significantly longer to heal in older animals. It may be that impaired wound healing in older people may be related to diseases, such as atherosclerosis, or hardening of the arteries, which contributed to ischemia of the wounded tissue.

10. Immune function also declines with age. The thymus atrophies and there is a progressive decline in the function of T lymphocytes.

11. Numerous well-documented defects may occur in the cardiovascular system as it ages. Connective tissues, which are essential components of blood vessel walls, lose elasticity and this increases the rigidity of the vessels. Blood vessels are also prone to calcification and hardening of the arteries leading to atherosclerosis. The narrowing of the lumen of blood vessels by arteriosclerosis leads to an increase in blood pressure in the elderly. With age, the heart muscle also becomes less efficient and the heart enlarges due to accumulation of fibrotic tissue, leading to a decline in cardiac output. A consequence of these changes is a reduced delivery of blood to peripheral tissues in the heart itself.

CAUSES OF AGING

12. A number of theories have been proposed to explain cellular aging. These theories can be divided into two broad groups: those that are based on 'wear and tear' and those that propose a genetic basis.

'WEAR AND TEAR' THEORIES

13. 'Wear and tear' theories suggest that aging processes in cells are due to a continual exposure to harmful agents from both inside and outside the cell throughout life. These agents include: free radicals, glycated proteins, waste products and products of erroneous biosynthesis, the error-catastrophe theory.

FREE RADICALS

14. Free radicals are molecules that have an unpaired electron. This makes them a highly reactive although they can be stabilized by the donation of electrons to, or removal from, other molecules. As a result of this process new radicals are produced and a chain reaction can be propagated. Free radicals are produced in phagocytic cells in processes aimed at destroying pathogens. They may also be produced during endogenous enzymatic reactions, especially oxidation-reducing reactions associated with hyperglycemia or following exposure to tobacco smoke or ionizing radiation.

15. The most studied free radical *in vivo* is the highly reactive hydroxyl radical ($OH_2^{\bar{}\bullet}$) formed by the action of ionizing radiation and from some intermediates in biochemical processes. The superoxide radical ($O_2^{\bar{}\bullet}$) is less toxic and is produced, for example, by metabolic reactions of the electron transport chain where oxygen is normally reduced to water by accepting electrons. During this process, a small proportion of this oxygen can be released as the superoxide radical after having accepted only one electron.

$$O_2 + e^- \rightarrow O_2^{\bar{}\bullet}$$

16. While phagocytes routinely produce superoxide radical as part of their antibacterial defence, it has been estimated that each cell in the body is exposed to attack by around 10 000 free radicals per day. This sustained exposure is thought to cause progressive damage to cells. The damaging chain reactions cease when two radicals meet and form a covalent bond, or when they react with a molecule that acts as a free radical trap. The latter includes vitamin E which acts as a free radical scavenger and, by virtue of its lipid solubility, may help to prevent damage to biological membranes. Glutathione (GSH), a tripeptide present in most cells, contains a thiol (–SH) group that is readily oxidized. Glutathione is usually maintained in a reduced state in the cytosol of cells and protects against free radical damage. The enzyme superoxide dismutase removes superoxide radicals by converting them into hydrogen peroxide and dioxygen. The hydrogen peroxide is then oxidized to water by the catalase.

Superoxide dismutase

$$2H^+ + 2O_2^{\bar{}\bullet} \rightarrow H_2O_2 + O_2$$

Catalase

$$2H_2O_2 \rightarrow H_2O + O_2$$

17. There is evidence that dietary antioxidants, such as vitamins E and C, may delay the aging process and increase life expectancy in rats, mice and some nonmammalian species but it is not known whether they act solely by reducing free radical damage.

