chapter 18:

AGING AND DISEASE

OBJECTIVES

After studying this chapter you should be able to:

- describe some of the effects of aging on cells, tissues, organs and systems;
- list the possible causes of the effects of aging;
- describe a number of age-related clinical conditions;
- discuss how some of the clinical and social problems of aging may be managed.

18.1 INTRODUCTION

Aging is difficult to define but is perhaps most widely understood to be a decrease in the ability to survive. As people age (*Figure 18.1*), 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 (*Chapter 14*), cancer (*Chapter 17*), and diabetes type 2 (*Chapter 7*) are age-related. With aging comes **senescence**, that is, a decline in functions of almost all parts of the body and at all levels of organization, from cells to organ systems. Senescence changes may be responsible for some disease 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 high proportion of the health budget is devoted to the care and treatment of the elderly.

Figure 18.1 Characteristic appearance of a 70-year-old man with his young grandchildren.

The average length of life of individuals in a population is known as the **life expectancy**. Life expectancy has increased over the past 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 species is inherent, humans are able, to a certain extent, to increase their life expectancy by controlling their environment.

18.2 AGING OF CELLS, TISSUES, ORGANS AND SYSTEMS

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

CELLS

Cellular functions decline in efficiency with advancing age. For example, the abilities of mitochondria to survive a 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.

TISSUES

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 fibers. 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.

ORGANS

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 the 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 (*Chapter 14*).

The weight and volume of kidneys may decrease between 20–30% with age as nephrons are lost and replaced by scar tissue. This results in a decrease in the rate of filtration and hence the excretory capacity (*Chapter 8*). Older people are thus more at risk of developing renal disease.

The liver also shrinks in size due to loss of cells. There is a concomitant decline in some liver functions especially in the metabolism and detoxification of drugs and xenobiotics (*Chapter 12*). This is clinically significant because it means that many medications are metabolized and cleared from the body more slowly, a fact that must be taken into account when prescribing drugs for the elderly.

Loss in the function of sense organs occurs with age. A decline in the ability of the lens to change shape makes focusing on near objects more difficult

and wearing of spectacles becomes a necessity. Changes also occur in the lens proteins, the **crystallins**, causing them to become more cross-linked and browner in color. This results in more scattering and absorption of light, with less light reaching the retina. With age there is also a general physiological deterioration of the auditory system.

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 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** (*Section 18.3*) 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.

SYSTEMS

Changes to the skin are among the most easily recognized effects of aging (*Figure 18.2*). 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 graying and loss of hair. Skin wrinkling is caused by changes to collagen, with increased cross-linking and a reduction in elasticity. The follicles producing gray 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.

Figure 18.2 Wrinkled skin on the hand of an elderly person.

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 contributes to ischemia of the wounded tissue (*Chapter 14*).

There is evidence to suggest that endocrine function declines with age because of a reduction both of hormone production and of the numbers of hormone receptors on target cells. For example, there is an age-related decline in the functions of the reproductive organs, altered thyroid hormone status and an increase in the risk of developing diabetes (*Chapter 7*).

Immune function also declines with age. The thymus atrophies and there is a progressive decline in the function of T lymphocytes (*Chapter 4*). There is a concomitant decrease in the production of antibodies, possibly due to loss of regulatory T cell function together with an increase in the development of autoimmune reactions, leading to an increased susceptibility to infections in the elderly coupled with autoimmune injury to cells and tissues.

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 (*Chapter 14*). 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 and to the heart itself.

BOX 18.1 Sunlight and skin

Type I collagen is the major collagen (*Figure 18.3A, B* and *C*) in the dermis of the skin. Its destruction, along with damage to other structural components of the skin occurs over decades and is thought to underlie the characteristic alterations in appearance of aged skin (*Figure 18.2*).

Ultraviolet light (UV) from the sun is a major factor contributing to the premature aging of skin. This effect is called **photoaging.** The clinical features of photoaging include fine and coarse wrinkling, blotchy pigmentation and rough skin texture, often described as 'leathery'. These sun-induced changes are additional to intrinsic aging processes. For this reason, people who spend long periods in the open air, either through occupation or choice, are strongly advised to use protective UV-blocking creams. The healthiest skin is found on areas usually well covered, such as that of the genitalia and buttocks.

The mechanisms underlying collagen degradation in photoaging are not fully understood but are at least in part due to the action of matrix metalloproteinases (MMPs) released from keratinocytes and fibroblasts. The levels of these collagen-degrading proteases in skin increase as a function of age and are also transiently increased in response to the action of UV light. In addition, the synthesis of new collagen decreases as aging takes place. All these effects mean there is a progressive damage and loss of function of the collagen in the dermis. The difference between young and old skin is, in part, a reflection of an intrinsic reduction in the capacity of old fibroblasts to synthesize collagen.

