

CHAPTER

2

CELLS, TISSUES AND ORGANS

THE CELL MEMBRANE

There are over 200 different types of cell in the human body including skin cells, bone cells, blood cells and nerve cells. They are essentially tiny parcels of chemicals enclosed by a thin plasma membrane and it is extraordinary to think that we all originated and developed from just one of these microscopic units. Following conception, cell multiplication takes place and cells with different structural specialisations develop (see Chapter 14). Human cells vary greatly in sophistication

and function from relatively simple skin cells to highly specialised nerve cells (neurons). For the most part, human cells require three basic components: a cell membrane, cytoplasm (cyte + plasma = cell + water) and a nucleus. There are some notable exceptions that do not have a nucleus including red blood cells (erythrocytes). Although, in actual fact, they do have a nucleus but just for a very short period of time – it is ejected (extruded) as they mature. Anyway, let's not quibble. All cells need some form of plasma membrane in order to maintain structural integrity.

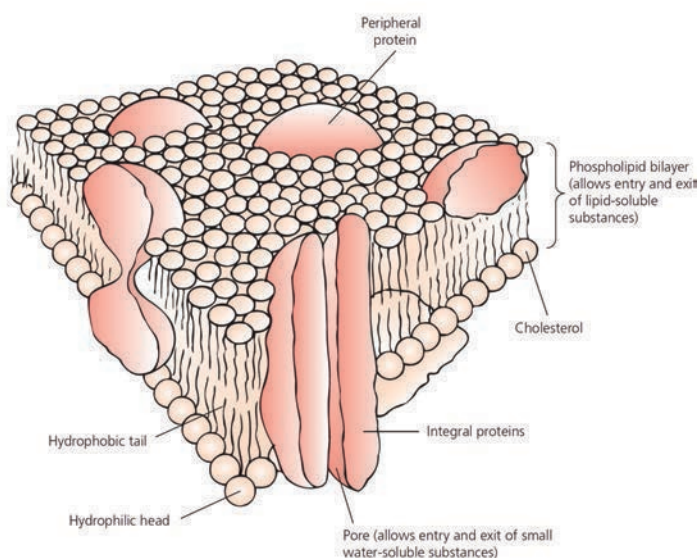


Figure 2.1 Phospholipid bi-layer of the cell membrane.

Human cell membranes consist of two layers of phospholipids, sometimes referred to as a fatty bi-layer. This provides a barrier that ensures water and ions remain in the correct concentrations within the cell (cytoplasm) and outside the cell (interstitial fluid). It is able to do this because each lipid molecule contains a hydrophilic (water-loving) head and a hydrophobic (water-hating) tail (Figure 2.1). The bi-layer is arranged like a sandwich with the hydrophilic layers on the outer surfaces (the bread) and the tails on the inside (the butter). In other words, the hydrophilic head of the molecule is attracted to water whilst the hydrophobic tail is repelled. The same principle helps to explain how washing-up liquid works! If, like me, you do a lot of washing-up you will be well aware that fat does not dissolve in water. It either floats on top of the water, making crazy psychedelic patterns, or it stubbornly refuses to let go of whatever piece of crockery it has come into contact with. The hydrocarbon chains found in washing-up liquid also have hydrophilic and hydrophobic ends (they are said to be amphipathic). The hydrophobic ends attach themselves to the grease on the plate and surround it with their hydrophilic ends pointing outwards (towards the water). This makes the enclosed oil particles water-soluble and they can be washed away. Those of you who use dishwashers are missing out on this daily battle of wits. Anyway, in human cells, amphipathic phospholipid molecules are arranged in a continuous bi-layer and provide a highly impermeable barrier (which is fortunate for the cell since it is constantly exposed to water of some description).

ION CHANNELS

Embedded into the phospholipid bi-layer (the plasma membrane) are protein molecules known as ion channels. These facilitate the transport of ions and non-fat-soluble substances in and out of the cell. We have already observed in Chapter 1 that water is transported from a high concentration to a low concentration, across a

semi-permeable membrane, depending on the relative osmolality of the two solutions. But how do these ions or solutes move between the intracellular and extracellular compartments? Firstly, ions are present in different concentrations in different fluid compartments. For example, sodium (Na^+) is the most abundant ion in the extracellular (outside the cell) fluid, whilst potassium (K^+) is the most abundant ion in the intracellular (inside the cell) fluid. Because they are present in such small concentrations in body fluids they are expressed in millimoles per litre (mmol/l). The concentration of sodium in extracellular fluid, therefore, is 135–145 mmol/l but only 10 mmol/l in intracellular fluid. The concentration of potassium, on the other hand, is 3.5–5 mmol/l in extracellular fluid and a whopping 140 mmol/l in intracellular fluid. Given the significant difference in the concentrations of both ions in different compartments it is not always necessary (or practical) for them to travel from a high to a low concentration and frequently they have to be transported in the opposite direction (e.g. against the gradient). Ion channels only allow ions of a certain size and/or electrical charge (e.g. cation or anion) to pass through the cell membrane. This is known as selective permeability. In many cases, movement of ions through the channel is governed by a 'gate' which is opened or closed in response to a chemical or electrical signal (Figure 2.2).

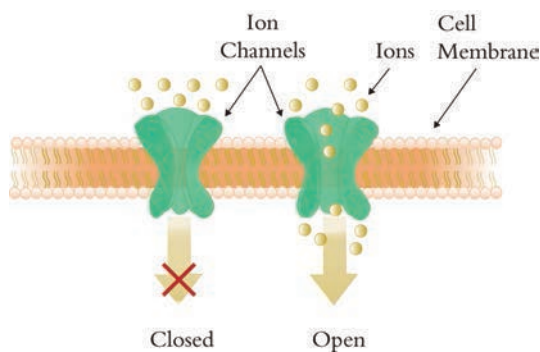


Figure 2.2 Ion channel.

ACTIVE TRANSPORT

When ions want to move from an area of low concentration to an area of high concentration they require energy to do so. Imagine that you are in a boat again but this time for fun (rather than faced with the dilemma of drinking sea water or your own urine). If you are travelling with the current, there is no need to expend energy paddling in the same direction – you simply go with the flow. If, on the other hand, you are travelling against the current you will need to expend a great deal of energy in order to make any progress at all (in fairness, that probably isn't much fun unless you really enjoy a challenge). The same applies to our ions. The energy required for an ion to be transported against the concentration gradient is provided by a chemical produced in the cells known as adenosine triphosphate or ATP (energy is stored in the covalent bonds between the phosphates). This process is called active transport since it requires the expenditure of chemical energy/ATP. Sodium and potassium also use ATP to move in and out of the cell in a form of active transport known as the sodium-potassium pump. In simple terms, three sodium ions from inside the cell bind to the ion channel (gate) whilst ATP provides the energy to open (or change the shape of) the channel. One phosphate group from the ATP (remember it was a *triphosphate*) remains bound to the channel and the sodium is released into the interstitial compartment outside the cell. The new shape of the ion channel can now accommodate two potassium ions and when they bind to it, the phosphate group is released back into the cytoplasm of the cell. This, in turn, allows the channel to return to its original shape and the potassium ions are transported from outside to inside the cell. This process is repeated over and over again. However, the most important characteristic of this mechanism is that both sodium and potassium are transported from an area of low to an area of high concentration and this can only be achieved through the expenditure of chemical energy in the form of ATP (hence active transport).

