

Key Points Revision

1 Homeostasis and the physiology of proteins

1. Homeostasis is the ability of physiological systems to maintain conditions within the body in a relatively constant state of equilibrium.
2. Each cell in the body benefits from homeostasis, and in turn each cell contributes its share towards the maintenance of homeostasis.
3. The most common type of regulation of physiological variables is by negative feedback.
4. A negative feedback system comprises: detectors, comparators and effectors.
5. Some physiological responses use positive feedback, causing rapid amplification, but this is inherently unstable and requires a mechanism to break the feedback loop; examples include action potentials and hormonal control of childbirth.
6. Normal functioning of proteins is essential for life and usually requires binding of proteins to other molecules. The shape of proteins is essential for the binding to occur and small changes in the environment surrounding proteins can modify the shape of proteins. Homeostatic mechanisms prevent such changes from arising in normal circumstances.

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2 Body water compartments and physiological fluids

1. Osmotic pressure depends on the number of osmotically active molecules per litre, and is expressed in terms of osmoles. Osmolarity is osmoles per litre, whereas osmolality is osmoles per kg water, which is preferred as it is temperature independent. Isotonic solutions have the same osmotic potential as plasma. Plasma osmolality is ~ 290 mosmol/kg H_2O , and is mostly due to Na^+ and Cl^- ions.
2. Biological membranes are semi-permeable, as they allow movement of water but not ions or other molecules. Thus creation of osmotic gradients is the primary method for movement of water in biological systems. Osmolality of body fluids is therefore closely controlled.
3. Crystalloid osmotic pressure is due to ions and small molecules that, like water, can easily diffuse across capillary walls. There is therefore no difference in crystalloid osmotic pressure between plasma and interstitial fluid. Proteins cannot cross capillary walls easily, and so exert an oncotic or colloidal osmotic pressure across capillary walls; this is critical for fluid movement across capillaries.
4. Intracellular fluid accounts for $\sim 65\%$ of total body water. Extracellular fluid includes the plasma and interstitial fluid volumes. Transcellular fluid compartments are derived from extracellular fluid, but are secreted or regulated by specialised membranes (e.g. cerebrospinal fluid, secretions in the gut).
5. The ionic concentrations of extracellular and intracellular fluids differ considerably, particularly for K^+ , Na^+ and Ca^{2+} . These differences are critical for cell function and signalling, and are responsible for the membrane potential. The differential distribution of ions is related to the semi-permeable nature of the membrane which has different permeabilities to different ions. At rest they are much more permeable to K^+ and Cl^- than other ions.
6. Fixed intracellular negative charges on proteins and other impermeable anions attract positively charged K^+ and Na^+ and repel Cl^- , but the low permeability to Na^+ limits its entry into the cell, and the Na^+ pump ($Na^+ - K^+$ ATPase) constantly pumps out Na^+ in exchange for K^+ , leading to a high intracellular K^+ and low intracellular Na^+ .

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3 Cells, membranes and organelles

1. Eukaryotic cells are enclosed by a fluid bilayer of phospholipids known as the plasma membrane or plasmalemma. Intracellular organelles such as the endoplasmic reticulum, nucleus and Golgi apparatus are also enclosed in lipid membranes.
2. Signalling and other proteins float within or across the membrane according to the location of hydrophilic and hydrophobic residues. This gives rise to the fluid mosaic model of cell membranes.
3. Membrane proteins include ion channels, receptors and enzymes. Some such as integrins allow interaction between the extracellular matrix and cell, and act as anchoring points for the cytoskeleton. The cytoskeleton consists of filaments such as actin and other molecules that allow the cell to maintain or alter its shape.
4. G-protein-coupled receptors activate small guanosine triphosphate (GTP)-binding proteins (G-proteins) which cleave GTP and, according to type (e.g. G_s , G_i , G_o), activate or inhibit membrane-bound enzymes such as adenylate cyclase.
5. The nucleus contains the chromosomes and nucleolus, which makes ribosomes. The ribosomes move to the rough endoplasmic reticulum where they are responsible for protein assembly, and with the Golgi apparatus post-translational processing of new proteins. Lysosomes degrade unwanted or damaged proteins.
6. The major cellular energy source is ATP. Glycolysis in the cytosol generates a small amount of ATP and does not require O_2 (anaerobic respiration). Its product pyruvate and O_2 are utilised by mitochondrial oxidative phosphorylation to generate much larger amounts of ATP. This involves the citric acid (Krebs') cycle and the electron transport chain to generate an H^+ gradient across the inner membrane, which drives the ATP synthase.

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4 Membrane transport proteins and ion channels

1. Movement of ions, water and other molecules across cell membranes is facilitated by transporters, pores and ion channels formed of proteins that extend across the membrane. Movement through pores and ion channels is due to passive diffusion driven by the electrical and concentration gradients for that molecule.
2. Transporters use energy to transport molecules, either by direct use of ATP (primary active transport), or indirectly by using the gradient of another molecule (often Na^+) as an energy source (secondary active transport). Some use the gradient of the transported molecule itself (facilitated diffusion).
3. A uniporter transports one molecule only (e.g. Ca^{2+} ATPase); a symporter transports molecules of different types in the same direction; an antiporter transports one molecule in one direction in exchange for another in the other direction (e.g. Na^+-K^+ ATPase, or Na^+ pump). The Na^+ pump is the most important form of primary active transport, and transports three Na^+ out of the cell in exchange for two K^+ into the cell.
4. Ion channels may be highly selective for just one ion (e.g. Na^+ , Ca^{2+} , K^+) or ions of a similar type (e.g. Na^+ and Ca^{2+}). Ions carry charge, so movement of ions through a channel causes an ionic current.
5. Ion channels are either open or closed; transition between these states is called gating. Voltage-gated channels are regulated by membrane potential; receptor-gated channels are regulated by second messengers or binding of a ligand to channel proteins (ligand gating).
6. The voltage-gated fast inward Na^+ channel, responsible for the upstroke of the action potential in nerve and muscle, has two gating mechanisms. It activates when the membrane potential depolarises to $\sim -55\text{mV}$ (threshold), but then inactivates as the potential becomes positive. It can only reactivate when the membrane potential become more negative than $\sim -60\text{mV}$ again.

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5 Biological electricity

1. A potential difference exists across the membranes of all cells (membrane potential, E_m), with the inside negative relative to the outside. Only excitable tissues generate action potentials. In excitable tissues resting E_m is usually between -60 and -90mV .
2. The equilibrium potential of an ion across a semi-permeable membrane is the potential at which the electrical forces exactly balance those due to the concentration gradient. This can be calculated from the extracellular and intracellular concentrations of that ion using the Nernst equation. The electrochemical gradient for an ion is the difference between its equilibrium potential and the actual membrane potential.
3. At rest, the cell membrane is most permeable to K^+ , so the resting membrane potential is close to the equilibrium potential for K^+ , E_K , and primarily dependent on the ratio of extracellular to intracellular $[\text{K}^+]$. It is not equal to E_K because there is some permeability to Na^+ . As the electrochemical gradient for Na^+ is large ($E_{\text{Na}} = \sim +65\text{mV}$), some Na^+ leaks into the cell causing a small depolarisation.
4. In nerves an action potential is initiated when activation of ligand-gated Na^+ channels increases Na^+ permeability further. If the stimulus is strong enough, the cell depolarises sufficiently to reach threshold for voltage-gated Na^+ channels, which activate and cause Na^+ permeability to become much greater than that for K^+ . The membrane potential therefore moves towards the equilibrium potential for Na^+ . There are no significant changes to the intracellular concentrations of K^+ or Na^+ .
5. As E_m becomes positive, the Na^+ channels inactivate and additional K^+ channels activate, causing the K^+ permeability to again be much greater than that for Na^+ , so the cell repolarises towards E_K and the resting state again.

Another action potential cannot be initiated whatever the stimulus until most Na^+ channels are reactivated, which occurs when the cell is almost repolarised (absolute refractory period). The additional K^+ channels are slower to close, and therefore cause a small temporary hyperpolarisation after the action potential. This means a stronger than usual stimulus is required for another action potential to be initiated (relative refractory period).

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6 Conduction of action potentials

1. The action potential is a local event occurring in all excitable cells and is an all-or-nothing response, leading to a change in polarity from negative on the inside of the cell (-70mV) with respect to the outside. This polarity is abolished and reversed ($+40\text{mV}$) for a short time during the course of the action potential, so called depolarisation.
2. This depolarisation moves along each segment of an unmyelinated nerve successively until it reaches the end.
3. Conduction in myelinated nerves is faster, up to 50 times that of the fastest unmyelinated nerve, because the depolarisation jumps from one node of Ranvier to another by a process called saltatory conduction.
4. Nerve fibres vary in size from 0.5 to $20\mu\text{m}$ in diameter, the smallest unmyelinated fibre being the slowest conducting and the largest myelinated fibres the fastest conducting.
5. There are two classification of nerve fibres. Erlanger and Gasser use $A\alpha$, β , γ and δ , B and C; Lloyd and Hunt use Ia, Ib, II, III and IV.
6. A compound action potential is recorded if all the nerve fibres in a nerve bundle are synchronously stimulated at one end of the nerve and recording electrodes are placed a short distance further down the length of the nerve bundle.

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7 The autonomic nervous system

1. The autonomic nervous system (ANS) mediates homeostatic reflexes (e.g. control of blood pressure) and involuntary control of most organs. It is divided into sympathetic and parasympathetic systems, which work in concert and are often antagonistic in effect.
2. ANS preganglionic neurones originate in the central nervous system and synapse with non-myelinated postganglionic neurones in peripheral ganglia; they release acetylcholine in the synapse, which acts on cholinergic nicotinic receptors on the postganglionic fibre.
3. Parasympathetic peripheral ganglia are generally close to or within their target, whereas sympathetic peripheral ganglia are in chains beside the vertebral column, or in diffuse visceral plexuses of the abdomen and pelvis. Sympathetic preganglionic neurones directly innervate the adrenal medulla.
4. Sympathetic postganglionic neurones release the catecholamine noradrenaline (norepinephrine) and the adrenal medulla both noradrenaline and adrenaline (epinephrine). These act on α and β adrenergic receptors, which are further divided into subtypes. α_1 receptors are linked to Gq-proteins and are associated with smooth muscle contraction. β -receptors are linked to Gs-protein and activate adenylyl cyclase to make cAMP; this causes relaxation of smooth muscle, but increases heart rate and force. A few sympathetic neurones release acetylcholine at the effector.
5. Parasympathetic postganglionic neurones release acetylcholine, which acts on cholinergic muscarinic receptors to cause glandular secretion, and contraction or relaxation in some smooth muscles, though not most blood vessels.
6. Action potentials reaching nerve endings induce influx of Ca^{2+} which causes release of neurotransmitters from vesicles, which bind to receptors in the synapse or tissue. Acetylcholine is broken down by cholinesterase; noradrenaline is recycled into the neurone by uptake-1, and may be metabolised by monoamine oxidase (MAO). Catecholamines in the blood are metabolized by catechol-O-methyl transferase (COMT) and MAO.

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8 Blood

1. Plasma proteins include albumin (the most prevalent), α -, β - and γ -globulins and fibrinogen. All but γ -globulins are synthesised by the liver. Plasma proteins exert the oncotic pressure that determines fluid transport across capillary walls, act as buffers, bind and transport hormones and minerals, and are components of the haemostasis and immune systems.
2. Red cells (erythrocytes) have no nucleus, contain haemoglobin and live for ~ 120 days. They are formed by erythropoiesis from stem cells in the red bone marrow of the adult, and liver and spleen of the fetus. Erythropoiesis is stimulated by erythropoietin, released from the kidney in response to hypoxia, and requires iron, folate and vitamin B₁₂.
3. Aging or damaged red cells are destroyed in the liver and spleen by macrophages. Haem is converted to biliverdin and bilirubin. Iron is recycled via transferrin or stored in ferritin.
4. Anaemia is an inadequate amount of red cells or haemoglobin, and can be caused by blood loss or insufficient iron, folate or vitamin B₁₂. Abnormalities of haemoglobin also cause anaemia.
5. Antigens on the surface of red cells form the basis of blood groups. The presence of specific plasma antibodies causes agglutination and haemolysis. The most important blood groups are the ABO and Rhesus systems.
7. White cells are derived from stem cells in the bone marrow, and are a vital component of the immune system. Granulocytes (neutrophils, eosinophils and basophils) mature in the bone marrow, phagocytose pathogens and release mediators and cytotoxic materials. Lymphocytes include B cells which make antibodies, T cells which coordinate the immune response, and natural killer (NK) cells which kill infected cells. Monocytes migrate to tissue to become phagocytic macrophages.