WASTE PRODUCTS

18. During aging, increasing amounts of waste material accumulate in the cytoplasm of cells. Many of these are waste products of normal cellular metabolism. For example, lipofuscins are yellow-brown pigments produced by degeneration of cell membranes and organelles, probably by the free radical peroxidation of membrane lipids. Lipofuscins accumulate with age in many types of cells, particularly nondividing cells such as those of muscle. Lipofuscins are chemically inert, strong cross-linked molecules that are stored in mysosome-like structures. They are not susceptible to enzymatic digestion by the lysosomal enzymes. It has been suggested that a gradual accumulation of substances like lipofuscins within cells interferes with their normal function, though there is no conclusive evidence for this. Futhermore, there is no correlation between the amount of lipofuscin accumulated and the reduction in cell function and survival.

ERROR-CATASTROPHE THEORY

19. The error-catastrophe theory suggests that cellular dysfunction and, ultimately, cell death arises due to an accumulation of abnormal proteins. Protein synthesis involves transcription of DNA to give mRNA, which is transported to the cytoplasm and is translated to form polypeptides. Random errors in transcription and/or translation will lead to formation of abnormal proteins whose accumulation might impair cellular function. If the protein in question is an enzyme, such an error may lead to a malfunctioning enzyme and cellular dysfunction. Although enzyme activity is known to decline with aging, it has not always been possible to demonstrate any changes in enzyme structure with age. It seems that proteins are synthesized appropriately in older cells and most subsequent changes to their structures occur posttranslationally.

20. Some studies have indicated that certain enzymes have a changed conformation in an older cell. This suggests that enzyme molecules retained inside the cell for long periods are slowly denatured and consequently lose their biological activity. In younger cells, the original shapes of proteins can be restored by cycles of denaturation followed by renaturation. Weak interactions that confer shape to the denatured form of protein molecules are broken, allowing them to fold back to their original shape. This process therefore corrects the defective shape of denatured enzymes and produces molecules that are as efficient as a newly synthesized enzyme. Unfortunately, such repair mechanisms lose their efficacy as the cell ages.

GENOME-BASED THEORIES

21. There is evidence to suggest that aging is under genetic control. A number of genetic based theories have emerged, including those that suggest programmed aging and those that propose gene mutations.

PROGRAMMED AGING

22. The theory of programmed aging suggests that each species has an in-built biological clock and that aging involves a genetically programmed series of events. In the 1960s, Hayflick demonstrated that cells are restricted in the number of times they can enter the cell cycle by an in-built genetic program of senescence. He showed that cultural fibroblast cells derived from human embryos could undergo 50 cell divisions, whereas those from adults were limited to about 20. In culture, the number of divisions is constant for each type of cell. This is referred to as the Hayflick limit. Furthermore, the factors that control the number of divisions are intrinsic to the cell and are not influenced by their environment. For example, if the nucleus of an old cell is transplanted into a young cell from which the original nucleus has been removed, the resulting cell has a lifespan that reflects that of a transplanted nucleus.

23. When cells grown in culture are frozen and then recultured, they appear to retain the memory of the number of times they have already divided in the original culture. Hence they only complete the 'unused' number of cell divisions. It therefore appears that there is a biological clock within all cells. This biological clock, at least in part, resides in the telomeres, which are extensions of DNA found at the end of chromosomes. Telomeric DNA protects the ends of the DNA molecule from damage. When DNA is replicated prior to cell division, telomeric DNA does not replicate. After each cell division the telomere becomes shorter in length. Once the telomeres shorten to a particular length, the cell can no longer divide and dies. The activity of telomerase can prevent the shortening of telomeres and enable the cell to divide continuously. Most somatic cells contain an inactive form of telomerase although a number of cell types, such as hemopoietic cells and cancer cells, have a permanent telomerase activity. These cells can divide indefinitely and are therefore potentially immortal.

GENE MUTATIONS

24. It is well known that mutations occur in genes during the lives of cells and that these mutations can alter the activities of the cells. The gene mutation theory suggests that accumulation of mutations during the course of life leads ultimately to tissue and organ malfunctions and eventually death.

25. Genes are composed of DNA. The cell has several mechanisms to repair damage, that is, mutated DNA. Enzymes within the cell excise the damaged region of the gene and add back a new set of nucleotides using the undamaged DNA strand as a template. The gene mutation theory suggests that, with time, these DNA repair mechanisms become less efficient and some mutations are not repaired leading to functional changes.