CELL-EATING AND DRINKING

Another form of transport that requires the use of ATP is bulk transport or the movement of large (macro) molecules such as proteins and polysaccharides (long chain sugars) in and out of the cell. There are two types of bulk transport: endocytosis (into the cell) and exocytosis (out of the cell). The most common types of endocytosis are phagocytosis (cell-eating) and pinocytosis (cell-drinking) and both involve the cell membrane. Both of these processes put me in mind of the 1958 science fiction movie *The Blob*. In this movie, a giant amorphous 'blob' from outer space wreaks ponderous havoc on a small US town as it engulfs hapless victims into its gelatinous mass. During phagocytosis the cell membrane surrounds or engulfs a macromolecule from outside the cell and 'buds off' to form a food vacuole (cavity) or phagosome (devouring body). Once ingested in this way, the phagosome fuses with a small intracellular vesicle called a lysosome (separating or splitting body) whose enzymes digest the food particles contained within it. Pinocytosis is a similar process in which the cell membrane engulfs or drinks a small quantity of fluid by 'pinching' it and forming a vacuole around it. This process is non-selective and any solutes present within the fluid will also be 'drunk' in this way. Exocytosis, on the other hand, refers to the process by which waste products and other substances such as hormones are exported out of the cell by secretory vesicles (such as lysosomes) and deposited into the interstitial compartment outside the cell. Before we move on to look at some of the structures to be found inside the cell it is important to quickly mention that the cell membrane also contains a number of hormone receptors on its outer surface which will be discussed in Chapter 13.

CYTOPLASM

The second 'essential' component of a human cell is cytoplasm (essentially cell water). The liquid component of cytoplasm is known as

cytosol and accounts for approximately 70% of the total volume of a typical human cell. We have already observed that the intracellular compartment contains approximately 25 litres of fluid (about 40% of our body weight) so it is no surprise that much of the cell comprises this watery substance. The cytoplasm helps maintain the structural integrity of the cell and provides a medium for transport and the many chemical reactions that take place within the cell. Cytoplasm also contains a high percentage of solutes and ions, chief amongst which, as we know, is potassium (K^+). The final 'vital' component of a human cell (except when it's a red blood cell) is the nucleus.

THE NUCLEUS AND DNA

The nucleus contains the cell's genetic material, deoxyribonucleic acid (DNA), which it uses to control cellular activity. DNA is essentially *information* and is sometimes compared to a blueprint since it contains the instructions

necessary to control the cell and, in most cases, the organism as a whole. Just like a builder uses an architectural blueprint to build a house, therefore, DNA is used to ensure that an organism is constructed and functions correctly. Unless you have an identical twin, no other human has your exact DNA code (unless you believe in parallel universes). As you can imagine, you require an awful lot of information to build and maintain a human being. If, like me, you have ever picked up a car manual and then quickly put it down again (thoroughly intimidated after a few pages) spare a thought for the people currently working on the Human Genome Project. These clever folk are attempting to map the sequence of chemical base pairs which make up human DNA in order to identify the totality of human genetic information. DNA exists as tightly wound packages called chromosomes. If we were to unravel a chromosome and look at the DNA strand at extremely high magnification, we would see the DNA double helix (Figure 2.3). This is the unique twisted-ladder structure that makes DNA unlike any other molecule.

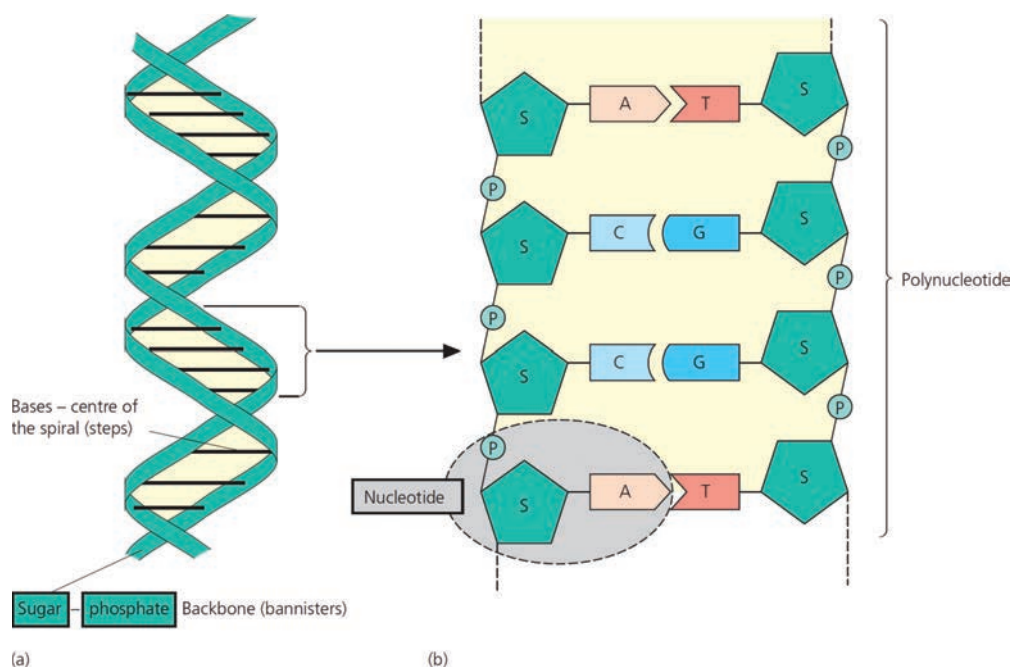


Figure 2.3 (a) DNA double helix. (b) DNA components: S = sugar (deoxyribose), P = phosphate, A = Adenine, C = Cytosine, G = Guanine, T = Thymine.

It was only confirmed in 1953 when James Watson and Francis Crick published the results of their research in *Nature* magazine (based upon the findings of Maurice Wilkins and Rosalind Franklin's X-ray studies). Watson and Crick's modelling of the double helix served to explain how DNA replicates and has enabled numerous advances in our understanding of the transmission of genetic information and disease. The discovery of DNA is also notable in that (according to Crick) it was first announced in a pub (The Eagle in Cambridge).

GENETIC INFORMATION

The sides or strands of the DNA double helix 'ladder' are composed of alternating sugars (deoxyribose) and phosphates. The 'rungs' between the strands, on the other hand, are made up of paired nucleotides or bases: adenine (A), thymine (T), cytosine (C) and guanine (G). The key to understanding this molecule is that these four bases bond together in a very precise fashion: adenine only bonds with thymine (A-T) and cytosine only bonds with guanine (C-G). The DNA code is then 'read' as a three-letter phrase (codon) that make up much longer sequences (on each side of the strand) called genes. You may be thinking that this seems a rather unlikely way to store huge amounts of sophisticated information. However, if we consider that computers can encode and store massive amounts of data simply using two binary digits (0 and 1) it seems quite generous. Other forms of communication that transmit information using limited means include Morse code (on/off tones) and Braille (six dot positions). The easiest way to conceptualise DNA, therefore, is to think of the bases as letters in an alphabet. By putting them together in sequences it becomes possible to form words or phrases. These words are then stored or collected as genes which represent a book of information. Genes (or books) are arranged along the length of each chromosome in a comparable fashion to books on a shelf. Finally, there are 46 chromosomes in the nucleus of a typical human cell which represents the stored information from these

many shelves in a similar fashion to a great library of knowledge. This may be a little simplistic but it helps to conceptualise the cumulative organisation of information from simple bases to human blueprint.