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9 Platelets and haemostasis

1. Platelets are not cells but fragments of megakaryocytes produced by the bone marrow. They contain dense granules containing serotonin (5-HT), ADP and other mediators. They change shape and form pseudopodia on activation.
2. Primary haemostasis initially involves vasoconstriction in response to vascular damage which limits blood loss, and subsequent platelet adhesion to the damaged area and activation due to exposure of subendothelial matrix.
3. Platelet activation stimulates production of thromboxane A_2 (TXA₂) by cyclooxygenase (COX), and consequent release of dense granules. Aggregation of platelets is stimulated by ADP via P2Y₁₂ receptors, and involves activation of GPIIb/IIIa receptors which bind fibrinogen, which sticks the platelets together. TXA₂ and 5-HT contribute to the vasoconstriction.
4. Clotting is initiated by exposure of tissue factor-bearing cells to plasma clotting factors, leading to activation of factor Xa and formation of small amounts of thrombin. This activates the amplification and propagation phases by forming tenase and prothrombinase on the surface of platelets, leading to a massive thrombin burst that cleaves fibrinogen to fibrin.
5. Fibrin monomers spontaneously polymerise and then are cross-linked by factor XIIIa, which is activated by thrombin.
6. Fibrin is broken down by plasmin, which is activated by tissue plasminogen activator (tPA) when bound to fibrin.

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10 Defence: Inflammation and immunity

1. Physical defence against pathogens is provided by the skin, and epithelia of the gut and airways. Pathogens that evade these are targeted by the immune system.
2. The innate immune system is immediate but non-specific. Invading pathogens activate tissue phagocytes (e.g. macrophages), which release cytokines that attract circulating neutrophils to the tissue (chemotaxis). Release of inflammatory mediators causes pain by stimulating nociceptors, heat and redness due to vasodilation, and swelling due to increased endothelial permeability and fluid extravasation (oedema).
3. Complement is a cascade of plasma proteins that opsonises (facilitates phagocytosis) and kills pathogens, activates phagocytes and induces inflammation. Complement is activated by pathogen proteins and antibodies which have tagged a pathogen.
4. Adaptive immunity encompasses humoral and cell-based immunity. It takes days to become effective and depends on antibodies, which are made by lymphocytes. Antibodies neutralise toxins, prevent attachment of pathogens, target, opsonize or agglutinate antigens for phagocytosis or complement, and act as antigen receptors on lymphocytes.
5. Humoral immunity: B lymphocyte activate when their antigen receptors recognise a surface antigen. They undergo clonal expansion before transforming into plasma cells which generate large amounts of antibody to that antigen. If the antigen is a protein, B cells present it in a complex with MHC II to T helper (T_H) cells, which release cytokines that strongly potentiate B cell performance.
6. Cell-based immunity is directed towards antigens within cells. MHC I is present on all cells and displays cytosolic antigens (e.g. viral proteins). Cytotoxic T_C lymphocytes kill infected cells on recognising the MHC I–antigen complex. MHC II is only found on antigen-presenting cells (APCs; dendritic cells, macrophages), and displays antigens contained within vesicles (e.g. that have been phagocytosed). APCs present the antigen–MHC II complex to T_H cells, which undergo clonal expansion and release cytokines that stimulate B cells and regulate the activity of many other immune cells.

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11 Principles of diffusion and flow

1. Materials are carried by bulk flow in blood or air, and by passive diffusion down a concentration gradient. Diffusion is only sufficient over small distances.
2. Flow through a tube is dependent on the pressure difference across it ($P_1 - P_2$) and the resistance to flow (R): $\text{Flow} = (P_1 - P_2)/R$ (analogous to Ohm's law).
3. Resistance to flow depends on length and radius of the tube and viscosity of the fluid. This relationship is described by Poiseuille's law, which provides the important principle that $\text{flow} \propto (\text{radius})^4$.
4. Drag on the fluid from the tube wall creates a velocity gradient with maximum flow at the centre; this is laminar flow. Blood cells accumulate in the centre where there is maximum flow (axial streaming), effectively reducing blood viscosity (the Fåhræus–Lindqvist effect).
5. High fluid velocity and/or large diameter tubes leads to turbulence and loss of laminar flow, greatly increasing resistance. Turbulence causes the sound of cardiac murmurs and wheezing in asthma when blood and air velocity is greatly increased.
7. Pressure in a flexible tube or sphere stretches the walls and increases wall tension, as described by Laplace's law: $P = (\text{tension} \times \text{wall thickness})/\text{radius}$. This also shows that increasing radius will reduce pressure, so a large bubble has a smaller pressure than a small bubble, and will collapse into it. This would occur in alveoli if there was no surfactant.

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12 Skeletal muscle and its contraction

1. Muscles make up about 50% of the adult body mass.
2. Skeletal muscles and the skeleton function together as the musculoskeletal system. Skeletal muscle is sometimes called voluntary muscle because it is under voluntary control.
3. Muscle fibres have the ability to shorten considerably and the function of muscle tissue is to develop tension and to shorten the muscle. This is brought about by the molecules that make up the muscle sliding over one another.
4. The main components of the muscle fibre are myofibrils and each myofibril is subdivided into thin and thick myofilaments.
5. Thin filaments consist of the proteins actin, tropomyosin and troponin and the thick filaments consist primarily of the protein myosin.

The interaction of the thin and thick filaments, sliding over one another using cross-bridges and the release of calcium, bring about contraction of the muscle. This mechanism is called the sliding filament theory.

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13 Neuromuscular junction and whole muscle contraction

1. The neurones that innervate skeletal muscles are called α -motor neurones, and their branched endings make contact with the surface of the individual muscle fibres at specialised structures called the motor end plate; together they are called the neuromuscular junction.
2. The motor neurone axon terminal has a large number of vesicles containing the neurotransmitter acetylcholine.
3. Acetylcholine is released from the vesicles by a process called exocytosis.
4. When an action potential reaches the prejunctional membrane, the increased permeability to Ca^{2+} ions due to the opening of voltage-gated Ca^{2+} channels causes an increase in the exocytotic release of acetylcholine.
5. Acetylcholine diffuses across the synaptic cleft between the nerve and muscles cells, and stimulates a large number of receptors on the postsynaptic membrane, which in turn produce an end plate potential that is large enough to trigger an action potential in the muscle fibre followed by a contraction of the muscle fibre.
6. Isometric contraction occurs when the two ends of the muscle are held at a fixed distance apart, and stimulation of the muscle causes the development of tension within the muscle without a change in muscle length. Isotonic contraction occurs when one end of the muscle is free to move and the muscle shortens whilst exerting a constant force. In practice, most contractions are made up of both isometric and isotonic contractions.

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14 Motor units, recruitment and summation

1. A single α -motor neurone and all the muscle fibres it innervates is called the motor unit.
2. The ratio between the number of α -motor neurones and the total number of skeletal muscles fibres in a muscle is small in muscles such as the extraocular muscles that involve fine smooth movements (1:5), and large in muscles such as the gluteus maximus that need to generate powerful but course movements (1:>1000).
3. Muscle fibres are classified into three types: slow oxidative (Type I), fast oxidative and glycolytic (Type IIA) and fast glycolytic (Type IIB).
4. During graded contraction, there is a recruitment order of the motor units in that the smallest cells discharge first and the largest last (size principle).
5. The force of contraction is controlled not only by varying the unit recruitment, but also by varying the firing rate of the motor units. The tension developed is dependent on a process called summation.
6. If the muscle fibres are stimulated repeatedly at a faster frequency, a sustained contraction results. This is called tetanus. The tension of tetanus is much greater than the maximum tension of a single, double or triple stimulation of the nerve and muscle.

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15 Cardiac and smooth muscle

1. Cardiac muscle (myocardium) is striated and formed of branched myocytes. Contraction is initiated within the heart, and modulated by the autonomic nervous system. The mechanisms regulating contraction are similar to those in skeletal muscle, except for those causing the elevation of intracellular Ca^{2+} .
2. Intercalated discs between myocytes contain desmosomes for structural attachment, and gap junctions formed of connexons that provide an electrical connection. This allows contraction to be synchronised. Cardiac muscle is said to be a functional syncytium.
3. Smooth muscle is not striated as actin and myosin filaments are not regularly arranged. It provides involuntary and homeostatic functions in many tissues, and cells vary considerably in size. Contraction is much slower than in cardiac muscle, and can be sustained for long periods (tonic contraction) at low energy cost.
4. Unitary smooth muscle contains many gap junctions so muscle bundles contract synchronously or in rhythmic waves. Autonomic nerves therefore affect the whole bundle. Examples include gut, blood vessels and bladder. Multiunit smooth muscle does not contain gap junctions, and each cell is separately innervated, so providing precise control. Examples include ciliary muscles in the eye and skin piloerector muscles.
5. Neural control varies between smooth muscle types, and depends on the type of innervation (sympathetic, parasympathetic), neurotransmitter and receptors. Smooth muscle function is also strongly regulated by hormones, local mediators (e.g. prostaglandins, nitric oxide), metabolites and pH.
6. Smooth muscle does not contain troponin. Instead, Ca^{2+} binds to calmodulin, which activates myosin light chain kinase (MLCK); this phosphorylates myosin light chain (MLC) causing contraction. MLC is dephosphorylated by myosin light chain phosphatase (MLCP), so inhibition of MLCP potentiates contraction. Many agents contract smooth muscle by both elevating Ca^{2+} and inhibiting MLCP.

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16 Introduction to the cardiovascular system

1. The cardiovascular system comprises the heart and blood vessels, and transports gases, nutrients, hormones and heat around the body. Most of the cardiovascular system is arranged in parallel, but the heart and lungs are in series. Portal circulations transport blood from one organ to another, e.g. hepatic portal system, taking blood from the gut to the liver.
2. The heart is a four-chambered pump with an intrinsic pacemaker. Cardiac output ranges from $\sim 5\text{L}/\text{min}$ at rest to $>20\text{L}/\text{min}$ during exercise. Stroke volume (volume ejected per beat) is $\sim 70\text{mL}$ at rest. The ventricles perform the work of pumping; atria assist ventricular filling. Valves maintain unidirectional flow. Cardiac contraction is called systole, the relaxation and refilling phase diastole.
3. Left ventricular pressure rises to $\sim 120\text{mmHg}$ during systole, and blood is ejected into the aorta. Arterial blood pressure is expressed as systolic/diastolic pressure (e.g. 110/80mmHg), where diastolic pressure is that just before systole. The difference between systolic and diastolic pressures is the pulse pressure. Mean arterial blood pressure (MAP) is calculated as diastolic pressure plus one-third of the pulse pressure.
4. Blood vessels are lined with endothelial cells which release important mediators. All but the smallest contain smooth muscle. Large arteries are elastic and store energy during systole, which is used during diastole to partially maintain pressure. They divide into smaller muscular, resistance arteries, the smallest of which are called arterioles. These control blood flow through dense networks of capillaries in the tissues.
5. The capillaries converge into venules and then veins. Gas and fluid exchange occurs across capillaries and small venules (exchange vessels), which do not contain smooth muscle. Veins have thinner walls and less smooth muscle than arteries, so are more compliant (stretchy). Large veins contain valves and act as capacitance vessels, containing a high proportion of the blood volume. The vena cava returns blood to the right atria.
6. The pulmonary circulation is low resistance and low pressure ($\sim 20/15\text{mmHg}$). Blood enters the lungs from the right ventricle via the pulmonary artery, and gas exchange occurs in capillaries around the alveoli. Oxygenated blood returns to the left atrium via the pulmonary vein. The metabolic requirement of the lungs is met by the separate bronchial circulation, which comes from the aorta.