26. In support of this theory, DNA obtained from liver cells of older mice has been found to have a greater number of mutations compared with similar cells from younger mice. In addition, liver cells obtained from strains of mice with a short lifespan show a higher incidence of mutations compared with similar cells from a strain of mice with longer lifespan. Radiation is known to cause mutations and shorten the lifespan of cells. It has been suggested that natural radiation might accelerate the aging process.

AGE-RELATED DISEASES

CANCER

27. In general, the incidence of most cancers increases with age with more than half of all cancers occurring in people over the age of 65. Two main hypotheses have been proposed to explain the link between cancer and age. First, an age-related accumulation of carcinogenic substances may increase the incidence of cancers in the elderly. This process is independent of the senescence changes described above that occur in the aging of the body. The second hypothesis proposes that age-related changes may make cells more vulnerable to becoming cancerous. Changes in immune, nutritional, metabolic and endocrine status occur with age and may create a more favourable environment for the induction of cancer. Such physiological changes may affect a number of cell processes such as the detoxification of mutagenic agents and the repair of damaged DNA.

CARDIOVASCULAR DISEASE

28. Many of the changes in the cardiovascular system may be caused by disease rather than old age *per se*. The concentration of cholesterol in the plasma increases with age. Elevated levels over the years are thought to contribute to the high incidence of mortality from coronary heart disease especially if other risk factors are present. This risk may be decreased by changes to lifestyle, since eating an inappropriate diet, smoking and a lack of exercise are known to be associated with atherosclerosis.

PARKINSON'S DISEASE

29. Parkinson's disease affects between 1 and 2% of individuals over the age of 70. The major defect in Parkinson's disease is degeneration of dopamine-secreting nerve cells although other neurons and neurotransmitters may also be affected. Patients have severe attacks of tremors that affect one hand and then spread to the leg on the same side and then to other limbs. The average survival time is eight to 10 years after diagnosis. Parkinson's is distinct from Alzheimer's disease in that different nerve cells are affected and this is loss of motor function, which is usually unaffected in Alzheimer's disease. A further feature of Parkinson's disease is the presence of cytoplasmic inclusions called Lewy bodies in some of the surviving neurons. Some researchers believe that an excess of free radicals causes the degeneration of these neurons.

HUTCHINSON-GILFORD SYNDROME (PROGERIA) AND ALZHEIMER'S DISEASE

30. Hutchinson-Gilford syndrome or progeria is a disorder that causes premature aging. The name progeria comes from the Latin and Greek words *pro* and *geraios* that mean early and old age respectively. The syndrome was described by two British doctors in 1886 (Hutchinson) and 1904 (Gilford). Children with progeria age about 10 times faster than normal; thus a child of eight to ten will look like an 80-year-old. The development and appearance is seemingly normal in the first two years of life after which the characteristic aging changes take place with a rapidity that can be shocking. The appearance of children with progeria is remarkably similar. Clinical features include thinning and wrinkling of skin, prominent scalp veins, loss of subcutaneous fat, alopecia (loss of hair), beak-like nose, short stature, thin limbs with stiff swollen joints, severe arthritis, osteoporosis, high-pitched (squeaky) voice and normal or high intelligence. Some features of aging are absent and these children often present with delayed development of teeth, delayed sexual maturity but no increase in incidence of cancers, diabetes or cataracts. The life expectancy is approximately 13 years with a range of 7 to 27 years. Death usually occurs from a heart attack or cerebrovascular disease.

31. The diagnosis of progeria is made on clinical grounds and can be difficult due to the rarity of the condition and its insidious onset in the early stages. Given its rarity, children with progeria often think they are the only ones with this disorder. At school these children perform very well and have a cheerful and open nature. However, because of their appearance, they are usually stared at by strangers and must learn to cope with such social problems from an early age. No treatment is available for progeria. Patients may be placed on low-dose aspirin therapy to delay symptoms of atherosclerosis.