MUTATION

From time to time, normal cells are transformed into cancer cells when their DNA mutates (undergoes a change that causes unusual characteristics to develop). A neoplasm or 'new growth' results from a series of mutations that occur to genes involved in controlling cell growth. This may result in uncontrolled cellular proliferation (rapid multiplication) and the exaggeration of some normal cellular activities. In simple terms, therefore, cancer cells are good cells gone bad. They no longer follow the same 'rules' as normal cells and can produce their own growth signals, ignore anti-growth signals, invade other tissue, replicate an unlimited number of times and evade programmed cell death (apoptosis). The mutated cells develop a degree of autonomy and grow at a rate that is uncoordinated with the needs of the host. A cinematic example of the way in which some cancer cells behave can be found in the *Matrix* trilogy of films. The character Agent Smith (played by Hugo Weaving) replicates himself over and over again until he threatens to destroy the system that created him in a similar fashion to some aggressive cancers and microorganisms (see Chapter 6).

GENETIC DIVERSITY

Each species has a different number of chromosomes in their cells and it is sobering to learn that, genetically at least, we are less diverse than dogs. Dogs have a whopping 78 chromosomes compared to humans 46. However, if you consider the enormous variability of characteristics that dogs exhibit it doesn't seem quite as improbable. For example, compare an Afghan hound with a chihuahua or a Saint Bernard with a Pomeranian. Practicalities allowing, they can successfully produce

crossed offspring that are still ‘dogs’ and are themselves able to reproduce. There are many comically named examples of crossed species including the labradoodle (Labrador/poodle cross), the chihuachshund (chihuahua/dachshund cross) and the cockapoo (cocker spaniel/poodle cross). Humans demonstrate some notable physical variations (such as differences in height, hair colour/ texture, eye colour/ shape and of course skin colour) but none of these mark us out as particularly different. However, it would be wrong to say that simply because an organism has more chromosomes than another it is more sophisticated. For example, potatoes have two more chromosomes than humans (48), chickens have the same number as dogs (78) and some species of fern (e.g. adder’s tongue) have over a 1,000. The reasons that this occurs is because during the type of cell division that produces sperm and egg cells (see below) it is possible to include the original genetic material and the copy (in the cell nucleus) rather than just the copy. Consequently, the chromosomes are doubled but the information remains the same (since it is copy). In the case of adder’s tongue, it is likely that because this species has existed for such a long period of time in evolutionary terms (thought to date to the Tertiary Period between 1.8 and 65 million years ago) it has had plenty of time to undergo this process on more than one occasion.

CELL DIVISION

Human cells replicate (make a copy of themselves and their DNA) in two ways: mitosis and meiosis. Cells must divide in order for an organism to grow, reproduce and repair itself. The first type of cell division, mitosis, is also referred to as semi-conservative replication. This simply means that when it makes a copy of its DNA, one half of the old strand is always kept in the new strand. It sounds complicated but it isn’t. During mitosis, the DNA double helix unzips itself and divides into two strands (imagine a ladder dividing exactly down the middle into two halves). Facing one another are the rungs of the ladder or the nucleotide bases (A, T, C, G) in various combinations

along each side (Figure 2.3). Since we know that A can only bond with T, and C can only bond with G, it is possible to add new bases to each side of the unzipped strands of DNA. This results in two identical copies of the original DNA ladder – very clever. During mitosis, therefore, the cell duplicates all of its contents, including its chromosomes, and splits to form two identical daughter cells. Some cells divide more rapidly than others. Hair follicle cells, for example, have one of the highest rates of mitosis and an average hair grows about 0.3 mm a day or 1 cm per month. Other cells that divide rapidly are those that line our digestive tract and mucous membranes (e.g. gums). The second type of cell division, meiosis, only applies to the production of male and female sex cells or gametes (sperm and egg cells). This is sometimes referred to as reductive division since the number of chromosomes is halved from 46 to 23. When the male and female gametes unite (during conception) they produce a fertilised cell (zygote) containing the full complement of 46 chromosomes. This is why sexual reproduction produces offspring that resemble their parents but are not identical to them (the child has half of each parent’s genetic material). More of this in Chapter 14.

MITOCHONDRIA AND CELLULAR RESPIRATION

So far, we have seen that (on the whole) human cells require three essential components. Firstly, a cell membrane to ensure structural integrity and to facilitate the transport of substances in and out of the cell. Secondly, the liquid component of the cell, cytoplasm, that provides a medium for transport and the many chemical reactions that take place within the cell. Finally, the cell nucleus that contains DNA tightly wound into 46 chromosomes. DNA directs cellular activity and provides a blueprint for protein synthesis. At the same time, however, the cell also contains a number of other structures (located in the cytoplasm) called organelles that carry out highly specialised functions. These include: mitochondria, ribosomes, endoplasmic reticulum, the

golgi apparatus and lysosomes (Figure 2.4). Mitochondria are often described as sausage-shaped and produce chemical energy for the cell in the form of adenosine triphosphate (ATP). We observed earlier in the chapter, how important ATP is for the active transport of potassium and sodium ions in and out of the cell. Mitochondria work as the power plant of the cell to generate ATP through the catabolic process of cellular respiration. This process has three main stages: glycolysis (glyco + lysis = sugar + splitting), the citric acid cycle (also known as Krebs cycle) and electron transport. The first of these stages, glycolysis, refers to the process by which enzymes catabolise or split glucose, a six-carbon sugar ($C_6H_{12}O_6$), into two three-carbon molecules of pyruvic acid (Figure 2.5). Glycolysis can occur with or without oxygen but if no oxygen is present,

only a small amount of ATP is produced (fermentation). The second stage of cellular respiration, the citric acid cycle, commences after pyruvic acid (produced during glycolysis) is converted into another compound called acetyl coenzyme A (abbreviated to acetyl CoA). Acetyl CoA then combines with oxaloacetic acid to form a six-carbon molecule of citric acid. The citric acid undergoes a number of different reactions that produce ATP as well as two further compounds with the heroic names nicotinamide adenine dinucleotide (NAD) and flavin adenine dinucleotide (FAD). The citric acid cycle only occurs when oxygen is present but it doesn't use oxygen directly. It also results in the liberation of carbon dioxide (CO_2) and hydrogen atoms (H) which are accepted by NAD (as NADH) and FAD (as $FADH_2$).