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17 The heart

1. The heart contains two thick walled ventricles separated from the two thin walled atria by the annulus fibrosus, which provides electrical isolation and attachment for the cardiac valves. The inside of the heart is covered by endocardium (similar to endothelium), and the outside by epicardium.
2. The cardiac valves operate passively, and are formed of connective tissue covered in endo- or epi-cardium. The atrioventricular valves separate the atria and ventricles (right: tricuspid, three cusps; left: mitral, two cusps). Cordae tendinae from papillary muscles prevent eversion into the atria. The semilunar valves prevent backflow into the ventricles during diastole (right: pulmonary; left: aortic).
3. The heart beat is initiated by spontaneous depolarisation of cells of the sinoatrial node in the right atrium; rate is modulated by autonomic nerves. Action potentials are transmitted to the rest of the heart by gap junctions between myocytes. The annulus fibrosus prevents transmission directly to the ventricles.
4. The impulse is channelled from the atria to the ventricles through the atrioventricular node (AVN); its slow conduction allows atrial contraction and ventricular filling to be completed before ventricular systole begins. From the AVN the impulse travels rapidly through large, rapidly conducting cells in the bundle of His and Purkinje fibres to the inside of the ventricles, and then outwards through the myocardium to cause contraction.
5. The wave of depolarization passing through the heart causes local currents which can be detected as changes in voltage on the body surface (electrocardiogram, ECG). The size of these voltages at any point on the body surface depends on both muscle mass and direction of the wave of depolarisation – the voltages of the ECG are thus vector quantities.
6. The coronary arteries derive from the aortic sinus, and lead to an extensive capillary network. Most blood returns to the right atrium via the coronary sinus; some empties into the cardiac chambers. During systole coronary arteries are compressed by contraction of the myocardium, suppressing blood flow; this effect is greatest in the left ventricle where ventricular pressure is the same or greater than that in the arteries. Thus, >85% of left ventricular perfusion occurs during diastole.

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18 The cardiac cycle

1. Stroke volume: volume of blood ejected per beat; cardiac output: volume per minute. The ejection fraction is stroke volume as a proportion of end diastolic volume; normally ~60%.
2. Atrial systole completes the last ~15–20% of ventricular filling, and is associated with the a wave of atrial and venous pressures.
3. At the start of ventricular systole the rise in ventricular pressure causes the AV valves to shut, producing the first heart sound (S_1). This is followed by a short period of isovolumetric contraction before the ventricular pressure rises sufficiently to open the semilunar valve. The rise in pressure causes the AV valves to bulge into the atria, causing the c wave of atrial and venous pressures. Opening of the semilunar valve initiates rapid ejection, followed by reduced ejection.
4. When ventricular activation terminates, ventricular pressure falls below arterial pressure causing the semilunar valve to shut, producing the second heart sound (S_2). This is followed by a short period of isovolumetric relaxation before the ventricular pressure falls below the atrial pressure, when the AV valve opens and rapid ventricular filling begins. The v wave of atrial and venous pressures reflects the build-up of venous pressure immediately before the AV valve opens.
5. The ventricular pressure–volume loop is the plot of pressure versus volume; its area represents work done in a single beat. It is affected by ventricular contractility and compliance, and factors that alter refilling or ejection (e.g. CVP, afterload).
6. The third heart sound (S_3) is associated with rapid ventricular filling, and is commonly heard in the young and during exercise, or when the filling pressure is high (e.g. heart failure). S_4 is only heard during atrial systole when filling pressure is high. Cardiac murmurs are caused by turbulence in the blood, due to either valve stenosis (narrowing) or regurgitation (leaks).

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19 Initiation of the heart beat and excitation–contraction coupling

1. A ventricular muscle action potential (AP) is initiated when myocytes depolarise to the threshold for voltage-gated Na^+ channels, resulting in their activation and a fast AP upstroke. The initial depolarisation is caused by current through gap junctions from an adjacent, already depolarised myocyte.
2. The AP lasts $\sim 300\text{ms}$ due to activation of L-type voltage-activated Ca^{2+} channels and Ca^{2+} entry (plateau region), not present in nerves or skeletal muscle. In contrast sinoatrial (SAN) and atrioventricular node (AVN) APs have a slow upstroke due to activation of L-type Ca^{2+} channels only, not Na^+ channels.
3. The SAN (and AVN) spontaneously depolarise (pacemaker potential) due to slow decay of an outward K^+ current; an AP is initiated when the potential reaches threshold for L-type channels. The rate of decay of the SAN pacemaker potential is fastest and thus determines heart rate. This is slowed by parasympathetic stimulation (acetylcholine) and increased by sympathetic stimulation and adrenaline (epinephrine) (chronotropes).
4. Ca^{2+} entry during the AP plateau triggers myocardial contraction. However, it only accounts for $\sim 25\%$ of the rise in cytosolic Ca^{2+} . Ca^{2+} entering via L-type channels in the T-tubules causes a local increase in Ca^{2+} , which activates Ca^{2+} release channels in the sarcoplasmic reticulum (SR) through which stored Ca^{2+} enters the cytosol (Ca^{2+} -induced Ca^{2+} release; CICR).
5. At the end of contraction Ca^{2+} is rapidly sequestered back into the SR by the Ca^{2+} ATPase. Ca^{2+} that entered the cell is more slowly removed by the membrane $\text{Na}^+-\text{Ca}^{2+}$ exchanger (NCX), driven by the Na^+ electrochemical gradient; this continues during diastole.
6. Factors that increase cardiac muscle force independent of stretch (contractility) are called positive inotropes. Sympathetic stimulation and noradrenaline (norepinephrine) increase Ca^{2+} entry via L-type channels and thus force by activating β -adrenoreceptors and increasing cAMP. Cardiac glycosides (e.g. digoxin) inhibit the Na^+ pump, so reducing the Na^+ gradient which drives NCX; thus less Ca^{2+} is removed from the cell. Increased heart rate means there is less time to remove Ca^{2+} during diastole, so force increases (Treppe or staircase effect).

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20 Control of cardiac output and Starling's law of the heart

1. Cardiac output (CO) is influenced by filling pressure (preload), cardiac muscle force and afterload, which are modulated by the autonomic nervous system (ANS). The heart and vasculature are in series and interdependent; except for transient differences venous return *must* equal CO.
2. Ventricular filling pressure (EDP) determines EDV and hence stretch of the ventricular wall. This influences the force of contraction (Starling's law of the heart). The relationship between EDP and stroke volume is the ventricular function or Starling curve. At normal EDP the curve is steep, so small changes in EDP cause large changes in force.
3. The key importance of Starling's law is that it allows the outputs of the right and left ventricles to be matched. An increase in the right ventricular filling pressure (or CVP) will consequently affect both ventricles and increase cardiac output.
4. The ANS regulates cardiac output by actions on heart rate and cardiac muscle contractility, arterial vasoconstriction (increases peripheral resistance and afterload) and venoconstriction (decreases venous compliance, mobilises blood and increases CVP).
5. An increase in CVP impedes venous return because it reduces the arterial–venous pressure difference. The vascular function curve shows the relationship between CVP and venous return.
6. However, CO must equal venous return. By plotting the vascular function curve on the same axis as the ventricular (or cardiac) function curve, it can be seen that equilibrium can only occur where the lines cross, i.e. where $CO = VR$ (Guyton's analysis). This can be used to show how the function of the heart and vasculature are integrated, and how perturbations (e.g. inotropes, vasodilators, increased CVP) lead to a new equilibrium.

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21 Blood vessels

1. Arteries and veins have an inner layer (tunica intima) containing endothelial cells; middle layer (tunica media) containing smooth muscle cells; and outer layer (tunica adventitia) containing collagen, nerves and fibroblasts.
2. Capillaries and postcapillary venules lack smooth muscle and nerves, and are formed of endothelial cells on a basal lamina. There are three types of capillaries: in ascending order of permeability these are termed continuous, fenestrated and discontinuous (or sinusoidal).
3. Vasoconstrictors activate phospholipase C which produces inositol 1,4,5-triphosphate (IP₃) and diacylglycerol (DAG), and via depolarisation. IP₃ causes release of Ca²⁺ from the sarcoplasmic reticulum; depolarisation activates Ca²⁺ entry via voltage-activated Ca²⁺ channels. Both elevate intracellular [Ca²⁺] and so promote contraction.
4. Many vasoconstrictors also cause Ca²⁺ sensitization (more force for any given rise in Ca²⁺), as a result of inhibition of myosin phosphatase caused mainly by rho kinase.
5. Smooth muscle relaxation is generally caused by stimuli that increase cyclic GMP or cyclic AMP. These second messengers act through protein kinases to reduce intracellular [Ca²⁺] by sequestration into the SR and removal from the cell.
6. The endothelium releases important vasoactive compounds in response to local mediators, stretch and flow. These include the vasorelaxants nitric oxide (increases smooth muscle cGMP) and prostacyclin (increases cAMP), both of which also inhibit haemostasis, and vasoconstrictors such as endothelin-1 and thromboxane A₂.

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22 Control of blood pressure and blood volume

1. Tissues control their blood supply by altering their resistance. This requires regulation of the driving force, mean arterial pressure (MAP). $MAP = \text{total peripheral resistance (TPR)} \times \text{cardiac output}$; cardiac output is dependent on central venous pressure (CVP) and thus blood volume.
2. Baroreceptor reflex: MAP is detected by baroreceptors (stretch receptors) in the carotid sinus and arch of aorta. A fall in MAP decreases baroreceptor activity and firing of afferent nerves to the brain stem. Efferent sympathetic activity increases, causing heart rate and cardiac contractility to increase, peripheral vasoconstriction and an increase in TPR, and venoconstriction which increases CVP. A decrease in parasympathetic activity contributes to the rise in heart rate. The baroreceptor reflex is important for short-term regulation of MAP, e.g. during exercise and changes in posture, and contributes to long-term control of MAP.
3. The key mechanisms for long-term control of MAP and blood volume are regulation of renal Na^+ and water excretion. A fall in MAP reduces renal perfusion pressure and, via the baroreceptor reflex, causes constriction of renal afferent arterioles, so reducing filtration and excretion of Na^+ and water. Sympathetic stimulation activates the renin–angiotensin system, increasing angiotensin II, which causes peripheral vasoconstriction, and release of aldosterone, which promotes renal Na^+ reabsorption.
4. Blood volume is detected by stretch receptors in the venoatrial junction and atria. A fall in blood volume activates the sympathetic system and thus the renin–angiotensin system and vasoconstriction. It also causes release of antidiuretic hormone (ADH) from the hypothalamus which potentiates renal reabsorption of water. Release of atrial natriuretic peptide from the atria is reduced, also increasing Na^+ reabsorption. ADH and angiotensin II stimulate thirst.
5. Cardiovascular shock is an acute condition occurring when body blood flow becomes inadequate, often with a fall in MAP. The most common cause is haemorrhage (hypovolumic shock); others include profound vasodilatation (low-resistance shock, anaphylaxis) and acute heart failure (cardiogenic shock).
6. Blood loss of <20% is countered by the baroreceptor reflex which mobilizes blood from capacitance vessels and maintains MAP. Volume is restored within 24h as fluid moves from tissues into the plasma, urine production is suppressed, and ADH and angiotensin II stimulate thirst. Greater loss (30–50%) is survivable with transfusion within ~1h. After this, irreversible shock may develop as a result of tissue ischaemia, toxins and acidity, which can lead to multiorgan failure.

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23 The microcirculation, filtration and lymphatics

1. The microcirculation consists of the terminal arterioles and exchange vessels: capillaries and small venules. Blood flow into the microcirculation is regulated by the sympathetic system and local metabolic products.
2. Most capillaries are continuous, with tight junctions between endothelial cells that are relatively impermeable to proteins but allow water, ions and small molecules to pass. Fenestrated capillaries are 10 times more permeable because of pores (fenestrae), and are found in joints, gut and the kidney. Discontinuous (sinusoidal) capillaries have gaps large enough for blood cells to pass (bone marrow, spleen, liver).
3. Fluid movement across exchange vessels is determined by the balance between hydrostatic and oncotic pressures. The hydrostatic pressure gradient drives water out of capillaries (filtration), whilst the oncotic pressure gradient draws water into capillaries (absorption). The oncotic pressure gradient is determined by the difference in protein concentration in plasma and interstitial fluid.
4. Fluid movement (flow) across exchange vessel walls is described by the Starling equation: $\text{Flow} = (\text{capillary pressure} - \text{interstitial pressure}) - \sigma(\text{plasma oncotic pressure} - \text{interstitial oncotic pressure})$. The difference in oncotic pressure is about $\sim 17\text{mmHg}$. σ is the reflection coefficient.
5. Over the whole body these gradients are well balanced, and net filtration is only about 8L. An imbalance can cause excess filtration and accumulation of fluid in tissues (oedema). Inflammation causes oedema because it increases capillary permeability and allows protein to leak into the interstitium. Increased venous pressure can also lead to oedema, e.g. standing without moving the legs prevents the operation of the muscle pump, local venous pressure rises and the legs swell.
6. The lymphatic system returns fluid filtered by the microcirculation to the blood. Lymphatic capillaries are blind-ended tubes lined with endothelial cells that allow entry of fluid, proteins and bacteria. They merge into larger lymphatic vessels containing smooth muscle and unidirectional valves, and then lymph nodes, where bacteria and other foreign materials are removed by phagocytes. Lymphatics are important for lipid absorption in the gut.