Overexposure of the skin to UV light, from the sun and from tanning beds, is also associated with an increase in skin cancer especially malignant melanoma, a particularly aggressive form of cancer (*Chapter 17*) which can also occur in the pigmented retina of the eye.

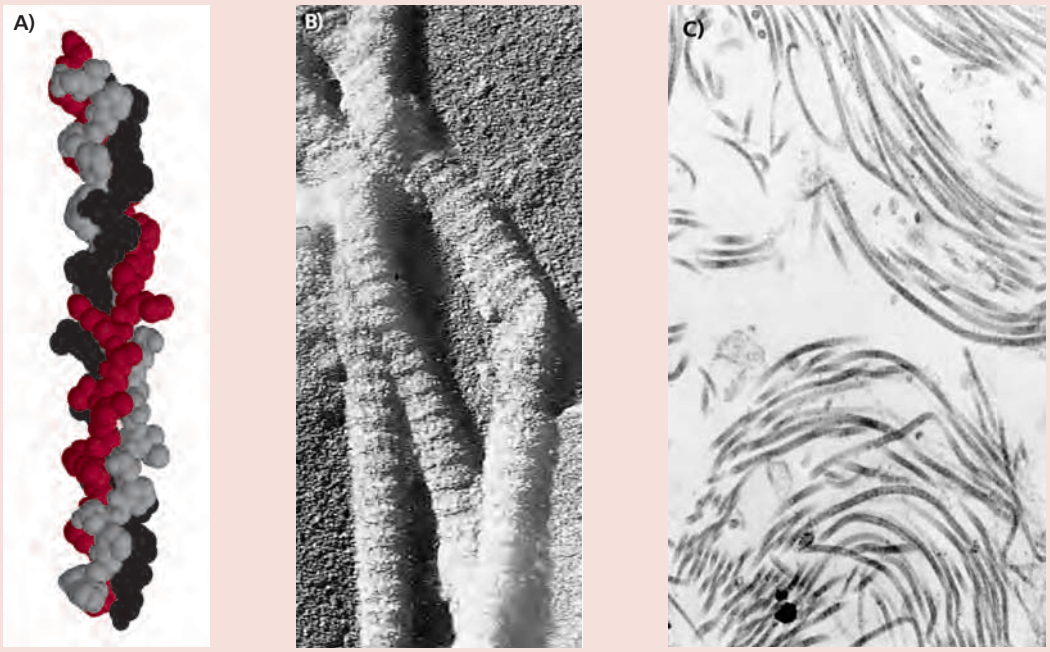

Figure 18.3 (A) Molecular model of portion of a collagen molecule. PDB file 1BKV. (B) Electron micrograph of collagen. (C) Collagen fibers in a sample of tissue.

18.3 CAUSES OF AGING

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

'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

Free radicals are molecules that have an unpaired electron. This makes them 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–reduction reactions associated with hyperglycemia or following exposure to tobacco smoke or ionizing radiation.

The most studied free radical *in vivo* is the highly reactive hydroxyl radical ($OH^{\bullet}$) formed by the action of ionizing radiation and from some intermediates in biochemical processes. The superoxide radical ($O_2^{\bullet-}$) 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:

$$O_2 + e^- \longrightarrow O_2^{\bullet-}$$

While phagocytes routinely produce the 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 (*Figure 18.4*). Glutathione is usually maintained in a reduced state in the cytosol of cells and protects against free radical damage. The enzyme superoxide dismutase (*Figure 18.5*) removes superoxide radicals by converting them into hydrogen peroxide and dioxygen. The hydrogen peroxide is then oxidized to water by the catalase (*Figure 18.6*):

$$\text{superoxide dismutase}$$

$$2H^+ + 2O_2^{\bullet-} \longrightarrow H_2O_2 + O_2$$

$$\text{catalase}$$

$$2H_2O_2 \longrightarrow 2H_2O + O_2$$

There is evidence that dietary antioxidants, such as vitamins E and C (*Chapter 10*) 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.

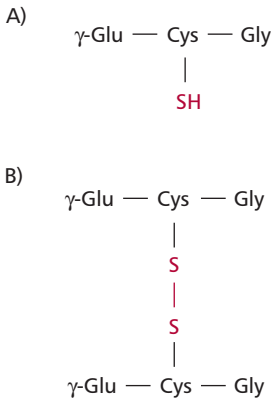

Figure 18.4 The (A) reduced and (B) oxidized forms of glutathione. See also *Figures 12.6* and *13.25*.