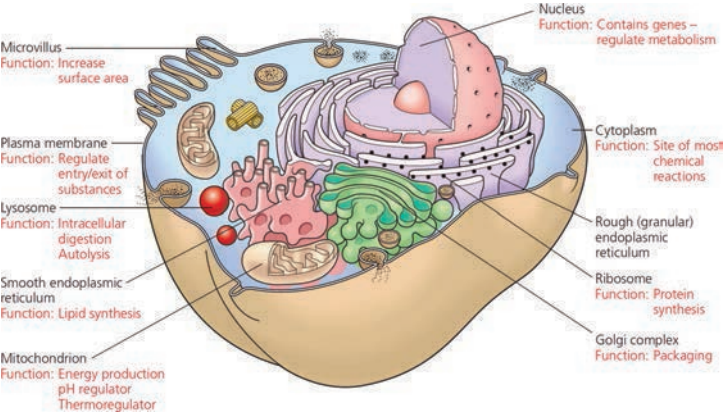


Figure 2.4 Structure and function of a typical cell.

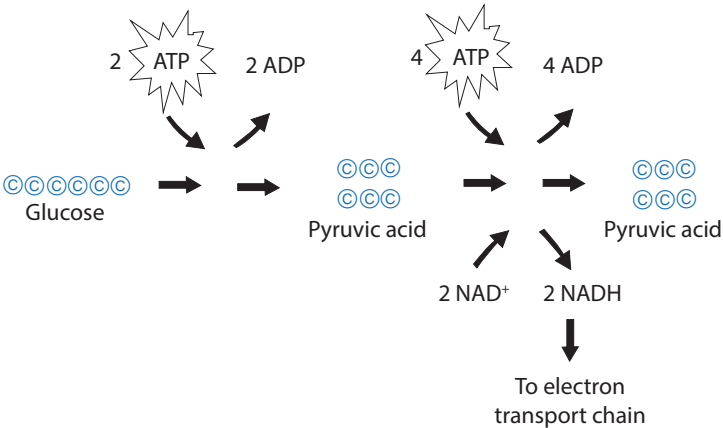
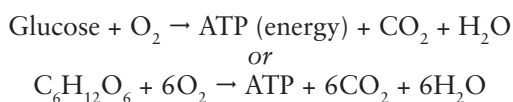


Figure 2.5 Glycolysis.

CELLULAR ENERGY

The final stage of cellular respiration is electron transport which also requires oxygen to be present. During this phase, carrier molecules on the inner lining of the mitochondrial membrane bond with electrons from the hydrogen atoms carried by NADH and FADH₂. These carrier molecules transport the electrons through a series of oxidation-reduction reactions in the mitochondria. Oxidation refers to the loss of electrons, and reduction (in chemistry) refers to the acquisition of electrons. For example, when NADH and FADH₂ are oxidised, they lose electrons which flow into the electron transport chain. These electrons ultimately encounter and bond with oxygen, thereby 'reducing' it to water (H₂O). Oxygen plays an important role in the electron transport system by attracting electrons along the chain of carriers. However, the key point is that this series of reactions liberates the energy contained within the electrons and generates ATP (chemical energy). During aerobic respiration (in the presence of oxygen) one molecule of glucose yields 38 molecules of ATP. The net (overall) gain is slightly less (36) since some ATP molecules are expended during this process. Mercifully, the production of ATP in the mitochondria is often simplified as the following equation:



This is certainly how I tend to think about cellular respiration from a practical point of view. However, it is still useful to look at the three stages of this process (glycolysis, citric acid cycle and electron transport) since it helps to explain where carbon dioxide (CO₂) and water (H₂O) have suddenly materialised from. We also noted that ATP can be produced in the absence of oxygen (anaerobic respiration) but that it is much less efficient than aerobic respiration since it only yields two ATP for each molecule of glucose. This is important since it helps to explain why hypoxia (poor oxygen supply to the cells), and oxygen debt during intense exercise, can interfere with normal

cellular activity (see Chapter 9). Anaerobic respiration also produces a number of waste products including lactate which, if not cleared from the blood, can result in acidosis (abnormal increase in the acidity of blood plasma and other body fluid).

RIBOSOMES AND RNA

The next category of intracellular organelles are ribosomes (Figure 2.4). These tiny granular structures consist of two unequal parts (one large and one small subunit) that fit together in order to manufacture proteins from amino acid building blocks using a ribonucleic acid (RNA) template from the nucleus. The name ribosome (ribo + some) is derived from ribonucleic acid and the Greek word for body *soma*. Ribosomes are produced in a specialised part of the nucleus called the nucleolus and made from protein and RNA. We have already spent quite a lot of time poking around in the nucleus looking at DNA but what is RNA? In many ways it is very similar to DNA but it differs from its close relative in a number of important respects. Firstly, RNA is built from the sugar ribose instead of deoxyribose hence ribonucleic acid instead of deoxyribonucleic acid (DNA). Secondly, DNA has a double helix and RNA consists of a single strand of nucleotides (bases). Thirdly, the nucleotide thymine (T) in DNA is replaced on the RNA strand by uracil (U) which also binds with adenine. Finally, RNA is able to transfer genetic material, needed for protein synthesis, from the nucleus to the ribosomes (also constructed from RNA) in the cytoplasm. This feature is extremely important for the maintenance of normal cellular activity.

MANUFACTURING PROTEINS

There is a direct relationship between the linear sequence of nucleotides that make up a gene, and the linear sequence of amino acids in a protein molecule. That is to say, it is possible to copy the information stored on DNA in order to produce new proteins. This

is known as the one gene – one protein (or one gene - one polypeptide/chain of amino acids) hypothesis. The process begins when the genetic information necessary for protein synthesis (a particular series of nucleotides/bases) is copied or transcribed from a strand of DNA onto a strand of RNA. This is known as transcription (Figure 2.6). The new RNA strand is referred to as messenger RNA (mRNA) since it carries the coded information out of nucleus and into the cytoplasm of the cell. When mRNA arrives at the ribosome it reassembles itself so that the large and small parts (subunits) are arranged around the mRNA strand. They then proceed to ‘translate’ the information coded on the mRNA into a specific protein. In order to do this, the ribosome relies on the interaction between mRNA and another type of RNA called transfer RNA (tRNA). As its name suggests, tRNA transfers

or transports individual amino acids to the mRNA (within the ribosome) where they are incorporated into the growing amino acid chain.