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24 Local control of blood flow and special circulations

1. Autoregulation involves the myogenic response and vasodilating metabolites. Increased tissue metabolism causes local increases in factors that cause metabolic vasodilation (hyperaemia), such as adenosine, K^+ ions and hypercapnia.
2. The endothelium releases vasoactive compounds in response to local mediators, stretch and flow. These include nitric oxide (increases smooth muscle cGMP) and prostacyclin (increases cAMP), and vasoconstrictors such as endothelin-1 and thromboxane A_2 .
3. Skeletal muscle: Takes 15–20% of cardiac output at rest, up to 80% during exercise. Capillaries are recruited during exercise by metabolic hyperaemia, caused by release of K^+ , CO_2 and adenosine from muscle. This overrides sympathetic vasoconstriction in working muscle; the latter reduces flow in non-working muscle, conserving cardiac output
4. Brain: Takes ~15% of cardiac output. The endothelial cells of cerebral capillaries have very tight junctions, and contain transporters that tightly regulate the composition of the cerebrospinal fluid (blood–brain barrier). Autoregulation of cerebral blood flow is strong, maintaining a constant flow over a wide range of blood pressures. CO_2 and K^+ are particularly important metabolic regulators of cerebral blood flow.
5. Coronary circulation: The heart has a high metabolic demand and a dense capillary network. It can extract a high proportion of O_2 from the blood (~70%). The heart controls its blood flow via a strong metabolic hyperaemia. In exercise adenosine, K^+ and hypoxia increase perfusion and override sympathetic-mediated vasoconstriction. Circulating adrenaline (epinephrine) causes vasodilatation via β_2 -adrenergic receptors.
6. Cutaneous circulation: Main function is thermoregulation. Arteriovenous anastomoses allow a high blood flow and radiation of heat, and are found mostly in the hands, feet and face. Temperature is sensed by peripheral thermoreceptors and the hypothalamus. Low temperatures induce sympathetic-mediated cutaneous vasoconstriction, and piloerection traps insulating air. Increased temperatures cause vasodilatation, and activation of sympathetic cholinergic fibres promotes sweating and release of bradykinin.
7. Pulmonary circulation: No autonomic or metabolic control. The most important mechanism is hypoxic pulmonary vasoconstriction (HPV), where small arteries constrict to hypoxia (unique to the lung). HPV diverts blood from poorly ventilated areas and maintains ventilation–perfusion matching.

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25 Introduction to the respiratory system

1. The left lung has two lobes, the right three; they are covered by the visceral pleura, continuous with the parietal pleura lining the thorax. The space between the pleura is filled with pleural fluid. The trachea and bronchi contain cartilage and smooth muscle. The smaller bronchioles (<1mm) do not contain cartilage. Terminal bronchioles lead to respiratory bronchioles and thence alveolar sacs, which form the alveoli and contain only epithelial cells.
2. The trachea, bronchi and bronchioles are lined with ciliated columnar epithelial cells, and contain mucous-secreting goblet cells and submucosal glands. Mucociliary clearance moves mucus and debris to the mouth. The alveoli contain thin squamous epithelial cells (type I pneumocytes) which with pulmonary capillaries form the gas exchange surface (alveolar–capillary membrane). A few type II pneumocytes secrete surfactant.
3. The main respiratory muscles (e.g. diaphragm, intercostals) are inspiratory, and expand the thoracic cage to draw air into the lungs. Expiration is normally passive, due to elastic recoil of the lungs and chest wall.
4. Tidal volume: volume of air inhaled in normal breathing; vital capacity: maximum tidal volume; inspiratory and expiratory reserve volumes: difference between resting and maximal inspiration and expiration volumes, respectively; total lung volume: volume at maximum inspiration; residual volume: volume after maximum expiration.
5. Functional residual capacity is the lung volume at the end of a normal breath, when the muscles are relaxed. It depends on the balance between inward recoil of the lungs and outward recoil of the chest wall. The pleural fluid couples the lungs to the chest wall, so intrapleural pressure is negative.
6. Dead space: the volume of air in the airways that does not take part in gas exchange. Anatomical dead space includes everything except respiratory bronchioles and alveoli. The alveolar dead space includes alveoli incapable of gas exchange (normally zero). The physiological dead space is the sum of the anatomical and alveolar dead space.

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26 Lung mechanics

1. Static lung compliance: change in lung volume caused for changes in distending (transmural) pressure when there is no airflow. The transmural pressure is alveolar pressure – intrapleural pressure. Static lung compliance is measured as the slope of the steepest part of the pressure–volume plot.
2. Dynamic lung compliance is measured during normal breathing, and includes an element related to airway resistance (to air flow).
3. Surface tension in the fluid lining the alveoli contributes to lung stiffness, tends to collapse the alveoli, and sucks fluid from the alveoli. These effects are reduced or prevented by surfactant secreted by type II pneumocytes, which reduces surface tension.
4. The airways present a resistance to airflow (airway resistance) depending on their radius (Poiseuille's law). It is increased by bronchoconstriction and increased by mucus production. Parasympathetic nerves and inflammatory mediators cause bronchoconstriction, whereas sympathetic stimulation and β_2 -adrenoceptor agonists cause bronchodilation.
5. Forced expiration increases intrapleural and alveolar pressure, thus forcing air towards the mouth, and when the lungs are fully inflated is effort dependent. Towards the end of the breath however, the intrapleural pressure may exceed that in small bronchi, causing them to collapse and so preventing airflow. At this point expiration is effort independent.
6. Lung volumes are measured with a spirometer. Peak expiratory flow rate (PEFR) decreases as airway resistance increases (e.g. asthma). A plot of forced expiratory volume (FEV) against time provides forced expiratory volume (FVC), and the volume expired in 1s (FEV_1) is an indication of airway resistance. This is normally expressed as FEV_1/FVC to correct for lung volume.
7. A low FEV_1/FVC suggests an obstructive disease (increased airway resistance), whereas decreased lung compliance (restrictive) reduces both FEV_1 and FVC, so FEV_1/FVC may be unchanged or even increase.

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27 Transport of gases and the gas laws

1. The fractional concentration (F) of a gas in a mixture reflects its quantity in moles, e.g. the FO_2 of dry air is 0.21. The partial pressure of a gas in a mixture is the proportion of the total pressure that is exerted by that gas. So, in dry air at atmospheric pressure $PO_2 = 0.21 \times 110\text{kPa} = 21.2\text{kPa}$.
2. Water vapour acts as any other gas; saturated water vapour pressure is 6.3kPa at 37°C. Inspired air is rapidly saturated with water, so water vapour dilutes the other gases. The PO_2 will therefore be reduced to $0.21 \times (110 - 6.3) = 19.9\text{kPa}$. Gas volumes and partial pressures have to be standardised, commonly to standard temperature and pressure, dry (STPD; 0°C, 101kPa, dry gas) or body temperature and pressure, saturated (BTPS; 37°C, 101kPa, saturated with water).
3. The amount of gas dissolved in a fluid depends on the partial pressure of that gas in the air above it and the solubility of the gas in the fluid. Solubility differs between gases, e.g. CO_2 is 20 times more soluble in water than O_2 , so if they had the same partial pressure, the fluid would contain 20 times more CO_2 than O_2 .
4. The rate of gas flow across the alveolar–capillary membrane = permeability \times area \times (difference in partial pressures of that gas). Permeability depends on membrane thickness, gas molecular weight and solubility in the membrane. CO_2 crosses the membrane faster than O_2 because it is more lipid soluble.
5. For gas transfer across the lungs, area and permeability are combined as the diffusing capacity (D_L). Thus the rate of O_2 transfer = $D_L O_2 \times (\text{alveolar } PO_2 - \text{lung capillary } PO_2)$. $D_L O_2$ is sometimes called the transfer factor, and can be estimated using low concentrations of CO as this immediately binds to haemoglobin in the blood, so the lung capillary PCO is effectively zero.
6. The rate of transfer of CO is only limited by the exchange membrane, as at low concentrations it will not saturate haemoglobin (diffusion limited). O_2 however is poorly soluble, and as it is present in large quantities, it rapidly saturates haemoglobin. Its transfer is thus increased if flow is increased, as more deoxyhaemoglobin is brought in (perfusion limited).

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28 Carriage of oxygen and carbon dioxide by the blood

1. O₂ has a low solubility and most is carried by haemoglobin (Hb) in red cells. For a normal [Hb] of 150g/L, blood carries a maximum of 200mL O₂/L (O₂ capacity). The actual O₂ content depends on PO₂ and percentage O₂ saturation (content/capacity x 100). Each Hb molecule binds four O₂ in a cooperative manner; the O₂-haemoglobin dissociation curve is thus steep and sigmoidal.
2. High PO₂ facilitates O₂ binding to Hb in the lungs, whereas low PO₂ in tissues encourages release. This is also encouraged by a right-ward shift in the dissociation curve caused by acid pH, increased PCO₂ (Bohr shift), increased temperature and the metabolite 2,3-DPG, which occur in active tissues. The reverse changes occur in the lungs.
3. CO₂ is transported from the tissues as bicarbonate (60%), carbamino compounds (30%) and dissolved in plasma. CO₂ combines with water to form carbonic acid (H₂CO₃), which is accelerated by carbonic anhydrase in red cells, and thence bicarbonate: $\text{CO}_2 + \text{H}_2\text{O} \rightarrow \text{H}_2\text{CO}_3 \rightarrow \text{HCO}_3^- + \text{H}^+$. The HCO₃⁻ diffuses out of red cells in exchange for Cl⁻ (chloride shift).
4. H⁺ binds to deoxygenated Hb, so formation of HCO₃⁻ is not impeded by an increase in [H⁺]. It binds less well to oxygenated Hb, so an increase in [H⁺] shifts the equation above to the left, facilitating offloading of CO₂ in the lungs. This process contributes to the Haldane effect: For any PCO₂, the CO₂ content of oxygenated blood is less than for deoxygenated blood.
5. CO₂ reacts with protein amino groups (carbamino compounds). Hb is the most prevalent such protein in blood, but formation of carbaminohaemoglobin occurs more readily for deoxygenated than oxygenated Hb, thus contributing to the Haldane effect.
6. Hyperventilation is defined as a PCO₂ <5.3kPa, hypoventilation as a PCO₂ >5.9kPa. Rapid breathing in exercise is not hyperventilation. A fall in PCO₂ (hypocapnia) during hyperventilation causes light-headedness, cerebral vasoconstriction (visual disturbances) and muscle cramps (tetany). Hypoventilation causes a high PCO₂ (hypercapnia) and low PO₂ (hypoxia).