Figure 18.5 Molecular model of superoxide dismutase. Its Cu and Zn atoms are shown in red. PDB file 1PUO.

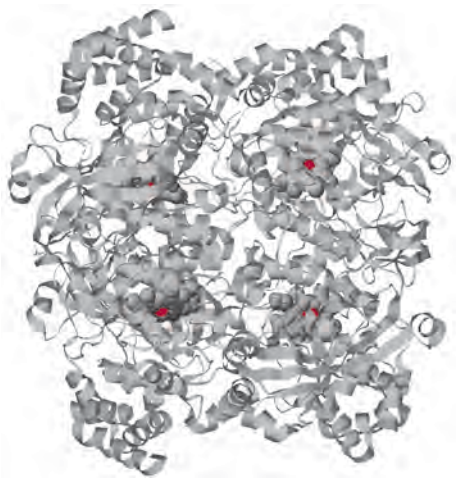

Figure 18.6 Molecular model of catalase. There are four heme groups and their associated Fe atoms are shown in red. PDB file 1DGF.

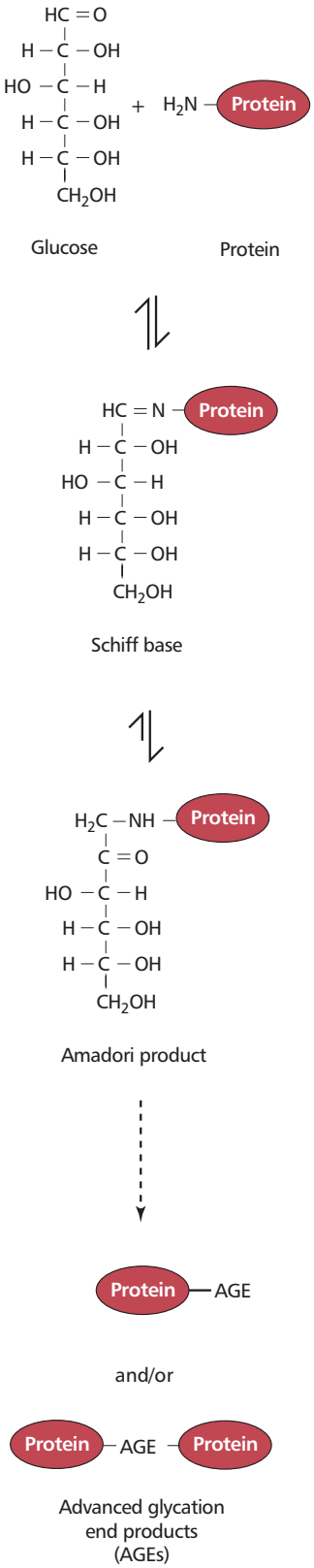

Figure 18.7 The reaction between glucose and a protein to form a glycated protein (Schiff base and Amadori product) and its subsequent conversion to an advanced glycation end product (AGE).

Glycated proteins

Both intra- and extracellular proteins are subject to posttranslational changes during aging. For example, proteins exposed to reducing sugars may undergo glycation. This occurs as a nonenzymatic reaction between free carbonyl groups of reducing sugars in their acyclic form and amino groups of the protein to form a Schiff base in a freely reversible reaction (*Figure 18.7*). The Schiff base is unstable and rearranges to a more stable Amadori product, the reaction being effectively irreversible.

The extent of glycation *in vivo* depends on the degree and duration of hyperglycemia. Glycated proteins may undergo further reactions to form cross-linked fluorescent structures called advanced glycation end products (AGEs). Advanced glycation end products accumulate with age, particularly on structural proteins, such as collagen which has a long half-life, and they can cause increased cross-linking of individual proteins. Such changes have deleterious effects since excessive cross-linking decreases the elasticity and permeability of the extracellular matrix and impairs the flow of nutrients into and waste products out of cells. Since a high proportion of the elderly population have diabetes or impaired glucose tolerance (*Chapter 7*), their proteins are more likely to be glycated.

Waste products

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, strongly cross-linked molecules that are stored in lysosome-like structures (*Figure 18.8*). They are not susceptible to enzymatic digestion by the lysosomal enzymes (*Chapter 16*). 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. Furthermore, there is no correlation between the amount of lipofuscin accumulated and the reduction in cell function and survival.

Error-catastrophe theory

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.

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

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

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 cultured 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 the transplanted nucleus.

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 ends of chromosomes (*Figure 18.9*). 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.

The suggestion that aging is genetically programmed has received some criticism. For example, the number of divisions occurring *in vitro* may be different from those that occur *in vivo*. Furthermore, some cells, such as cardiac muscle cells and neurons, do not divide after birth, and so programmed aging may not apply to these cells.