TRANSLATION

Translation occurs in three phases: initiation, elongation and termination. During initiation, the small ribosomal subunit sticks to the mRNA and unites with the large ribosomal subunit. The mRNA is now ready to receive the first amino acid and a tRNA molecule aligns with the start codon (three-letter sequence of nucleotides). The next stage, elongation, sees the mRNA slide through the ribosome one codon at a time (imagine a conveyor belt). As each new codon enters the

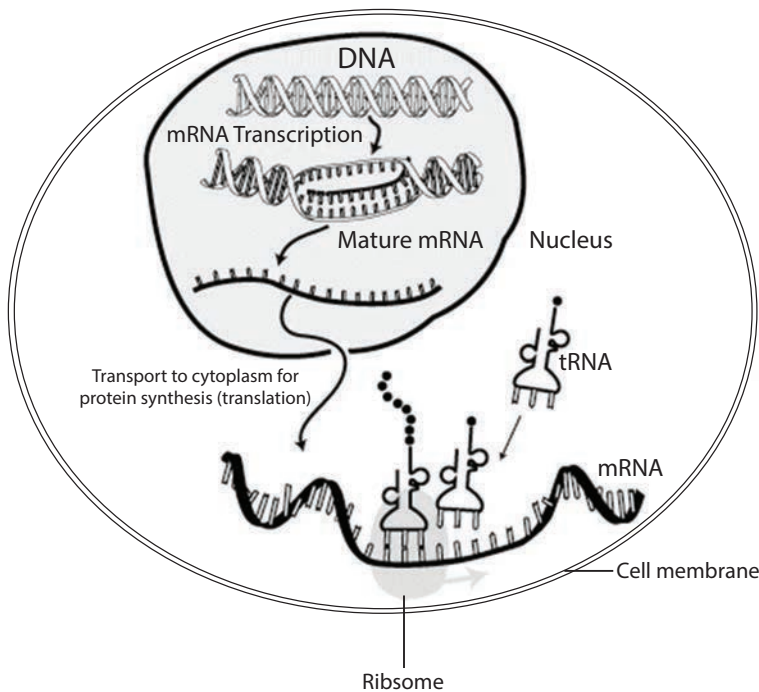


Figure 2.6 Transcription, translation, mRNA and tRNA.

ribosome, a complementary tRNA provides a new amino acid. When the amino acids are aligned next to one another, the ribosome constructs a peptide bond between them. The resulting protein chains can be hundreds of amino acids in length and synthesising these molecules requires a great deal of chemical energy (ATP). Finally, when the last part of the mRNA enters the ribosome (the stop codon), translation ends and the ribosomal subunits, mRNA and protein, separate. The protein is then folded into the correct shape and is ready to be transported to wherever it is required. If a coding error occurs during the elongation phase of this process it can produce an entirely different protein. For example, because each section of the polypeptide chain is constructed using codons, consisting of three nucleotides (e.g. adenine/thymine/adenine), if a single nucleotide is 'deleted' it will change the entire sequential arrangement after that point. This type of nucleotide 'spelling mistake' helps to explain why we exhibit different physiological characteristics and variations. Blood type A and blood type B, for example, both possess the same number of nucleotides (1,062) but blood type B has a slightly different sequence of amino acids (7). This simple difference in 'spelling' has important implications for transfusion compatibility as we will see in Chapter 5.

ENDOPLASMIC RETICULUM AND GOLGI BODY

The next intracellular organelle is the wonderfully named endoplasmic reticulum (ER). ER is a series of interconnecting membranous canals that are continuous with the nuclear membrane and encompass a large amount of space within the cell (Figure 2.4). ER is classified as either rough or smooth. Rough ER is studded with ribosomes on the cytoplasmic side of the membrane and contributes to the production of proteins (as described in the preceding section). In pancreatic cells, for example, the rough ER produces insulin (a peptide hormone). Smooth ER, on the other

hand, has no ribosomes and manufactures lipids and steroid hormones (see Chapter 13). It is also associated with the detoxification of some drugs and compounds particularly in the cells of the liver. In muscle cells, the ER is known as the sarcoplasmic reticulum and releases calcium ions during muscular contraction (and absorbs and stores them during relaxation). The golgi body (also referred to as the golgi complex or golgi apparatus) is also found in the cytoplasm and is often compared to a pile of flattened sacs. These sacs are actually a series of flattened membranous canals known as cisternae and they manufacture, store and transport cellular products (particularly those from the ER). One end of the golgi body (the *cis* face, usually closest to the ER) acts as the receiving area whilst the other end (the *trans* face) acts as the 'shipping' area. I can't help thinking of a giant warehouse where 'goods' are transported in and shipped out again. Proteins and other substances are conveyed to and from the golgi body in tiny, fluid-filled, membranous sacs called transport vesicles. Some of these are used within the cell and some extruded into the extracellular compartment (exocytosis). Depending on the type of cell, there may be many golgi bodies or there may be very few.

LYSOSOMES

The final intracellular organelle discussed in this chapter is manufactured in the golgi body and is called a lysosome (lyse + soma = splitting + body). As its name suggests, it is not the friendliest of the intracellular community. Lysosomes are small vesicles that contain hydrolytic enzymes used to digest cellular molecules. The enzymes themselves are produced in the ER and transported to the receiving (*cis*) face of the golgi body. Lysosomes then 'bud off' the shipping (*trans*) face and patrol the cytoplasm for macromolecules (large molecules) or bacteria which may have been ingested by the cell via endocytosis. Earlier we observed how lysosomes combine with food vacuoles or phagosomes in order to digest the particles contained within it. Lysosomes also fuse with old organelles (e.g. mitochondria) in

order to degrade and recycle their components for use in the manufacture of new structures. If the lysosome's membrane ruptures for any reason, enzymes are released that can damage or destroy the cell which is why they have acquired the nickname 'suicide bags'. Consequently, lysosomes seem to play an important role in the process of programmed cell death or apoptosis.

AGEING

We have observed that most somatic or body cells (with a few notable exceptions) reproduce via mitosis. During mitosis the cell nucleus divides, resulting in the formation of two daughter cells, each with exactly the same chromosome/DNA content as the original parent cell. So why don't they continue to divide over and over again, producing perfect copy after perfect copy? Or, to put it another way, why do we age and die? This is actually a very sensible question and a huge amount of money is invested into researching why we get older and what can be done about it. There are various theories as to why we age, including physiological, cellular and genetic explanations. One physiological theory suggests that ageing is simply the result of cumulative wear and tear and is strongly linked to chance environmental factors. Another physiological explanation proposes that as metabolic waste products accumulate in the cell (and elsewhere) they become inappropriately attached to one another (cross-linked) and increasingly difficult to break down and remove. For example, the amino acids that make up collagen eventually cross-link leading to loss of flexibility in the skin, joints and blood vessels. Cell doubling theory, on the other hand, is based on the idea that cells are only capable of replicating a certain number times. Eventually, therefore, cell numbers decline to the point where normal cell functioning is difficult to maintain. Free radical theory proposes that, over time, the body becomes less able to withstand the effects of free radicals on its DNA and phospholipids, leading to genetic and cellular damage. Free radicals are unstable molecules (including oxygen ions)

that 'attack' the nearest stable molecule in order to steal an electron from its outer shell (remember bonding from Chapter 1). In normal circumstances, molecules called antioxidants neutralise free radicals before they can do significant damage to the cell. As we age, however, fewer antioxidants are produced/available and free radical mediated damage becomes more common.

PROGRAMMED CELL DEATH

The final theory listed here (there are many others) is programmed cell death (apoptosis) initiated and executed by lysosomes and lysosomal enzymes. This theory is genetic in nature and proposes that our cells are programmed (after conception) to age and die. That is not to say that environmental factors are irrelevant. If you smoke twenty cigarettes a day you are undoubtedly increasing your chances of developing cardiovascular disease, chronic obstructive pulmonary disease (COPD) and lung cancer – all of which may shorten your projected lifespan. However, even though the genetic mechanism that is responsible for ageing remains unclear at the present time, it seems likely that genetic makeup is an important factor in determining longevity. The genetic argument for ageing is supported by the existence of rare genetic conditions such as Progeria and Werner's syndrome (adult Progeria). Progeria derives its name from the Greek for 'prematurely old' and causes physiological changes that resemble accelerated ageing. The development of symptoms is comparable to ageing at 6–8 times faster than normal and is characterised by limited growth, alopecia (hair loss) and progressive degeneration of the cardiovascular system. Symptoms typically commence during the first years of life (although diagnosis may occur later) and those with the disease rarely live beyond their mid-teens. Werner's syndrome is also characterised by premature ageing but growth and development are often normal until puberty. Diagnosis is typically made in the early 20s and life expectancy is about 50 years.