32. Progeria is a rare condition affecting one in 10 million people and about 100 cases have been identified to date. In 2005, Europe had about 10 cases, with approximately 30 known cases worldwide. The disease is not restricted to any particular race or geographical area but males are affected one and half times more frequently than females. Although originally classified as an autosomal recessive condition, the precise mode of inheritance is still unclear. More recent studies have suggested a sporadic dominant mutation. This mutation results in the production of a truncated form of lamin A, a protein necessary to maintain the structure of the nucleus and control the movement of materials between the nucleus and cytoplasm. Indeed, a single base change in the lamin A gene (LMNA) on chromosome 1 can cause the syndrome. The identification of the mutation has enabled a diagnostic genetic test to be developed that should allow an earlier identification or elimination of progeria in symptomatic children. In most cases, the mutation is probably 'fresh' and has occurred only by chance in the child and is not found in either parent.

33. Fibroblasts isolated from patients with progeria and grown in tissue culture have a shorter life span than fibroblasts from normal individuals of a similar age. This is due to the chromosomes of progeria sufferers having short telomeres, which results in cells having a lower Hayflick limit. Furthermore, some studies have shown a decrease in the ability of cells from patients with progeria to repair damaged DNA, although this finding has not been supported by other studies.

34. Alzheimer's disease (AD) is a degenerative condition of the brain in which some nerve cells lose function and die. Late-onset AD is the most common cause of dementia in the elderly and accounts for about half of such cases of dementia. In the UK, about 5 to 10% of the population over the age of 65 develop AD and this increases to over 20% of those over the age of 80.

35. Alzheimer's disease is characterized by the presence of extracellular plaques in the brain, usually in the hippocampus, temporal and parietal regions. The patches are resistant to enzymatic or chemical digestion and remain in the brain tissue even after neuron death. They consist mainly of a core of β-amyloid peptides (Aβ) consisting of 40-42 amino acid residues entangled with tau protein and surround degenerating nerve terminals. The Aβ peptides are formed by two specific hydrolytic cleavages of a β-amyloid precursor and γ-secretase respectively. The function of APP is unclear, although it shows some resemblance to certain cell-surface membrane receptors.

36. Approximately 5 to 10% of AD cases are familial, that is inherited forms of the condition. However, most cases are sporadic or senile AD and the risk of developing the disease increases with age. Familial or early-onset AD is associated with mutations in two presenilin (PS) genes, PS1 and PS2. The pathological mechanisms by which these mutations cause AD is unclear. Mutations in PS1 are more common and appear to cause more aggressive forms of AD, in some cases with onset occurring before the age of 30 years, although 45 to 60 would be more likely for early-onset AD. Sporadic cases of AD are more likely to occur in people with the gene for the variant apolipoprotein E, called apoEε4, especially if they are homozygous. A number of environmental risk factors, including exposure to aluminium, head injuries and viral infections are also associated with AD. Alzheimer's disease is also associated with a decline in choline acetyltransferase, an enzyme required for the synthesis of acetylcholine. Indeed, there is a correlation between a reduction of choline acetyltransferase activity, the number of plaques and severity of dementia.

37. The clinical features of AD can be divided into three stages. The first stage may last two to four years and is associated with memory loss, personality changes and disorientation to time and date. The memory loss in this first stage is difficult to distinguish from the normal forgetfulness that occurs in the elderly. The second stage may last for several years and includes confusion, depression, inappropriate social behaviour, agitation and inability to carry out the activities of daily living. The memory lapses become more frequent and the patients often forget what they were doing only a few minutes previously. During this stage, personal hygiene is often neglected and vocal communication becomes impaired as the patient has difficulty remembering words. The final stage lasts for as long as 10 years. During this stage the affected individual fails to recognize their family, suffers from urinary and fecal incontinence and cannot communicate. The affected individuals are usually institutionalized at this stage.

38. The onset of AD is insidious, starting with periods of forgetfulness, leading to a confused state and eventually frank dementia. Once severe dementia develops, life expectancy is about two or three years. The clinical course is about eight years and patients often die due to infections such as pneumonia, accidents and occasionally respiratory arrest.