Gene mutations

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 (*Chapter 15*). The gene mutation theory suggests that accumulation of mutations during the course of life leads ultimately to tissue and organ malfunctions and eventually death.

Genes are composed of DNA. The cell has several mechanisms to repair damaged, 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.

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

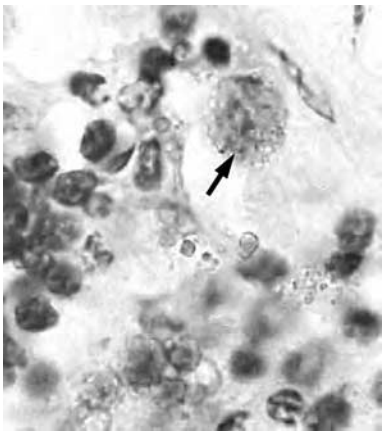

Figure 18.8 Light micrograph of a portion of a macrophage containing lipofuscin inclusions derived from lysosomes. A lipofuscin particle is indicated. Courtesy of Dr T. Caceci, Morphology Research Laboratory, Virginia-Maryland Regional College of Veterinary Medicine, USA.

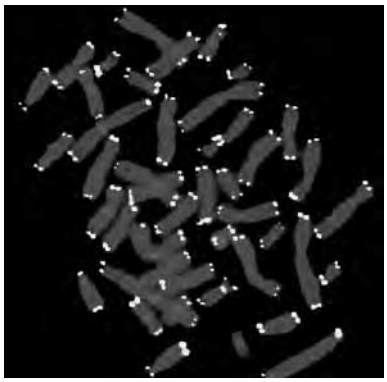

Figure 18.9 Telomeres of human chromosomes are stained to appear brighter than the rest of the chromosomes. Note these structural components of chromosomes are situated at the ends of the chromosomes. See also *Chapter 17* and *Figure 17.24*. Courtesy of Dr C. Counter, Department of Pharmacology and Cancer Biology, Duke University, USA.

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.

18.4 AGE-RELATED DISEASES

Factors that may contribute to causing disease in the elderly include the physiological and biochemical changes associated with normal aging, the cumulative exposure to harmful agents, and an increased sensitivity to agents or the environment. A number of diseases in particular show an increased incidence in older people. These include cancer, cardiovascular disease, type 2 diabetes, cataracts, arthritis, Parkinson's disease and Alzheimer disease. The latter, and Hutchinson-Gilford syndrome, which affects children, are described in *Box 18.2*.

CANCER

In general, the incidence of most cancers increases with age (*Figure 18.10*) with more than half of all cancers occurring in people over the age of 65 years. 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 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 favorable 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 (*Chapter 17*).

CARDIOVASCULAR DISEASE

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

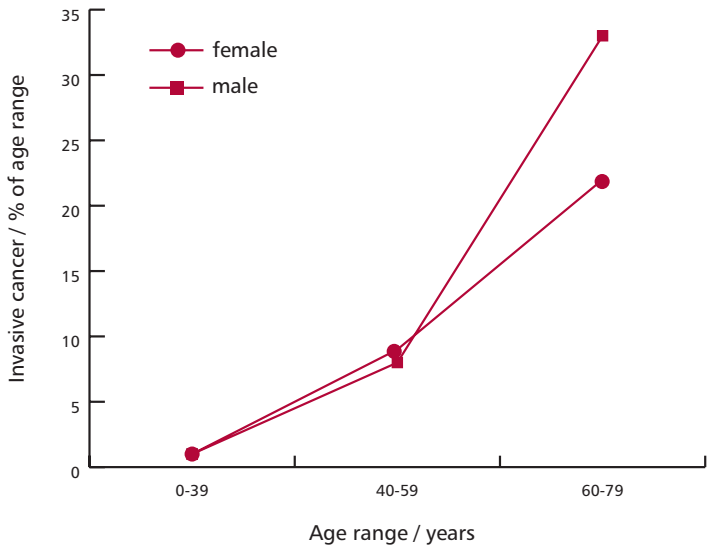

Figure 18.10 Graph showing the increasing incidence of cancers with age. Redrawn from DePinho, R.A. (2000) The age of cancer. *Nature* **408**: 248–254.

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 lack of exercise are known to be associated with atherosclerosis.

DIABETES MELLITUS TYPE 2

Many older people have some degree of impaired glucose tolerance that can be severe enough to be classified as type 2 diabetes mellitus. The main reason for high concentrations of blood sugar in the elderly is increased resistance to the effects of insulin in peripheral tissues that is associated with increased insulin levels after a meal. Diabetes in older people is strongly influenced by diet and exercise.