PREDICTING DEATH

A team of scientists at Stockholm's Karolinska Institute analysed data from almost half a million UK adults aged 40 to 70 years, of whom 8,352 died in the following five years. They then worked out which factors were most strongly linked to risk of death and developed a test to predict the percentage risk of dying in the next five years for those in this age range. Their report is published in *The Lancet*¹ and the test can be taken online at www.ubble.co.uk if you are interested (and aged 40–70). On a less serious note, if you would like to predict your day of death for 'fun' you can take the test at the appropriately named website: The Death Clock. It uses a number of modifiable variables to provide a personalised day of death. You can then share your day of death with your friends via social media or download your own 'death clock' to your computer or blog (relentlessly counting down to the appointed hour). Apparently, my day of death is Tuesday, 24 October 2045 (at least I know not to buy tickets for Fireworks Night that year). I would stress that this will not accurately predict your day of death (although statistically it must get it right every so often) but it does provide some useful motivation to get assignments, jobs, etc. finished as you watch the seconds of your life tick away.

TISSUE TYPES

So far we have looked at the body on an atomic, molecular and a cellular level. In terms of size and complexity, the next functional unit of the body is tissue. Tissue is simply a collection or aggregation of cells acting cooperatively to perform one or more specific function in the body. There are four distinct categories of tissue: epithelial, connective, muscular and nervous. The first type, epithelial, has three important functions: protection, secretion and absorption. The best way to imagine epithelial tissue is as a continuous sheet of cells that cover the outside and the inside surfaces of the body. For example, the skin, the lining of the cardiovascular system,

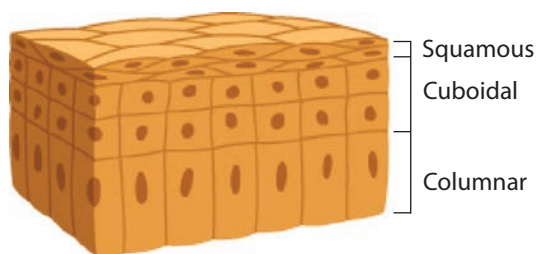


Figure 2.7 Epithelial cells.

the digestive tract, the urinary tract, the respiratory tract and the reproductive tract are all composed of epithelial cells. Epithelial tissue that covers the outer surfaces of the body (including the mucous membranes of the gastrointestinal and urinary tracts that communicate with the outside of the body) is referred to as epithelium. Whilst epithelial tissue that is only found on inner surfaces of the body, such as within the blood and lymphatic vessels, is known as endothelium. In either case, the cells are arranged in a number of ways. The simplest way to classify them is by shape (Figure 2.7). They can be columnar (like columns – upright), cuboidal (like cubes) or squamous (from the Latin for 'fish-scale' – flat). Just pause to remember that they are cells like any other and exhibit exactly the same characteristics discussed above (they have a plasma membrane, nucleus and cytoplasm, etc.).

EPITHELIAL CELLS

Columnar (column-like) cells are typically found in the lining of the stomach and digestive tract where they absorb and secrete a number of substances/molecules. They are also found in the nose, ear and tongue (taste buds) where they help to transmit sensory information towards the brain. 'Goblet cells' are specialist columnar epithelium that secrete mucin, a substance that dissolves in water to produce mucus (picture a goblet of mucus). Others are covered in fine hair-like structures called cilia (ciliated epithelium). These are capable of rapid, rhythmic wafting in order to

propel mucus out of the respiratory tract or, in the case of those found in the female reproductive tract, they waft the egg cell (ovum) along the fallopian tube towards the uterus (see Chapter 14). Cuboidal (cube-like) epithelial cells are often found in glandular (secretory) tissue and in the lining of the tubules of the kidney (nephrons). They also make up the germinal cells which produce the ova in the female ovary and the sperm in the male testes. Finally, squamous (flat) epithelial cells make up the outer layer of the skin and line a number of cavities and internal structures including the mouth, blood vessels, cervix and lungs. You may have heard of squamous cell carcinoma which refers to a type of cancer or neoplasm that derives from these cells. Examples include skin cancer, some forms of lung cancer and the most common type of cervical cancer. Epithelial cells can also be classified in terms of their structure or arrangement. They can be simple (in a single layer), stratified (one on top of the other – in strata) or pseudo-stratified (in a single layer but appear to be stratified). For example, simple squamous epithelium can be found on the inside of blood vessels or lining the air sacs (alveoli) of the lungs. This simple arrangement allows rapid diffusion of gases such as oxygen and carbon dioxide between cell membranes. Stratified squamous epithelia, on the other hand, are found in the cornea of the eye or lining the oral (mouth) cavity. Stratified epithelium is well suited to areas of the body that are subject to abrasion since the layers can be shed and quickly replaced before the basement membrane is exposed.

CONNECTIVE TISSUE

The next type of tissue is connective tissue and, as its name suggests, it connects and supports a number of internal structures. Examples of connective tissue include cartilage, tendons, ligaments, fat (adipose), bone and blood. Yes, blood, it seems odd but I'll explain later. There are three broad categories of connective tissue: loose, dense and specialised. Loose connective tissue is typically found beneath epithelial membranes and glandular epithelium. It binds these tissues to other tissues and

contributes to the formation of organs. The cells and fibres that make up loose connective tissue tend to have large spaces between them and contain a high proportion of fluid. It is the most common type of connective tissue and includes fat or adipose tissue (which, at the risk of contradicting myself, has a low percentage of water). Fat is located in a number of key places including beneath the skin (subcutaneous fat), around internal organs (visceral fat) and in the yellow bone marrow. It is made up of adipocytes (fat cells) which store energy (as triglycerides), preserve heat and act as a shock absorber for the structures they surround.

DENSE AND SPECIALISED CONNECTIVE TISSUE

Dense connective tissue has a much greater concentration of fibres and tends to provide structural and mechanical support. One of the most important connective tissue fibres is collagen and although it is found in loose connective tissue, there is a much greater abundance in dense connective tissue. For example, in ligaments and tendons, collagen fibres are thick, long and tightly packed together in order to provide the tensile strength necessary to connect and move bones. In cartilage and bone, however, collagen fibres are coated in calcium and phosphate salts in order to provide solidity and strength (see Chapter 4). Dense connective tissue also makes up the lower layers of the skin (dermis) where it is arranged in sheets. Finally, bone, cartilage and blood are all examples of specialised connective tissue (see Chapters 4 and 5). Blood is classified as connective tissue since it contains proteins mixed with water (plasma) and can form a gel. In Chapter 1, we saw that blood consists of a cellular component (red blood cells, white blood cells, etc.) and a non-cellular matrix (plasma). The liquid plasma allows blood to transport a wide variety of substances around the body dissolved in solution or attached to cells. In this sense, therefore, it is supremely connective. The only difference with other connective tissue is that it does not contain the fibre elements.