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29 Control of breathing

1. The pattern and rate of breathing are controlled by a central pattern generator formed of diffuse neurones in the pons and medulla of the brain stem. This is modulated by numerous descending (temperature, emotion, etc.) and ascending inputs (chemoreceptors, lung receptors, etc.). The medullary respiratory groups drive the respiratory muscle motor neurones. Voluntary control is via cortical motor neurones in the pyramidal tract.
2. Chemoreceptors detect arterial PCO_2 , PO_2 and pH. Increasing PCO_2 causes a near linear increase in ventilation. The relationship shifts to the left in acidosis (higher ventilation for a given PCO_2), right in alkalosis. PO_2 only stimulates ventilation when below $\sim 8\text{kPa}$, but a fall in PO_2 and a rise in PCO_2 have a synergistic effect on ventilation.
3. The central chemoreceptor comprises diffuse neurones in the medulla which respond to changes in pH of the local cerebrospinal fluid (CSF). As polar molecules such as H^+ cannot cross the blood–brain barrier from the blood but CO_2 can, the CSF pH is determined primarily by arterial PCO_2 (not pH) according to the Henderson–Hasselbalch equation. The central chemoreceptor does not respond to changes in PO_2 .
4. Peripheral chemoreceptors: the carotid bodies are found at the bifurcation of the common carotid artery and are innervated by carotid sinus and thence glossopharyngeal nerves; aortic bodies are less important. They contain chemosensing glomus (type I) and sheath (type II) cells. Peripheral chemoreceptors respond to PCO_2 , H^+ and PO_2 .
5. Stretch receptors in the lung and proprioceptors in respiratory muscles provide the brain stem with information about the extent of lung inflation, and position and load of respiratory muscles. They are important for matching load and maintaining optimal tidal volume and frequency. Stretch receptors are also responsible for the Hering–Breuer inspiratory reflex (lung inflation inhibits inspiration).
6. Juxtapulmonary (J) receptors on alveolar and bronchial walls are stimulated by increased fluid, oedema, microembolisms and inflammation. They cause rapid shallow breathing, a fall in heart rate and blood pressure, laryngeal constriction and relaxation of skeletal muscles. Activation of irritant receptors causes bronchial and laryngeal constriction, cough and hyperpnoea. They are stimulated by irritant gases, smoke and dust, rapid large inflations and deflations, airway deformation, pulmonary congestion and inflammation.

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30 Ventilation–perfusion matching and right to left shunts

1. Optimal gas exchange is obtained when alveolar ventilation (V_A) matches lung perfusion (Q), i.e. the ventilation–perfusion ratio (V_A/Q) = 1. Significant variation from unity is called ventilation–perfusion mismatch, and can be caused by, for example, shunts.
2. Regions of the lung with a high V_A/Q cannot compensate for areas with a low V_A/Q because increased ventilation cannot increase O_2 content – haemoglobin is already saturated. When blood from an area with high V_A/Q combines with that from an area with low V_A/Q , the O_2 content and PO_2 of the mixture will always be low.
3. CO_2 is not as strongly affected by V_A/Q mismatch, as extra ventilation will increase loss of CO_2 , and any rise in PCO_2 stimulates ventilation. Significant V_A/Q mismatch therefore normally results in a low arterial PO_2 and normal or low PCO_2 . Hypoxic pulmonary vasoconstriction helps maintain V_A/Q by diverting blood from poorly ventilated areas.
4. Gravity causes blood pressure and thus flow in the base of the lung to be greater than at the top. It also affects intrapleural pressure, so alveoli at the base of the lung are less distended and can expand more than those at the top; so ventilation is greatest at the base of the lung. These effects on perfusion and ventilation do not quite cancel out, so V_A/Q is highest at the top of the lungs and lowest at the base.
5. Some venous blood from the bronchial and coronary circulations rejoins the circulation after the lungs, diluting oxygenated blood. This anatomical right to left shunt is normally <2% of cardiac output. Larger shunts occur when regions of the lung are not ventilated (e.g. pneumonia) or in cardiac malformations.
6. Blood from right to left shunts has a venous O_2 content, and dilutes oxygenated blood from the rest of the lung so arterial blood has a low O_2 content, and thus PO_2 (see O_2 dissociation curve). High PCO_2 and low PO_2 increases ventilation to reduce the PCO_2 , but as haemoglobin in the oxygenated blood is already saturated, it cannot correct for PO_2 or O_2 content. Right to left shunts therefore result in low arterial PO_2 and a normal or low PCO_2 .

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31 Introduction to the renal system

1. Bowman's capsule collects filtrate from glomerular capillaries and delivers it to the proximal convoluted tubule. The nephron then enters the medulla to form the descending and ascending limbs of the loop of Henle, before returning to the cortex as the distal convoluted tubule, which joins the collecting duct before the latter passes through the medulla to the calyx. The walls of the nephron are formed of epithelial cells which regulate reabsorption and secretion of solutes and water.
2. The proximal tubule contains columnar epithelial cells joined by tight junctions, with a luminal microvilli brush border and peritubular interdigitations to increase surface area. The main function of the proximal tubule is reabsorption.
3. The thin part of the loop of Henle has flat squamous cells, whilst the thick ascending loop has columnar epithelial cells but few microvilli. On re-entering the cortex, the nephron loops through the juxtaglomerular apparatus, where its walls contain macula densa cells. The loop of Henle is important for the production of concentrated urine.
4. The distal tubule and cortical collecting duct contain columnar epithelial cells. As the nephron progresses into the collecting duct, these principal cells become interspersed with intercalated cells which play a role in acid–base balance. The collecting duct is important for water homeostasis.
5. The relative resistance of the afferent and efferent arterioles determines the pressure and flow of blood between the glomerular capillaries, and thus filtration. Vasoactive agents may have differential effects on afferent and efferent arterioles. The efferent arterioles divide into a dense network of capillaries around the proximal and distal tubules; some descend into the medulla to form the vasa recta, the only blood supply to the medulla. The kidneys exhibit strong autoregulation.
6. Various hormones strongly affect renal function (antidiuretic hormone, renin, angiotensin II, aldosterone). Renin is secreted in the juxtaglomerular apparatus, and erythropoietin (stimulates red cell production) in the cortex. Vitamin D is metabolized in the kidney to its active form. Prostaglandins are produced in the kidney and affect renal blood flow.

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32 Renal filtration

1. The glomerular filtration rate (GFR) in humans is $\sim 125\text{mL/min}$ and renal plasma flow is $\sim 600\text{mL/min}$; so the filtration fraction is $\sim 20\%$.
2. The filtration barrier has three parts: a fenestrated glomerular capillary endothelium, a specialized basement membrane with negatively charged glycoproteins (main site of ultrafiltration), and filtration slits between the pedicel processes of podocytes, which engulf the capillaries.
3. Substances $<7000\text{Da}$ are freely filtered. Permeability progressively declines up to $\sim 70000\text{Da}$, above which filtration is insignificant. Negatively charged substances are further restricted. The filtrate is thus almost protein free, but otherwise has an identical composition to plasma.
4. GFR depends on the balance of hydrostatic and oncotic pressures between plasma and filtrate; filtrate contains no protein, so its oncotic pressure is zero. GFR is therefore primarily dependent on glomerular capillary pressure, which because of the arrangement of afferent and efferent arterioles is high ($\sim 48\text{mmHg}$). As fluid is filtered the protein concentration and oncotic pressure of plasma increases, reducing further filtration.
5. Clearance is the volume of plasma that would need to be completely cleared of a substance per minute in order to produce the amount in the urine: $= (\text{urine concentration} \times \text{urine volume}) / \text{plasma concentration}$. Clearance of something that is freely filtered and neither reabsorbed nor secreted in the nephron (e.g. creatinine) = GFR.
6. Clearance of a substance that is completely removed from the blood by filtration and secretion, so none remains in the venous blood (e.g. *para*-aminohippuric acid), equals renal plasma flow (RPF). Renal blood flow = $\text{RPF} / (1 - \text{haematocrit})$.

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33 Reabsorption, secretion and the proximal tubule

1. Reabsorption and secretion of substances in the nephron involves: paracellular pathways between epithelial cells driven by concentration, osmotic or electrical gradients, or transcellular pathways through the cells, usually driven by active transport in the apical or basolateral cell membranes.
2. Primary active transport uses ATP to pump substances; the most important is the $\text{Na}^+\text{-K}^+$ ATPase (Na^+ pump). Secondary active transport uses the electrochemical gradient of another substance as the driving force, usually Na^+ . Symporters transport substances in the same direction, antiporters in the opposite direction. Diffusion across cell membranes is facilitated by ion channels and facilitated diffusion.
3. The maximum rate of tubular absorption or secretion of a substance is the tubular transport maximum (T_m). For example, glucose is normally completely reabsorbed in the proximal tubule; if filtrate glucose concentration rises above threshold ($\sim 11\text{mmol/L}$), some and then all of its transporters reach their T_m , so glucose appears in the urine.
4. 60–70% of Na^+ , K^+ , Ca^{2+} , urea and water are reabsorbed in the proximal tubule, together with most glucose, amino acids, phosphate and bicarbonate. Na^+ is reabsorbed into proximal tubule epithelial cells down its electrochemical gradient, largely by the $\text{Na}^+\text{-H}^+$ exchanger. Na^+ is pumped from the epithelial cells back towards the capillaries by basolateral Na^+ pumps. The secretion of H^+ into the lumen by the $\text{Na}^+\text{-H}^+$ exchanger is important for bicarbonate reabsorption.
5. Reabsorption of Na^+ and bicarbonate increases the osmotic gradient across the tubular wall, causing passive reabsorption of water via transcellular and paracellular pathways. This increases tubular concentrations of Cl^- , K^+ , Ca^{2+} and urea, which diffuse down their concentration gradients via paracellular pathways. As reabsorption of Na^+ , Cl^- , K^+ , Ca^{2+} and urea in the proximal tubule is coupled to reabsorption of water, their concentrations and the osmolality are unchanged from filtrate, although their quantity is decreased by $\sim 70\%$.
6. Amino acids are reabsorbed by Na^+ -linked symporters. Phosphate is reabsorbed by a Na^+ -linked symporter, but as its T_m is close to the filtered load, an increase in plasma PO_4^{3-} leads to excretion. Organic acids and bases (some metabolites and drugs) are secreted into the tubule.

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34 The loop of Henle and distal nephron

1. The loop of Henle and distal nephron create a high osmolality in the medulla (up to $\sim 1400 \text{ mosmol/kg H}_2\text{O}^1$, which drives reabsorption of water in the collecting ducts so urine can be concentrated. This depends on regions of differential permeability, active transport and the counter-current multiplier.
2. The thin descending limb is permeable to water but impermeable to urea; the thin ascending limb is impermeable to water but permeable to urea, Na^+ and Cl^- . Na^+ , K^+ and Cl^- are actively reabsorbed in the thick ascending limb by the $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ cotransporter. Apical K^+ channels (ROMK) leak K^+ back into the lumen, causing it to become positive, and thus driving paracellular reabsorption of cations. Reabsorption of ions in the water-impermeable thick ascending limb leads to a hypotonic tubular fluid in the early distal tubule.
3. Water diffuses out of the descending limb into the more concentrated interstitial fluid, whilst Na^+ and Cl^- diffuse from the even more concentrated tubular fluid in the water-impermeable ascending limb. This counter-current arrangement means that interstitial osmolality increases as the loop of Henle descends into the medulla, creating a strong osmotic gradient. This is potentiated by recycling of urea between the collecting ducts and ascending limb, such that at the tip of the loop of Henle the interstitial fluid can reach $\sim 1400 \text{ mosmol/kg H}_2\text{O}^1$, due in equal parts to NaCl and urea.
4. The vasa recta also forms a counter-current system, so the osmotic gradient between the cortex and medulla is not dissipated. The vasa recta removes water reabsorbed from the loop of Henle and medullary collecting ducts.
5. The distal tubule and cortical collecting duct are impermeable to water and urea, except in the presence of antidiuretic hormone (ADH). In the presence of ADH, water diffuses into the interstitium and the tubular fluid, and hence urine becomes concentrated, such that at the end of the medullary collecting duct the fluid has the same osmolality as interstitial fluid at that level; it can reach $1400 \text{ mosmol/kg H}_2\text{O}$ with maximum ADH. In the absence of ADH urine is dilute ($\sim 60 \text{ mosmol/kg H}_2\text{O}$).
6. Most K^+ has been reabsorbed by the time the fluid reaches the distal tubule; excretion is regulated by secretion in principal cells, driven by the concentration gradient between the cytosol and tubular fluid. Increased tubular flow increases the gradient by washing away secreted K^+ , so increasing K^+ secretion. K^+ secretion is increased by aldosterone, which enhances Na^+ pump density and apical K^+ permeability.