CATARACTS

A cataract is a partial or complete opacity of the lens of the eye that causes blurred vision. This affects the passage of light through the lens causing blindness. There are many different types of cataracts but one of the most common is senile cataract. Another risk factor for cataract is diabetes. Cataracts are treated by removal of the opaque lens and its replacement with a plastic lens.

ARTHRITIS

Arthritis is inflammation of the joints producing swelling, pain and restricted movement. Osteoarthritis affects the joint cartilage and underlying bone. It is particularly associated with increasing age, although it can occur in younger individuals who excessively use their joints in work or athletic activities. Osteoarthritis affects fingers, hip joints and knees (*Figure 18.11(A)*) but, unlike rheumatoid arthritis, does not always cause pain and inflammation. X-raying of joints usually shows some degree of osteoarthritis in nearly all elderly patients although few present with any symptoms. In severe cases, the joints of the fingers often show overgrowth referred to as Heberden's nodes (*Figure 18.11(B)*) although these tend not to be painful. Osteoarthritis cannot be cured although mild exercise can improve joint mobility.

Rheumatoid arthritis is characterized by a chronic inflammation of the joints that usually arises from an autoimmune reaction (*Chapter 5*). It is also more common in the elderly, although its onset can occur in any age group. The result is severe pain and disability. What initiates rheumatoid arthritis is not clear although a variety of bacteria, especially mycobacteria, have been implicated. The treatment of rheumatoid arthritis involves using nonsteroidal anti-inflammatory drugs. The surgical replacement of hip or knee joints may also be required in patients who become severely disabled.

PARKINSON'S DISEASE

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 (*Box 18.2*) in that different nerve cells are affected and there 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.

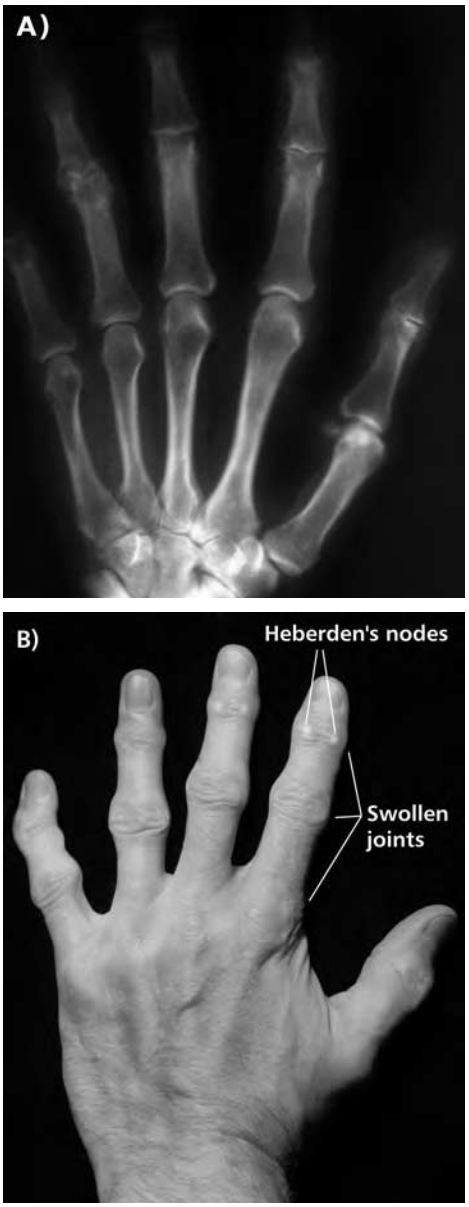

Figure 18.11 (A) X-ray image of a middle-aged female patient with osteoarthritis of the left hand who presented with pain and swelling in the finger joints. (B) The left hand of a sufferer of osteoarthritis. Courtesy of Dr. P. Young, Department of Radiology, University Hospitals of Cleveland, USA.

BOX 18.2 The young and old of aging: Hutchinson-Gilford syndrome (progeria) and Alzheimer's disease

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 (*Figure 18.12*). 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 7–27 years. Death usually occurs from a heart attack or cerebrovascular disease (*Chapter 14*).

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 usually 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.

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 a half times more frequently than females. Although originally classified as an autosomal recessive condition (*Chapter 15*), 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 (*Chapter 16*). 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.

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 (*Figure 18.9*), 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.

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 (*Figure 18.13*).