MUSCLE TISSUE

There are three types of muscle tissue: skeletal (voluntary), smooth (involuntary) and cardiac (heart muscle or myocardium). Skeletal or 'voluntary' muscle is the most abundant muscle type in the body and accounts for about 40% of total body weight. In almost all cases (there is always an exception to the rule) it is attached to the skeleton and is under voluntary control. For example, as you are reading this book or tablet, the skeletal muscles of your arms and shoulders are keeping it steady whilst the external skeletal muscles that control your eyes allow you to read the sentences on this page/screen. It is estimated that if you read for an hour (which I hope you do) your eyes will make nearly 10,000 coordinated movements. Anyway, skeletal muscle is composed of long cylindrical fibres that are banded at regular intervals with fine red and white lines called striations (stripes). These striations are actually very fine contractile fibres called myofibrils which not only give the muscle its striped appearance but also enable it to move or contract (shorten in size). Myofibrils are bathed in sarcoplasm (a type of cytoplasm) and bound together by a plasma membrane called sarcolemma. These bundles of muscle cells are organised into larger bundles called fascicles (enclosed by a sheath of connective tissue called perimysium). Skeletal muscle can perform a short, single contraction (twitch) or a long, sustained contraction (tetanus). You have probably heard of the condition tetanus that is caused by a nerve toxin (neuro-toxin) produced by the bacteria *Clostridium tetani* (found in soil and manure). If infection occurs, it results in prolonged contraction of skeletal muscle (tetanus) including those of the jaw which is why it is often referred to as 'lock-jaw'.

VOLUNTARY MUSCLE

I mentioned at the beginning of the previous paragraph that there was an exception to the rule regarding the 'voluntary' status of skeletal muscle. The intercostal muscles (located between the ribs) and the diaphragm

are collectively known as the muscles of respiration since they allow us to breathe. However, although both are composed of skeletal muscle, they are not strictly 'voluntary' in the true sense. This is fortunate, since, if skeletal muscle were purely voluntary, every time we went to sleep we would asphyxiate. Consequently, although breathing is typically an unconscious activity, controlled by the autonomic (automatic) nervous system (Chapter 12), we have the ability to consciously determine the rate and depth of respiration if required. This capacity to override automatic control is very useful since it allows us to hold our breath underwater, sing (sustain a note) or play a wind instrument (force air in an 'unnatural' fashion through a narrow aperture or reed). Voluntary control of our respiratory muscles also allows us to read out loud badly punctuated sentences such as the one that I am now writing which just go on and on and on without any indication where to pause or take a short breath and just make the readers more and more uncomfortable as their lungs slowly and progressively empty of air and I had better stop now before the world starts to spin and fade from vision. If you managed to read all of that in one breath, well done for showing your autonomic nervous system who is boss.

SMOOTH MUSCLE

Smooth or involuntary muscle lacks the striped or striated pattern of skeletal muscle and consists of long spindle (fusiform) shaped cells that appear smooth when examined under a microscope. It is also under the control of the autonomic nervous system and, unlike skeletal muscle, cannot be influenced voluntarily. Smooth muscle has the ability to stretch and maintain tension for a long period of time. This makes it perfect for use in organs such as the stomach and urinary bladder. Smooth muscle can also be found in the walls of the blood vessels, the female reproductive tract, the oesophagus and the iris of the eye (see Chapter 12). It may surprise you that the iris contains smooth muscle fibres but if you look into a mirror, shut your eyes for a few seconds and then open them again, you will

see your pupils involuntarily constrict (get smaller) in response to the sudden increase of light. Although the pupils change size, it is the contraction of the circular smooth muscle of the iris that provides the appearance of smaller pupils. Some drugs interfere with this process and the action of other smooth muscle groups. For example, opiates, such as diamorphine (heroin), cause involuntary constriction of the pupils known as miosis (not to be confused with the type of cell division meiosis). Cocaine and amphetamines, on the other hand, cause involuntary dilation of the pupil known as mydriasis. However, research has also shown that if someone is strongly attracted to you, they may also experience involuntarily dilation of the pupils. So next time you see someone looking at you with large, dilated pupils they may be (a) taking cocaine, (b) desperately in love/attracted to you, or (c) just noticed something utterly terrifying over your shoulder. If you go on a date with someone with abnormally constricted pupils, on the other hand, they may really dislike you or have taken some kind of opiate to get through the evening (either way, probably best not to exchange numbers). There are of course many other reasons (and medications) that may explain abnormal pupillary shape and size (e.g. cataract surgery and inflammation of the iris).

CARDIAC MUSCLE

The final type of muscle tissue is cardiac muscle or myocardium (myo + cardium = muscle + heart). This is a specialised type of striated (striped) muscle that is under involuntary control. The heart itself is essentially a muscular pump and, for obvious reasons, it is crucial that it doesn't stop working. Unlike skeletal muscle, that is only intended to contract for a limited period of time, cardiac muscle must continue to work in an uninterrupted fashion for about 80 years or so. It can't suddenly decide that it needs a little break and stop working for two or three minutes (occasionally it does of course – see Chapter 7). In order to ensure endurance and consistency, therefore, cardiac muscle demonstrates characteristics of both skeletal and smooth

muscle. For example, it can stretch in a limited way like smooth muscle and contract (twitch only) with the force of skeletal muscle. One of the reasons it is able to endure for so long is because myocardial cells (myocardiocytes) contain a higher than normal proportion of mitochondria. These sausage-shaped organelles produce cellular energy in the form of ATP that enables the heart to continue working and step-up activity if required (e.g. in the event that an ill-tempered bear takes a dislike to you and you need to run for your life). Another unique feature of cardiac muscle is that myocardiocytes are able to generate and transmit electrical impulses (intrinsic conductivity). However, this will be discussed in more detail in Chapter 7.

NERVOUS TISSUE

The final type of tissue is nervous tissue (not in the 'worried' sense). Nervous tissue comprises nerve cells (neurons) that generate, transmit and receive electrical impulses (action potentials), and supporting cells (glial cells) that nourish and protect the nerve cells. The two functions are often expressed as excitable and non-excitable. Nerve cells are highly specialised in their function and vary greatly in length. However, they still exhibit many of the same characteristics as other cells (e.g. nucleus, mitochondria, cytoplasm, etc.) and require oxygen and glucose to produce cellular energy (ATP). In this sense, they are susceptible to the same challenges as other, less-specialised cells and a few more besides. One interesting feature of 'excitable' neurons is that, for the most part, they are unable to undergo mitosis following maturation. Supporting cells, on the other hand, are capable of dividing mitotically and are essential for the maintenance of their more excitable neighbours. There are a number of different types of glial cells including astrocytes (cellular repair and clearance of neurotransmitters), microglia (clearance of cellular debris), oligodendrocytes and schwann cells (both produce an insulating material called myelin). However, we will look in much more detail at how neurons and glial cells work in Chapter 12.