39. There is no simple and completely accurate test to diagnose AD, although the need for one was identified in the USA (The Surgeon General's Report on Mental Health, 1999). A firm diagnosis of AD can only be given by a histological examination of brain tissue after death. However, brain imaging techniques are proving increasingly useful in diagnosis. Two particular imaging techniques have been developed that allow the structure and activities of the body, including the brains of AD patients, to be assessed. Magnetic resonance imaging (MRI) allows the structure of the brain to be studied in a noninvasive manner. The technique is based on the principle of nuclear magnetic resonance and uses powerful magnetic fields to obtain chemical and physical information about the molecules within the brain. A computer then uses this information to generate an image of the internal structure of the brain. Physical lesions to the brain of AD patients are clearly visible using MRI. Positron emission tomography (PET) is also an imaging technique but one that allows the activities in different parts of the brain to be estimated. This is achieved by adding labelled glucose or water to the blood and then monitoring the flow of blood through the brain or the rate of glucose metabolism in the different parts of the brain. Again, a computer is able to analyze this information to produce digital images that highlight differences in the activities of the brains of normal and AD patients.

40. Given the difficulty in diagnosis, cases of AD are under reported. Early diagnosis is of considerable benefit since it would allow all concerned to make informed, early social, legal and medical decisions about the treatment and care for the patient. An early diagnosis would allow drug treatment and care that would delay institutionalization and substantially reduce costs. Conversely, an early test that indicated an absence of AD in suspected cases would alleviate the uncertainty and anxiety faced by the patients and their families. However, even if a quick diagnosis were possible, there is no effective treatment for AD. Sufferers may be placed on medication to alleviate symptoms such as depression and anxiety. Drugs that inhibit the degradation of acetylcholine within synapses, such as acetylcholinesterase inhibitors, are used in treatment. These drugs can delay the impairment of cognition, behaviour and functional abilities. Vitamin E treatment has also been used, although some studies have suggested it is of little benefit.

CALORIE RESTRICTION AND AGING

41. A reduced energy intake ('calorie restriction') is known to slow down the rate of aging and onset of age-related disorders, such as cancer (breast, lymphomas, prostate), nephropathy, cataract, diabetes, hypertension, hyperlipidemia and autoimmune diseases. This has been demonstrated in a variety of species including chickens and rodents and is also believed to be true for humans. The effects of calorie restriction were demonstrated in the 1930s using laboratory rats. Rats were divided into two groups. One group was allowed to feed freely while the other was fed on a diet containing 30% of the calories of the first group, although they were provided with sufficient protein, fats, vitamins and minerals to maintain normal health. The calorie-restricted rats lived for four years compared with three years for those allowed to feed freely. In addition, the calorie-restricted rats developed fewer age-related diseases.

42. Studies on calorie restriction have been performed in primates with encouraging results. Long-term studies on rhesus monkeys showed that calorie restriction reduced the incidence of heart disease, diabetes, and hypertension and was associated with a decreased concentration of blood cholesterol. Calorie restriction may, however, be difficult to apply to humans because many people may be unable to reduce their calorie intakes by an appreciable amount for the extended period of time required. However, it may be possible to motivate people to do this, especially those with family histories of age-related diseases such as cancer and neurodegenerative disorders.

43. The mechanism by which calorie restriction increases the life span is unclear but studies have shown that it is associated with a reduction in age-associated mutations when compared with normal diets. This was demonstrated by examining mutations in lymphocytes at four weeks, six months and one year of age.

44. A high calorie diet may increase free radical-mediated damage as the increased availability of nutrients to mitochondria increases the production of the superoxide radical. Thus, a calorie-restricted diet appears to reduce free radical damage to lipids, protein and DNA and improved the antioxidant status. Calorie restriction in animals has also been shown to reduce levels of tissue AGEs. The benefits of calorie restriction, however, depend on preventing malnutrition and reducing overall calorie intake rather than a particular nutrient.

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