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35 Regulation of plasma osmolality and fluid volume

1. Increased plasma osmolality is detected by osmoreceptors in the anterior hypothalamus, which stimulate release of antidiuretic hormone (ADH) from the posterior pituitary. ADH is synthesised in the hypothalamus and stored in the pituitary. ADH stimulates thirst and water reabsorption. It binds to V2 receptors on renal principal cells, causing the incorporation of water channels (aquaporins) into the apical membrane. ADH also causes vasoconstriction via V1 receptors.
2. The relationship between plasma osmolality, ADH release and urine osmolality is steep. Maximum ADH reduces urine volume to ~400mL per day with the maximum osmolality of ~1400mosmol/kg H₂O. In the absence of ADH, urine volume may reach ~25L per day with the minimum osmolality of ~60mosmol/kg H₂O. Regulation of plasma osmolality is powerful and normally takes precedence over other considerations.
3. Following from the above, and as [Na⁺] is the major determinant of extracellular fluid osmolality, changes in Na⁺ will result in changes in extracellular volume, as the body will add or remove water to maintain osmolality. Control of body Na⁺ by the kidney is thus the main regulator of blood volume.
4. Changes in blood volume are detected by atrial and cardiopulmonary stretch receptors, and indirectly by arterial baroreceptors. A fall in volume increases sympathetic discharge with peripheral vasoconstriction, stimulation of water reabsorption, and release of renin, all of which stimulate Na⁺ and water retention.
5. Sympathetic stimulation or reduced renal perfusion pressure cause release of renin from granular cells in the juxtaglomerular apparatus. Renin cleaves angiotensinogen to angiotensin I, which is cleaved by angiotensin-converting enzyme (ACE) to angiotensin II. This is a potent vasoconstrictor, increases proximal tubule Na⁺ reabsorption, and stimulates ADH secretion, thirst and production of aldosterone.
6. Aldosterone increases synthesis of the Na⁺ pump, and Na⁺ and K⁺ channels in principal cells and H⁺ ATPase in intercalated cells, so enhancing Na⁺ reabsorption and K⁺ secretion. Atrial natriuretic peptide is released from atrial muscle in response to stretch caused by increased blood volume; its effects are to increase excretion of water and Na⁺.

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36 Control of acid–base status

1. Buffers are weak acids (HA) or bases (A^-) that donate or accept H^+ . The ratio between buffer pairs is determined by $[H^+]$ and the dissociation constant (K) as described by the Henderson–Hasselbalch equation: $pH = pK + \log([A^-]/[HA])$.
2. HCO_3^- and H_2CO_3 (carbonic acid) is the most important physiological buffer pair; haemoglobin provides ~20% of buffering in blood; phosphate and ammonium allow excretion of large quantities of H^+ in urine.
3. 80% of filtered HCO_3^- is reabsorbed in the proximal tubule. Luminal HCO_3^- combines with H^+ secreted by Na^+-H^+ antiporters to form H_2CO_3 , which in the presence of carbonic anhydrase rapidly dissociates to CO_2 and H_2O . CO_2 diffuses into tubular cells, where it recombines to form H_2CO_3 , which dissociates back to H^+ and HCO_3^- ; HCO_3^- is transported into the interstitium by $Na^+-HCO_3^-$ symporters. H^+ is effectively recycled.
4. Proximal tubular cells metabolise glutamine to form NH_3 , which is membrane permeable and enters the lumen. In acid conditions, NH_3 forms NH_4^+ , which cannot cross membranes. In the collecting duct secreted H^+ combines with NH_3 to form NH_4^+ , or with phosphate, effectively trapping acid for excretion in the urine.
5. Secretion of H^+ in the distal tubule promotes reabsorption of remaining HCO_3^- . H^+ secretion is at first largely by Na^+-H^+ exchange, but more distally by H^+ ATPase and H^+-K^+ ATPase in intercalated cells. These cells contain carbonic anhydrase, which promotes formation of H^+ and HCO_3^- from CO_2 . The H^+ is secreted into the tubule, whereas HCO_3^- is returned to the blood.
6. Respiratory acidosis and alkalosis refer to alterations in pH caused by changes in P_{CO_2} ; metabolic acidosis and alkalosis refer to changes unrelated to P_{CO_2} . Respiratory acidosis can be compensated by increased renal excretion of H^+ and production of HCO_3^- , so pH returns to normal (renal compensation). Metabolic acidosis can be compensated by increased ventilation and reduced P_{CO_2} (respiratory compensation).

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37 Gastrointestinal tract: overview and the mouth

1. The gastrointestinal tract is responsible for the breakdown of food into its component parts so that they can be absorbed into the body.
2. Different regions of the tract are involved in motility (transport), storage, digestion, absorption and elimination of waste. These functions are controlled by neuronal, hormonal and local regulatory mechanisms.
3. Mastication involves the coordinated activity of the teeth, jaw muscles, temporomandibular joint, tongue and other structures such as the lips, palate and salivary glands.
4. Saliva, produced by the parotid, submandibular, sublingual and minor salivary glands, moistens and lubricates the mouth both at rest and during eating and speech. It also dissolves food molecules, so that they can react with taste buds, eases swallowing, initiates the early part of digestion of complex sugars and protects the teeth with a biofilm. Saliva also contains immunoglobulins which have a protective role against bacterial infections.
5. The control of salivary secretion depends on reflex responses, which involve gustatory (taste) receptors, mechanoreceptors in the periodontal ligament and mucosa. Olfaction (smell) plays only a minor role in salivary flow when eating.
6. Swallowing occurs in a number of phases. Only the first phase is voluntary, involving the formation of the bolus of food. The remaining phases are reflex responses initiated by the stimulation of mechanoreceptors with afferent nerves in the IXth and Xth cranial nerves.

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38 Oesophagus and stomach

1. During the oesophageal phase of swallowing, the upper oesophageal sphincter relaxes, allowing the bolus to pass through it. It immediately closes and the food is propelled to the stomach by a process called peristalsis.
2. The swallowing centres in the medulla produce a sequence of events that lead to both efferent activity to somatic nerves (innervating skeletal muscles) and autonomic nerves (innervating smooth muscles).
3. Once the food passes through the lower oesophageal sphincter, it enters the stomach where the food is stored temporarily. Digestion begins by both mechanical and chemical processes using movement, acids and enzymes. There is a regulated release of chyme (semi-digested food) into the small intestine.
4. Gastric secretion occurs in three phases: cephalic, gastric and intestinal. The cephalic phase is brought about by the sight, smell, taste and mastication of food.
5. When food arrives in the stomach it stimulates the gastric phase of secretion of acid, pepsinogen and mucus. The main stimuli for this phase are the distension of the stomach and the chemical composition of the food.
6. The gastric phase normally lasts for about 3h and the food is converted into chyme, which enters the first part of the small intestine, the duodenum, through the opened pyloric sphincter, stimulated by the stretching followed by the contraction of the pyloric antrum by the chyme.

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39 Small intestine

1. The small intestine is the main site for the digestion of food and the absorption of the products of digestion, it comprises the duodenum, jejunum and ileum and it is a tube, 2.5cm in diameter and approximately 4 m in length.
2. When chyme first enters the duodenum from the stomach, there is a continuation of gastric secretion due to activation of G cells in the intestinal mucosa. This is short lived as the duodenum becomes more distended with further gastric emptying. A series of reflexes is initiated which inhibits the further release of gastric juices.
3. The lining of the small intestine is folded into many small, finger-like projections called villi.
4. Each villus contains a single, blind-ended lymphatic vessel, called a lacteal, and also a capillary network. Most nutrients are absorbed into the bloodstream via these vessels.
5. The small intestine absorbs water, electrolytes, carbohydrates, amino acids, minerals, fats and vitamins.
6. Carbohydrates are absorbed mostly in the form of monosaccharides, namely glucose, fructose and galactose. They are broken down into monosaccharides by enzymes released from the brush border (maltases, isomaltases, sucrase and lactase) and transported across the epithelium by means of cotransporter molecules that link their inward movement with that of Na^+ down its concentration gradient.

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40 The exocrine pancreas, liver and gallbladder

1. The exocrine pancreas secretes a major digestive fluid called pancreatic juice, which is secreted into the duodenum via the pancreatic duct.
2. Pancreatic juice is made up of a number of enzymes, secreted by the acinar cells of the pancreas. These enzymes include pancreatic amylase, which breaks down carbohydrates to monosaccharides; pancreatic lipase, which breaks down fats to glycerol and fatty acids; ribonuclease and deoxyribonuclease, which break down nucleic acids and free mononucleotides; and a variety of proteolytic enzymes, which break down proteins into small peptides and amino acids.
3. The liver is the largest organ in the body and its functions can be divided into two broad categories. It is involved in the processing of absorbed substances, both nutrient and toxic, and is responsible for the metabolism of a vast range of metabolised and absorbed substances. It also has an important exocrine function in that it is involved in the production of bile acids and alkaline fluids used in the digestion and absorption of fats and the neutralisation of gastric acid in the intestines; the break down and production of waste products following digestion; the detoxification of noxious substances and the excretion of waste products; and the detoxification of the substances in bile.
4. The main liver cells are called hepatocytes and they secrete hepatic bile which is isotonic and resembles plasma isotonicity. Hepatic bile contains bile salts, bile pigments, cholesterol, lecithin and mucus. As it passes through the bile duct, water and bicarbonate ions are added.
5. The gallbladder not only stores the bile but also concentrates it by removing non-essential solutes and water.
6. The formation of bile is stimulated by bile salts, secretin, glucagons and gastrin. The release of bile stored in the gallbladder is stimulated by the secretion of cholecystokinin (CCK) into the bloodstream when chyme enters the duodenum.

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41 Large intestine

1. The large intestine comprises the caecum, ascending, transverse, descending and sigmoid colon, rectum and anal canal.
2. The main function of the large intestine is to absorb most of the water and electrolytes. The initial 1.5L is reduced to about 150g of faeces which consists of 100mL of water and 50g of solids.
3. Movement of the chyme through the large intestine involves both mixing and propulsion. However, its main function is to store the residues of the food and to absorb water and electrolytes from it.
4. Several times a day there is increased activity within the colon, called mass movements. These result in emptying a large proportion of the content of the proximal colon into the more distal parts. This mass movement is initiated by a complex series of intrinsic reflex pathways started by distension of the stomach and duodenum.
5. When a critical mass of faeces is forced into the rectum, the desire for defecation is experienced. The sudden distension of the rectum walls produced by the final mass movement leads to a defecation reflex, comprising a contraction of the rectum, relaxation of the internal anal sphincter and, initially, contraction of the external sphincter. The faeces are expelled eventually following relaxation of the external sphincter under voluntary control.
6. Most bacteria that are present in the GI tract are found in the large intestine. Ninety-nine per cent are anaerobic and most are lost in the faeces. The bacteria are involved in the synthesis of vitamins K, B₁₂, thiamine and riboflavin, the breakdown of primary to secondary bile acids and the conversion of bilirubin to non-pigmented metabolites, all of which are readily absorbed by the GI tract.

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42 Endocrine control

1. Endocrine control is mediated by circulating hormones in the blood. Paracrine signalling occurs between neighbouring cells; autocrine signalling occurs on the same cell. Many hormones are secreted by specific glands, others by tissues with another function.
2. Hormones can be modified amino acids, peptides, proteins or fatty acid derivatives (steroids). Most hormones are stored in secretory granules and released by activation of the containing cell. Lipid-soluble steroids and thyroid hormones cannot be stored like this; steroids are made just before release, thyroid hormones are bound within a glycoprotein matrix. Some hormones bind to plasma proteins, which can act as a reservoir.
3. Hormones act on cells expressing specific receptors for that hormone. Most protein and peptide hormones activate membrane G-protein-coupled receptors (GPCR) or receptor tyrosine kinases. Lipid-soluble hormones (steroids, thyroid hormones) mostly act on intracellular receptors and modify gene transcription.
4. Endocrine secretion may be controlled by nerves, other hormones, or local metabolites; most hormones are subject to all of these. Hormones are strongly dependent on negative feedback; almost all inhibit their own release. Less commonly and associated only with reproduction, a hormone stimulates its own release (positive feedback).
5. The slow nature of hormonal signalling limits the type of process they can control. These fall into four broad categories: (i) homeostasis; (ii) reproduction; (iii) growth and development; and (iv) metabolism.