ORGANS AND ORGAN SYSTEMS

The next level of structural sophistication after tissue is the organ. Just as a tissue can be defined as a group of cells acting collectively to perform one or more specific function in an organ, an organ can be defined as a collection of tissues acting together to perform one or more specific function in an organism. The tissue of the organ is often said to consist of parenchyma (functional tissue) and stroma (secondary framework). In Greek, the word *stroma* means anything spread out for sitting or lying upon and essentially refers to the supporting framework of an organ. For example, the parenchyma of the heart is the myocardium or heart muscle whilst the stroma refers to nervous and connective tissues (including the blood). There are a large number of organs within the body organised into different organ systems. These systems work collaboratively to ensure a stable internal environment. We will look in detail at the organs and organ systems in the following chapters but some of the more notable and familiar include: the cardiovascular system (heart and blood vessels), the digestive system, the respiratory system, the immune (lymphatic) system and the reproductive system. I cannot overemphasise, however, that these organs and organ systems function in a highly cooperative fashion. If there is a problem with one organ or system, it is usually reflected in

the functioning of another. In some cases, the body is able to make compensatory changes in order to offset the immediate consequences of abnormal functioning. However, whilst this may work in the short term, it often results in maladaptive changes that can increase the problem in the long term. One of the common misconceptions regarding the terms acute and chronic is that the former is always worse than the latter. Acute disease simply refers to a condition where the signs and symptoms appear rapidly. It is correct that, in the worst case scenario, it might kill you! However, typically, the symptoms alert you to the fact there is a problem, persist for a short period of time and disappear following treatment (or of their own accord). Chronic disease, on the other hand, develops slowly and lasts for a long period of time (possibly the extent of your life). The problem with chronic illness is that you may not realise you have the disease (and therefore do not seek treatment) until you become symptomatic. By this time, however, the disease may be so far advanced that treatment is less effective. For example, chronic renal failure (long-term deterioration of kidney function) typically does not become apparent (symptomatic) until about 75% of the kidney is no longer functioning. This, as we shall see in Chapter 10, has significant implications for a number of other systems. However, before we do so, it is important to understand the concept of homeostasis or how the body maintains a stable internal environment in health (Chapter 3).

CHAPTER 2: TEST YOURSELF

- Q. How many different types of cell are there in the human body?
A. About 200.
- Q. What are the three principle constituents of a cell (in most cases)?
A. Nucleus, cell membrane and cytoplasm.
- Q. What is the human cell membrane made from and what does it do?
A. The human cell membrane consists of two layers of phospholipids sometimes referred to as a fatty bi-layer. This provides a barrier that ensures water and ions remain in the correct concentrations within the cell (cytoplasm) and outside the cell (interstitial fluid).
- Q. What is the function of the protein molecules (gates) embedded into the cell membrane?
A. They transport ions (and other substances) in and out of the cell.

- Q. What is the most abundant ion in the intracellular fluid and what is the most abundant ion in the extracellular fluid?
- A. Potassium (K^+) is the most abundant ion in the intracellular fluid, and sodium (Na^+) in the extracellular fluid.
- Q. What is meant by the term active transport?
- A. Active transport requires the expenditure of chemical energy (adenosine triphosphate/ATP) to transport a substance from an area of low concentration to an area of high concentration.
- Q. There are two types of bulk transport: endocytosis and exocytosis. What is the difference between the two?
- A. Endocytosis refers to the process where the cell membrane surrounds or engulfs something from outside the cell and transports it inside. Exocytosis refers to the process by which waste and other products are exported out of the cell by secretory vesicles.
- Q. The nucleus of the cell contains genetic material known as deoxyribonucleic acid (DNA). In simple terms, what is the function of DNA and how is it stored?
- A. DNA is essentially 'information' necessary to control the activity of the cell and produce proteins. It is comprised of paired nucleotides/bases – adenine (A), thymine (T), cytosine (C) and guanine (G) – that are arranged in sequences of three called codons (e.g. CTG) in a unique double-helix configuration.
- Q. How many chromosomes does a typical human cell contain?
- A. Forty-six chromosomes (23 pairs).
- Q. There are two types of cell division: mitosis and meiosis. What is the difference between the two?
- A. During mitosis the cell duplicates all of its contents, including its chromosomes, and splits to form two identical daughter cells (each with 46 chromosomes). Meiosis is sometimes referred to as reductive division since the number of chromosomes is halved, from 46 to 23, and contributes to the production of male and female sex cells (sperm and egg cells).
- Q. What is the function of the intracellular organelle mitochondria?
- A. Mitochondria use oxygen and glucose to produce chemical energy for the cell in the form of adenosine triphosphate (ATP).
- Q. Complete the following equation: $\text{Glucose} + \text{O}_2 \rightarrow \text{ATP} + ? + ?$
- A. $\text{Glucose} + \text{O}_2 \rightarrow \text{ATP} + \text{CO}_2 + \text{H}_2\text{O}$
- Q. What do ribosomes manufacture (using messenger RNA and transfer RNA)?
- A. Proteins.
- Q. What is the difference between smooth and rough endoplasmic reticulum (ER)?
- A. Rough ER is studded with ribosomes that contribute to the production of proteins and peptide hormones. Smooth ER has no ribosomes and manufactures lipids and steroid hormones.
- Q. What is the function of the golgi body?
- A. The golgi body manufactures, store and transports cellular products (e.g. from the ER).

(Continued)

(Continued)

Q. What is the principle role of lysosomes?

A. Lysosomes (lyse + soma = splitting + body) are small vesicles that contain hydrolytic enzymes used to digest cellular molecules.

Q. What are the four tissue types?

A. Epithelial, muscular, connective and nervous.

Q. What are the three types of epithelial cell (named after their shape)?

A. Cuboidal (like a cube), columnar (like a column) and squamous (flat like a 'fish-scale').

Q. What type of tissue is blood?

A. Connective.

Q. What type of muscle is the diaphragm and why is it unusual?

A. The diaphragm is voluntary (skeletal) muscle but is under autonomic control most of the time.

NOTE

- 1 Ganna, A. and Ingelsson, E. (2015) 5 year mortality predictors in 498,103 UK Biobank participants: a prospective population-based study. *The Lancet*, 386(9993): 533–540.



Taylor & Francis

Taylor & Francis Group

<http://taylorandfrancis.com>

Contents

Fuel – energy – waste	39
Negative feedback	40
Positive feedback	41
Oxytocin and breastfeeding	42
Integumentary system	42
Melanocytes	43
Merkel and langerhans cells	44
Dermis	44
Sweat glands	44
Apocrine glands	45
Hair	46
Hair structure	46
Tiny muscles	46
Sebaceous glands	47
Nerve endings	47
Pain receptors	48
Thermoreceptors	48
Thermoregulation	49
Circadian rhythm	49
Heat exchange	50
Radiation	50
Conduction	51
Convection	51
Evaporation	52
Warming up	52
Shivering and piloerection	53
Hypothermia	53
Treating hypothermia	54
Cooling down	55
Fever	55
Chapter 3: Test yourself	56