Alzheimer's disease is characterized by the presence of extracellular plaques in the brain (*Figure 18.14*), usually in the hippocampus, temporal and parietal regions. The patches are resistant to enzymatic or chemical digestion and remain in the brain

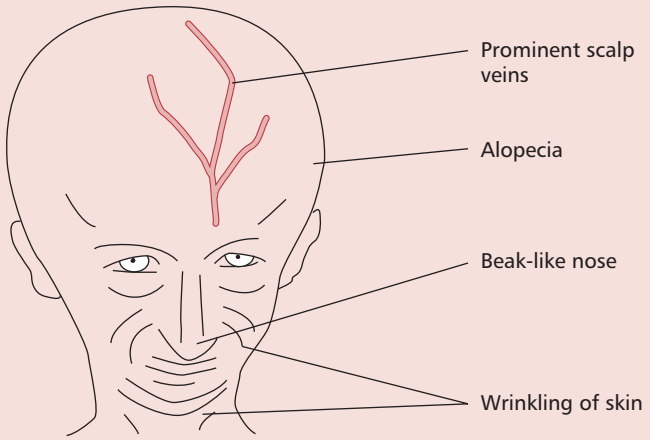

Figure 18.12 Schematic of the head of a progerian child.

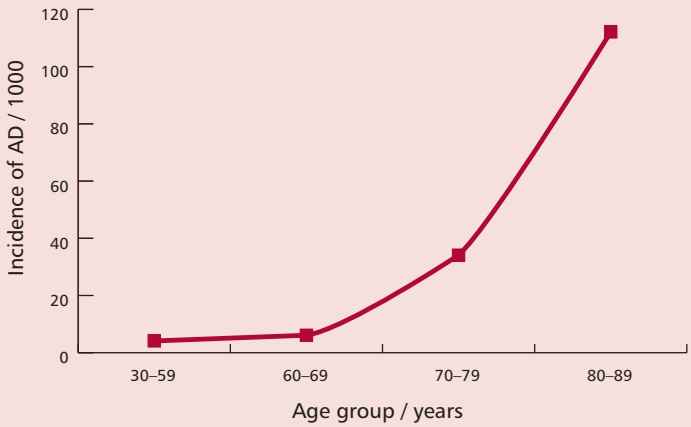

Figure 18.13 The increasing incidence of Alzheimer's disease with age. Redrawn from The Association of the British Pharmaceutical Industry website.

tissue even after neuron death. They consist mainly of a core of β-amyloid peptides (Aβ) consisting of 40–42 amino acid residues (*Figure 18.15*) entangled with tau protein and surround degenerating nerve terminals. The Aβ peptides are formed by two specific hydrolytic cleavages of a β-amyloid precursor protein (APP) and catalyzed by β-secretase and γ-secretase respectively (*Figure 18.16*). The function of APP is unclear, although it shows some resemblance to certain cell-surface membrane receptors.

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 (*Chapter 14*), called apoEε4, especially if they are homozygous. A number of environmental risk factors, including exposure to aluminum, 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.

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 behavior, 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 in remembering words. The final stage lasts for one to two years although it can last 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.

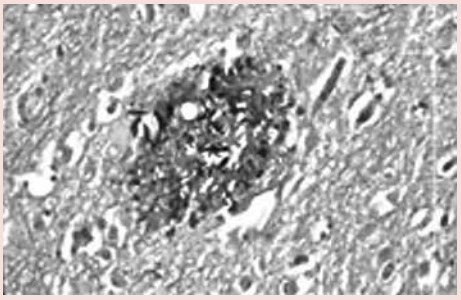

Figure 18.14 An amyloid plaque in the brain of a patient who died from Alzheimer's disease. Courtesy of Alzheimer's Disease Education & Referral Center, National Institute on Aging, USA.

Margin Note 18.1 Tau protein

The protein tau is mainly expressed in the brain where it stabilizes and orientates microtubules (MTs) necessary for transport of materials in axons. The dephosphorylation of tau promotes the rapid and extensive polymerization of MTs. In contrast, the phosphorylation of tau decreases its ability to promote their assembly. In Alzheimer's brains, tau is hyperphosphorylated, and the ability to stabilize MTs is impaired.

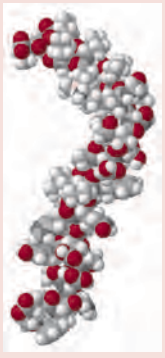

Figure 18.15 Molecular model of β-amyloid peptide. PDB file 1IYT.