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43 Control of metabolic fuels

1. Intermittent feeding means the body must be able to store metabolic fuels for release when required. The main storage molecules are glycogen and fats, and the main location of storage liver, skeletal muscle and adipose tissues. When required, glycogen is broken down into glucose, fats into free fatty acids and ketone bodies, and in prolonged fasts proteins are catabolized to provide amino acids that can be converted to glucose (gluconeogenesis).
2. The body alternates between the anabolic state, during which storage molecules are created, and the catabolic state, during which they are broken down. Switching between states is controlled by hormones; insulin and glucagon stimulate anabolic and catabolic processes, respectively. Other hormones also stimulate catabolic processes. Hormones from fat (e.g. leptin) and gut (e.g. ghrelin) are also involved in energy homeostasis, including controlling food intake, energy expenditure and adiposity.
3. Glucagon and insulin are made in the islets of Langerhans by peripherally located A (α) cells and centrally located B (β) cells, respectively. Insulin release is stimulated during eating by the parasympathetic system and gut hormones, but most strongly by the rise in plasma glucose that occurs after a meal. Fatty acids, ketone bodies and amino acids augment the effect of glucose.
4. Insulin activates a tyrosine kinase-linked receptor to stimulate glucose uptake and manufacture of glycogen and fats by adipose, muscle and liver cells. It thus decreases plasma glucose. Insulin release is reduced as blood glucose concentration falls, and is inhibited by catecholamines.
5. Glucagon release is the mirror image of insulin release. Low blood glucose initiates glucagon release directly and drives release of catecholamines, which activate β -adrenoceptors on A cells to augment glucagon release. Glucagon acts on G-protein-coupled receptors. In liver and skeletal muscle this causes inhibition of glycogen synthesis and activation of glycogen breakdown to increase circulating glucose. Insulin inhibits A-cell release of glucagon, but glucagon stimulates the release of insulin, which ensures a basal level of insulin release irrespective of glucose.
6. Diabetes mellitus is caused by failure of B-cell function, either by autoimmune attack (early onset) or pathologies (e.g. obesity) that impair insulin release (late onset). Untreated, it causes hyperglycaemia and overloading of kidney transporters so glucose appears in the urine. Long-term hyperglycaemia drives excessive lipolysis and ketoacidosis, causing cardiovascular problems.

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44 The hypothalamus and pituitary gland

1. The pituitary is located immediately beneath the hypothalamus, by which it is controlled. It comprises the anterior pituitary (adenohypophysis), intermediate lobe (almost vestigial) and posterior pituitary (neurohypophysis). All pituitary hormones are peptides or proteins.
2. Adenohypophyseal hormones are released under the control of releasing or inhibiting hormones from neurones in the hypothalamus. These hypothalamic hormones are transported to the anterior pituitary via hypophyseal portal vessels. Some hypothalamic hormones control more than one pituitary hormone.
3. Signalling by adenohypophyseal hormones forms a cascade allowing precise control: tiny amounts of hypothalamic hormones control release of larger quantities of pituitary hormone; at the target gland these stimulate release of still larger quantities of hormones such as steroids. This allows feedback control of hormone release at several points. The final hormone (and often intermediate signals) inhibit further activity to provide fine regulation. This is characteristic of anterior pituitary control systems.
4. The posterior pituitary secretes oxytocin (reproduction) and antidiuretic hormone (ADH; vasopressin; control of osmolality). These are manufactured in magnocellular neurones in the hypothalamus, and are transported via their axons to posterior pituitary. The signals driving release of posterior gland hormones are entirely neural (neuroendocrine reflexes).
5. Oxytocin and ADH operate over minutes, faster than most endocrine events (hours to days). Release of ADH is controlled by conventional negative feedback based on plasma osmolality. Oxytocin is involved in positive feedback mechanisms.
6. Hypothalamic hormones tend to be released in discrete pulses. This is achieved by synchronous activation of hormone-releasing neurones. Episodic release has profound implications for the operation of the endocrine system.

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45 Thyroid hormones and metabolic rate

1. The thyroid gland is formed of follicles of cells surrounding a gel-like matrix containing thyroglobulin. It releases the iodine-containing hormones thyroxine (T_4) and tri-iodothyronine (T_3) which increase metabolic rate and heat production, and have a crucial role in growth and development.
2. Tyrosine residues attached to thyroglobulin are iodinated and then coupled by thyroperoxidase to form T_3 or T_4 . Thyroglobulin prevents the highly lipophilic hormones from escaping, and acts as a storage medium.
3. Thyroid-stimulating hormone (TSH) from the anterior pituitary controls release of thyroid hormones. It causes follicle cells to pinocytose small quantities of colloid, and lysosomal proteases then liberate the hormones. Plasma concentration of T_3 is one-sixth of that for T_4 .
4. Most thyroid hormone is bound to thyroxine-binding protein in the blood. Free T_3 and T_4 cross cell membranes to bind to intracellular thyroid hormone receptors ($TR\alpha_1$). These are linked to thyroid-response element (TRE) which initiate gene transcription. Thyroid receptors are present in most tissues.
5. Basal levels of thyroid hormone are essential for normal metabolic rate. Thyroid hormones increase synthesis of Na^+K^+ ATPase and enhance production of uncoupling proteins (UCPs). UCPs uncouple the mitochondrial electron transport chain so it produces heat rather than driving ATP synthase. Thyroid hormones also increase protein turnover and potentiate responses to cortisol, glucagon, growth hormone and catecholamines. Low amounts of thyroid hormone are essential for normal postnatal growth.
6. Iodine insufficiency or failure of uptake produces hypothyroidism. In the fetus and neonate this impedes development; in adults the main symptoms are lethargy, sluggishness and an intolerance to cold. Severe cases give rise to myxoedema. Hyperthyroidism is characterized by exophthalmia, behavioural excitability, tremor, weight loss and tachycardia.

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46 Growth factors

1. Mitosis, cell growth and apoptosis (programmed cell death) are controlled by growth factors. These variably stimulate mitosis, promote growth (trophic effect) and inhibit apoptosis (promote cell survival). Growth factors are classified into families:
2. Neurotrophins (nerve growth factor, NGF) are important for development and survival of the nervous system. The epidermal growth factor (EGF) family includes the mitogens EGF and transforming growth factor- α (TGF α). Fibroblast growth factors are mitogenic and induce angiogenesis. The transforming growth factor- β (TGF β) superfamily is crucial for embryogenesis, tissue development and remodelling. Platelet-derived growth factor (PDGF) stimulates cell division, growth and survival, and is important in tissue repair. Insulin and insulin-like growth factors (IGF-1 and IGF-2) are mitogenic, trophic and act as survival factors.
3. Numerous other hormones have mitogenic properties, e.g. erythropoietin and cytokines drive red and white cell production and are described as growth factors.
4. Many growth factors activate receptor tyrosine kinases, and initiate a cascade of downstream proteins and kinases including mitogen-activated protein kinases (MAP kinase). These induce production of transcription factors that drive expression of further genes. The MAP kinase pathway is the main intracellular pathway for stimulation of mitosis.
5. The TGF β family acts via receptor serine–threonine kinases, and the downstream pathways involve proteins called SMADs, and eventually activate gene regulatory proteins. Growth hormone, erythropoietin and cytokines activate receptors signalling through Janus kinases (JAKs).
6. Cancer involves mutations in genes (oncogenes) that impact cell division and/or apoptosis. Genes related to control of MAP kinase pathways are commonly defective in tumours. EGF has been associated with maintenance of colorectal and breast cancers.

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47 Somatic and skeletal growth

1. Growth hormone is essential for normal growth, and stimulates growth in muscles, bones and connective tissue. It is released from the pituitary, with surges after birth and around puberty corresponding to phases of rapid growth; levels then decline steadily into old age. Release is driven by hypothalamic growth hormone-releasing hormone (GHRH) and inhibited by somatostatin. Levels vary throughout the day, being highest during deep sleep.
2. Growth hormone stimulates release of insulin-like growth factor-1 (IGF-1), which is responsible for most of its effects on growth. Adequate fuel supplies, growth factors, and thyroid and sex hormones are required for full expression of the effects of growth hormone.
3. Overproduction of growth hormone is associated with gigantism, underproduction with the more common dwarfism. Defects in the GH receptor or IGF-1 pathways cause growth retardation. Excess growth hormone in adults leads to acromegaly.
4. Bones are composed of a collagen–glycoprotein matrix into which hydroxyapatite is deposited. Cortical bone provides strength. Trabecular (spongy) bone surrounds the marrow. Bones grow from the growth plate. Collagen matrix is laid down by chondrocytes, followed by calcification by osteoblasts. The growth plate becomes calcified (epiphyseal closure) when growth is complete, driven by sex steroids at puberty.
5. Osteoblasts develop into osteocytes which maintain matrix integrity; they can also mobilise Ca^{2+} by dissolving hydroxyapatite. Osteoclasts are similar to macrophages and remove old matrix. Osteoblasts, osteocytes and osteoclasts are present in mature bone, and differentiate from bone marrow stem cells. They allow bone remodelling in response to changes in skeletal stress, and are essential for repair of broken bones.
6. IGF-1 and IGF-2 stimulate division, differentiation and matrix-secreting activity of osteoblasts and chondrocytes; the TGF β family of growth factors provides the same stimuli for osteoclasts. Loss of sex steroids after menopause increases interleukin-6 synthesis by osteoblasts. This stimulates differentiation of osteoclasts and thus bone reabsorption. Consequent weakening of the skeleton increases the risk of fracture in older women.

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48 Control of plasma calcium

1. Parathyroid hormone (PTH) is a peptide and the major controller of free Ca^{2+} in the body. It is released from chief cells in the parathyroid glands when plasma $[\text{Ca}^{2+}]$ falls. Binding of Ca^{2+} to Ca^{2+} -sensing receptors on chief cells normally inhibits release of PTH.
2. PTH activates receptors in bone, gut and kidney. Acutely, it stimulates osteolysis of bone to release Ca^{2+} , and in the longer term increases osteoclast activity. PTH acting with 1,25-dihydrocholecalciferol enhances absorption of Ca^{2+} in the gut and reabsorption of Ca^{2+} in the kidney; it also decreases reabsorption of phosphate. PTH also stimulates renal production of 1,25-dihydrocholecalciferol.
3. Calcitonin is a peptide released from C cells of the thyroid gland in response to high plasma Ca^{2+} . Calcitonin inhibits bone resorption by osteocytes and possibly renal Ca^{2+} reabsorption, thus reducing plasma $[\text{Ca}^{2+}]$.
4. Vitamin D includes ergocalciferol and cholecalciferol. The primary source is dietary; cholecalciferol is also formed in the skin in the presence of ultraviolet light. Vitamin D is converted to 1,25-dihydroxycholecalciferol in the kidney under the influence of PTH. 1,25-Dihydroxycholecalciferol is steroid-like and binds to intracellular receptors of the steroid receptor superfamily to drive gene transcription. Its major action is to enable Ca^{2+} absorption from the gut, but it also promotes renal Ca^{2+} reabsorption. Its effects are generally augmented by PTH.
5. Lack of vitamin D in children leads to inadequate bone calcification and rickets. In adults, insufficiency leads to bone wasting (osteomalacia), with similar symptoms to osteoporosis. Recent evidence suggests it also impairs the immune system.
6. Growth-promoting hormones (growth hormone, thyroid hormones and sex steroids) promote incorporation of Ca^{2+} into bones. Excess corticosteroids inhibit Ca^{2+} uptake from the gut and reabsorption from the kidney.

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49 The adrenal glands and stress

1. Chromaffin cells in the adrenal medulla synthesise and secrete the catecholamines adrenaline (epinephrine; 80%) and noradrenaline (norepinephrine). Production is enhanced by cortisol from the adrenal cortex (e.g. during stress). Secretion is stimulated by sympathetic preganglionic neurones.
2. Adrenaline and noradrenaline act via G-protein-coupled adrenoceptor subtypes. Responses include vasoconstriction (α_1 adrenoceptors), increased cardiac output (β_1) and increased glycolysis and lipolysis (β_2 , β_3). Noradrenaline has equal potency at all adrenoceptors; adrenaline only activates β -receptors at normal plasma concentrations.
3. The three zones of the adrenal cortex produce steroid hormones, which bind to intracellular receptors and initiate gene transcription through activation of specific response elements on DNA. The outer zona glomerulosa releases aldosterone (mineralocorticoid), which regulates renal handling of Na^+ and K^+ , in response to angiotensin II. The middle zona fasciculata produces cortisol, which has powerful effects on glucose metabolism (glucocorticoids), and some mineralocorticoid actions. The inner zona reticularis secretes dehydroepiandrosterone (DHEA), which like its metabolite androstenedione provides an important source of androgens for females, contributing to hair growth and libido.
4. Release of cortisol and DHEA is stimulated by adrenocorticotrophic hormone (ACTH) from the pituitary. Cortisol release is pulsatile, driven by corticotrophin-releasing hormone (CRH) neurones in the hypothalamus; there is often a surge in cortisol release after waking.
5. Stress is the prime stimulus for increased release of glucocorticoids. The stress response is driven by the amygdala; it causes fear and increases activity of: hypothalamic CRH neurones; the sympathetic nervous system; and parasympathetic nerves causing gastric acid secretion.
6. Catecholamines cause a rapid increase in cardiac output and mobilization of metabolic fuels. Corticosteroids produce a slower sustained response: they raise plasma glucose by increasing glycolysis and gluconeogenesis in the liver and reducing glucose transport into storage tissues; increase protein catabolism and so plasma amino acids; and increase mobilization of lipids from adipose tissue.