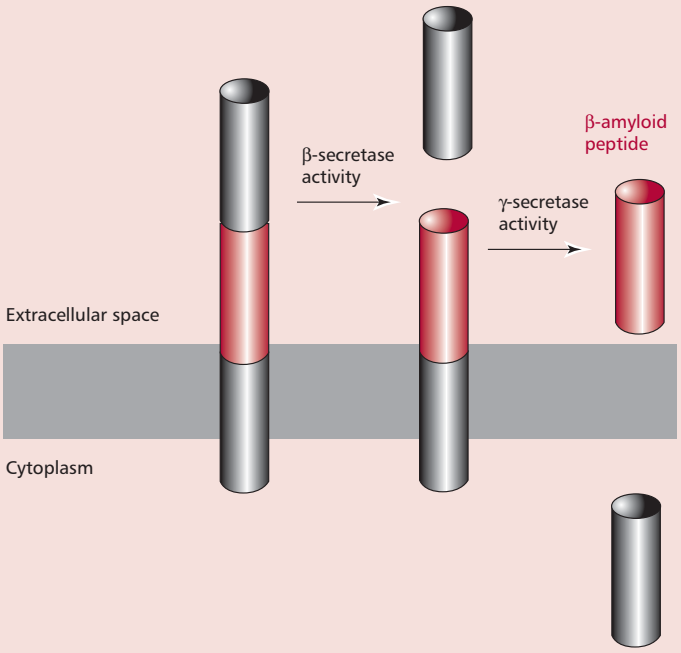

Figure 18.16 The release of β-amyloid peptide by the proteolytic activities of secretases. Redrawn from Haass, C. and Steiner, H. (2002) Alzheimer's disease – secretase: a complex story of GxGD-type presenilin proteases. *Trends in Cell Biol.* **12:** 556–562.

BOX 18.2 The young and old of aging: Hutchinson-Gilford syndrome (progeria) and Alzheimer's disease – *continued*

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.

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 brains of AD patients are clearly visible using MRI (*Figure 18.17(A)* and *(B)*). 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 labeled 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 (*Figure 18.18(A)* and *(B)*).

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 treatment and care for a patient. An early diagnosis would allow drug treatment and care that could 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, behavior and functional abilities. Vitamin E treatment has also been used, although some studies have suggested it is of little benefit.

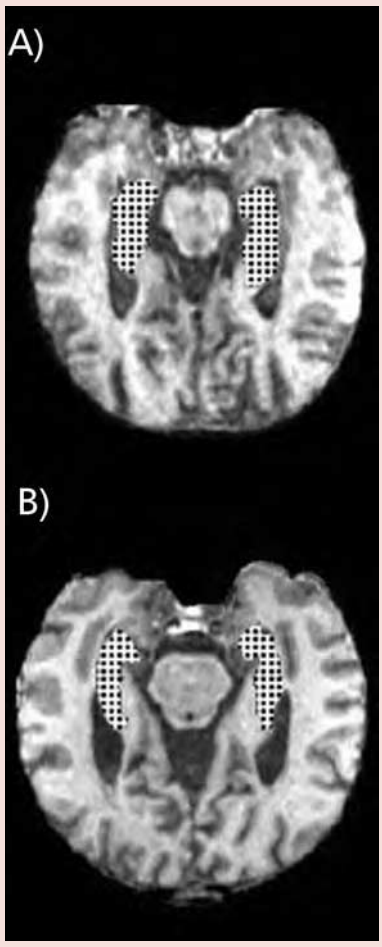

Figure 18.17 Magnetic resonance images (MRI) of (A) a normal brain and (B) a brain showing atrophy in the hippocampal area from an Alzheimer's disease patient. Courtesy of Dr M. de Leon, New York University School of Medicine, USA.

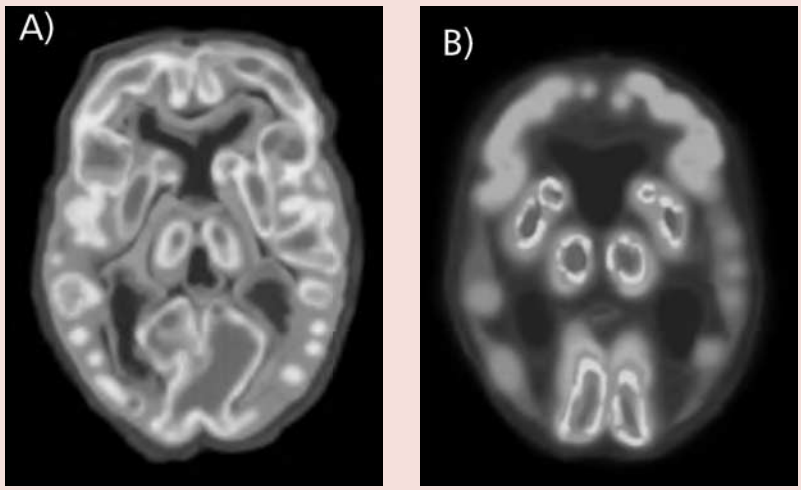

Figure 18.18 Positron emission tomography (PET) images showing activity of (A) a normal brain and (B) the brain of an Alzheimer's disease patient. Courtesy of Alzheimer's Disease Education & Referral Center, National Institute on Aging, USA.

18.5 CALORIE RESTRICTION AND AGING

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.

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.

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.

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 improves 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.

18.6 INVESTIGATIONS AND MANAGEMENT OF THE ELDERLY

Investigation and management of illness in the elderly poses a number of problems. Many conditions are more common in the elderly and often the presentation of some of these diseases may differ from that in younger people. For example, diabetes mellitus in the elderly often presents as a complication of, for example, renal failure or impaired healing of wounds, instead of the classical signs of polydipsia or polyuria (*Chapters 7* and *8*) first seen in younger patients. Elderly people, particularly those with poor mobility, may also suffer from poor nutrition. Furthermore, they are often on multiple medications that may affect test results. The high incidence of many diseases in the elderly population justifies screening programs for such conditions to increase the chances of detecting disease at a more treatable stage. Clinicians, hospitals and geriatric clinics can all carry out screening. Some of the common investigations are listed in *Table 18.1*.

Investigation	Abnormality detected
Plasma creatinine	renal impairment
Plasma calcium	hyperparathyroidism / osteomalacia
Plasma glucose	diabetes mellitus
Thyroid hormones	hypo- and hyperthyroidism
Fecal occult blood	large bowel carcinoma
Blood pressure	hypertension
Cholesterol	coronary heart disease
Mammography	breast cancer

Table 18.1 Common clinical tests used in elderly patients

CASE STUDY 18.1

Joyce, a 70-year-old woman presented with an ulcer on the sole of her right foot. This was causing her considerable pain and on examination her foot was cold and appeared ischemic. The doctor suspected Joyce might be diabetic but she did not complain of thirst or polyuria. A random blood and urine specimen were taken and tested for glucose. The following results were obtained:

	Results	Reference range
Urine [glucose]	positive	negative
Plasma [glucose]	16 mmol dm^{-3}	(3.0–5.5 mmol dm^{-3})

Questions

(a) Does Joyce suffer from diabetes?

(b) If so, what type is it likely to be (*Chapter 7*)?

CASE STUDY 18.2

Harry, a 64-year-old priest, was noted for making mistakes while delivering his sermons. His wife noticed that these were becoming more common and that he was suffering from increasing lapses of memory. Harry was persuaded to visit his doctor and during his examination he appeared to be fully orientated and held a normal conversation. However, he was only able to recall one out of every three words after five minutes. He was referred for a more detailed neurological examination that was largely normal, although an MRI scan of his brain showed some possible hippocampal atrophy. No other significant changes were noted.

Questions

(a) What is a possible diagnosis?

(b) What advice should Harry and his family be given?

(c) How should Harry be treated?

18.7 SUMMARY

The deleterious effects of aging processes are numerous and diverse. They affect cells, tissues, organs and systems. Aging may be caused by a combination of 'wear and tear' with the accumulation of harmful metabolic products, damaged proteins, genetic mutations and the in-built aging process that can be demonstrated in cultured cells. Calorie restricted diets have been shown to increase life span in animals. A number of diseases are associated with increasing age. These include cardiovascular disease, type 2 diabetes, Alzheimer's and Parkinson's disease. There is some evidence that antioxidants in the diet may delay the onset of the aging process. Ideally, elderly patients should be routinely screened for diseases associated with old age.

QUESTIONS

1. Which of the following enzymes is an established intracellular anti-oxidant?

   a) lactate dehydrogenase;

   b) phenylalanine hydroxylase;

   c) superoxide dismutase;

   d) sucrase;

   e) γ secretase.

2. Which of the following statements is the correct definition of the term 'life span'?

   a) the mean age of individuals in a population;
   b) the minimum age of individuals in a population;
   c) the age when individuals in a population reach puberty;
   d) the maximum age that can be attained by members of a population;
   e) the maximum age that can be attained by most members of a population.

3. Free radicals can be defined as:

   a) molecules with a positive charge;
   b) enzymes;
   c) cross-linked proteins;
   d) atoms or molecules with an unpaired electron;
   e) ions with a negative charge.

4. In less than 100 words, outline the role of protein glycation in aging.

5. List FOUR metabolic or molecular changes you might reasonably expect to see in aging cells.

6. List FIVE disorders that show an increased incidence with age.

7. Which of the following is NOT a characteristic feature of progeria?

   a) accelerated aging;
   b) increased incidence of cancers;
   c) osteoporosis;
   d) alopecia;
   e) short stature.

8. Complete the following table with respect to familial (early onset) and senile (late onset) Alzheimer's disease.

Feature	Familial AD	Senile AD
Age of onset / years		
Percentage of cases		
Associated gene or risk factor		

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