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50 Endocrine control of reproduction

1. Reproductive function in both sexes is controlled by the hypothalamus via gonadotrophin-releasing hormone (GnRH), which stimulates release of the gonadotrophins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. GnRH is released in pulses at intervals of 1–3h; this pulsatile pattern is essential for normal reproductive activity. Gonadotrophins act via G-protein-coupled receptors that increase cAMP.
2. In the male, LH acts on the Leydig cells of the testes to stimulate production of testosterone, which acts in concert with FSH on Sertoli cells of the seminiferous tubules to support spermatogenesis. Sertoli cells also produce inhibin, a peptide that inhibits release of FSH.
3. In females the situation varies with the menstrual cycle (~28 days), which is ultimately driven by hypothalamic GnRH neurones. The ovaries contain primordial follicles each of which contains an ovum; all follicles are present at birth, none is produced later. Follicles start to mature spontaneously, but ovulation only occurs when this coincides with the appropriate phase of the cycle.
4. Follicular phase: LH stimulates theca interna cells in developing follicles to produce testosterone, which is converted to oestrogen (mostly oestradiol) by aromatases in follicular granulosa cells, under the influence of FSH. Granulosa cells also produce inhibin. Oestrogens promote preparation of the uterus, and stimulate expression of LH receptors in granulosa cells, so greatly enhancing oestrogen release in response to LH.
5. Oestrogens normally inhibit LH release (negative feedback), but the large amounts produced by the mature follicle now stimulate it (switch to positive feedback), causing a massive increase in LH which initiates follicular rupture and ovulation. The granulosa cells then hypertrophy and the follicle develops into the corpus luteum.
6. Luteal phase: The corpus luteum produces progesterone and oestrogens in response to LH. Progesterone prepares the reproductive tract for pregnancy. If fertilization does not occur, the corpus luteum undergoes luteolysis after ~14 days. In the absence of progesterone and oestradiol, the endometrial lining degenerates and is shed (menstruation). After 30–40 years of menstrual activity, exhaustion of ovarian follicles causes menopause.

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51 Sexual differentiation and function

1. Two X chromosomes give a genetic female, X and Y chromosomes give a genetic male. Undifferentiated gonads are present at ~5 weeks of gestation, with Müllerian ducts (forerunners of the uterus and Fallopian tubes) and Wolffian ducts (forerunners of the vas deferens, epididymis and seminal vesicles). The early gonads secrete steroids which determine sexual phenotype. The *Sry* gene on the Y chromosome establishes development of the testes and Leydig cells, which secrete testosterone.
2. Testosterone stimulates development of male genitalia and brain neuronal pathways that determine sexual function and behaviour. The fetal testis secretes anti-Müllerian hormone (AMH) which causes regression of Müllerian ducts, preventing development of the uterus and Fallopian tubes. In the absence of *Sry* and thus testosterone, Müllerian ducts continue to differentiate whilst Wolffian ducts regress. Development of reproductive organs and brain connectivity defaults to a female pattern, dependent on oestrogens.
3. The gonadotrophic axis becomes quiescent after birth until puberty (8–14 years). This begins when GnRH stimulates release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary, which act synergistically. LH stimulates release of testosterone from Leydig cells in males and follicular oestrogens in females, and FSH spermatogenesis in males and follicle growth in females. This is accompanied by many physical changes. In females, the onset of cyclic LH release and thus oestrogens initiates menstruation (menarche) and development of the mature female body pattern.
4. Libido is determined by the hypothalamus, higher centres and hormones. In males, sexual arousal arises from physical stimulation of genitalia (spinal reflex) or psychological stimuli (hypothalamic pathways) that activate parasympathetic nerves causing release of vasodilators (acetylcholine, vasoactive intestinal peptide, nitric oxide). The penis becomes erect due to dilation of blood vessels entering the corpora cavernosum and corpus spongiosum and restriction of venous drainage.
5. The female sexual response, also mediated by parasympathetic nerves, mainly involves relaxation of vaginal smooth muscle and increased mucus secretion. The male and female responses facilitate entry of the penis into the vagina (intromission). Stimulation of mechanoreceptors in the penis and clitoris lead to reflex activation of sympathetic nerves and thus orgasm.
6. Peristalsis of the epididymis pumps sperm into the urethra where they mix with secretions of the bulbourethral gland, seminal vesicle and prostate to form semen. The secretions provide lubrication, energy, an alkaline barrier and prostaglandins that stimulate motility of both sperm and the female tract. Contractions of the urethra and bulbocavernosus muscle elicit ejaculation. The female orgasm results in rhythmic contractions of vaginal and uterine muscles to promote flow of semen into the uterus. Sperm move by their own motility and by beating of cilia on the uterine walls. Only a few hundred reach the oviducts.

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52 Fertilization, pregnancy and parturition

1. The female tract triggers sperm capacitation, involving remodelling of the membrane, increased metabolism and motility. Fertilization occurs when a capacitated sperm binds to the glycoprotein ZP3 on the zona pellucida surrounding the ovum, initiating the acrosome reaction. The acrosome on the sperm head releases proteolytic enzymes to digest a pathway allowing penetration of the ovum.
2. Depolarization of the ovum and release of granules prevent further sperm from binding (cortical reaction). After 2–3h the sperm head forms the male pronucleus which fuses with the female pronucleus, thus combining the parental genetic material to form the zygote.
3. The zygote is propelled through the Fallopian tube into the uterus, where it implants in the endometrium. En route, the zygote divides to form the morula, which develops into the blastocyst, embryonic cells surrounded by trophoblasts. Trophoblasts promote implantation and form the fetal portion of the placenta, under the influence of epidermal growth factor and interleukin-1 β .
4. After implantation the embryo and early placenta secrete human chorionic gonadotrophin (hCG). Detection of hCG in urine forms the basis of pregnancy testing kits. hCG is similar to LH and stimulates progesterone secretion from the corpus luteum. Progesterone increases steadily throughout pregnancy and falls sharply at term. It ensures the uterus remains quiescent during gestation and stimulates mammary gland development. The placenta secretes chorionic somatomammotrophin, a growth hormone-like protein that mobilizes metabolic fuels and promotes mammary gland growth, and also oestrogens that stimulate uterine expansion. Fetal development occurs within a protective amniotic membrane.
5. After ~40 weeks, parturition is preceded by increased synthesis of prostaglandins by fetal and uterine tissues, which stimulate production of uterine oxytocin receptors and change uterine activity to regular, deep contractions that move the fetus into the cervix, which dilates. This activates mechanoreceptors, initiating a spinal sympathetic reflex that causes myometrial contraction and secretion of oxytocin from the pituitary. By this time the amniotic membrane has ruptured.
6. Oxytocin causes further contraction of the myometrium which pushes the fetus further into the cervix, resulting in further stimulation of mechanoreceptors and release of oxytocin (i.e. positive feedback). The spinal reflex and waves of oxytocin generate large, regular contractions that expel the fetus and placenta. Oxytocin then limits maternal bleeding by causing vasoconstriction, and in the fetus closes the ductus arteriosus.

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53 Lactation

1. Milk is produced by mammary glands under the influence of prolactin from the anterior pituitary. The glands comprise lobules composed of acini which empty into lactiferous ducts. As these approach the nipple they open into lactiferous sinuses before narrowing to emerge at the ampulla. Milk collects within the ducts and sinuses, which are lined by myoepithelial cells that expel milk from the breast. Full development of the mammary glands during the late stages of pregnancy is under the influence of several hormones.
2. Milk is formed by epithelial cells lining the acinus (galactopoiesis) as an isotonic liquid containing roughly 4% fat, 1% protein and 7% sugar, plus Ca^{2+} , trace nutrients, immunoglobulins and growth factors. Colostrum, the first secretion after birth, is richer in protein but has less sugar than mature milk, and contains high levels of immunoglobulins. Production of milk involves exocytosis, lipid synthesis and secretion, secretion of ions and water, and transcytosis of hormones, albumin and immunoglobulins.
3. Plasma prolactin levels increase during pregnancy and promote mammary growth. Placental progesterone and oestrogen prevent the lactogenic effects of prolactin before birth, but prepare the mammary glands so that they can respond to prolactin after birth. Loss of these placental steroids after birth allows prolactin to stimulate milk production in the presence of cortisol and insulin. Prolactin increases blood flow to the gland and stimulates delivery of nutrients into milk (lactogenesis).
4. Prolactin is released constitutively, and the primary control from the hypothalamus is inhibitory via dopamine. Prolactin inhibits luteinizing hormone (LH) release from the pituitary and maintains the mother in a low state of fertility until the infant is weaned. After birth, the main stimulus for prolactin release is suckling.
5. Stimulation of areolar mechanoreceptors by suckling activates a neural pathway to the hypothalamus which secretes pulses of oxytocin into the blood at 2–10-min intervals. Oxytocin stimulates myoepithelial cells to pump milk from the nipple. Milk let down encourages further suckling, which leads to more oxytocin release, a positive feedback system that operates until the infant is sated.
6. The milk ejection reflex is also stimulated by crying infants as a result of psychological conditioning, but is strongly inhibited by maternal stress, one of the most common causes of failure of lactation in new mothers.

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54 Introduction to sensory systems

1. There are a number of common steps in sensory reception: a physical stimulus (i.e. touch, pressure, heat, cold, light, etc.); a transduction process (i.e. the translation of the stimulus into a code of action potentials); and a response (i.e. taking a mental note or triggering a motor reaction).
2. The specialized nerve endings or sensory receptors, afferent axons and their cell bodies, together with the central synaptic connections in the spinal cord or brain stem, are known as primary afferents.
3. The information is then transmitted to the brain in the form of frequency-coded action potentials. These frequency-coded signals can transmit the following information: the modality or specificity of the system; the intensity or quantity of the stimulus; the duration of the stimulus; and the localisation and resolution (acuity) of the stimulus.
4. The net result is sensation and, when interpreted at a conscious level in the light of experience, this becomes perception.
5. Both convergent and divergent connections make up an avalanche-like spread of excitation at progressively higher levels of the central nervous system. There is a phenomenon called lateral inhibition which normally causes the excessive spread of excitation at each synaptic relay by recruiting inhibitory interneurons.
6. In almost all sensory systems, higher centres can also exert inhibitory effects on all those at lower levels in a phenomenon called descending inhibition. Like lateral inhibition, descending inhibition can function as a means of regulating the sensitivity of the afferent transmission channels.

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55 Sensory receptors

1. The sensory receptor is a specialized cell. They fall into five groups: mechanoreceptors, nociceptors, chemoreceptors and photoreceptors. Each receptor responds to one stimulus type, a property called the specificity of the receptor. The stimulus that is effective in eliciting a response is called the adequate stimulus.
2. Mechanoreceptors are found all over the body. Those in the skin have three main qualities: pressure, touch and vibration (or acceleration).
3. Receptors can be divided into three types on the basis of their adaptive properties: slowly adapting receptors that continue to fire action potentials even when the pressure is maintained for a long period; moderately rapidly adapting receptors that fire about 50–500ms after the onset of the stimulus; and very rapidly adapting receptors that fire only one or two impulses.
4. Skin nerves, in addition to the large myelinated afferents, contain a large number of A δ and C fibres (small myelinated and unmyelinated) that end in free nerve endings and are involved in thermoreception and nociception.
5. Thermoreceptors mediate the sensation of cold and warmth, and there are specific cold and warm points on the skin.
6. Nociception is the reception, conduction and central processing of noxious signals. This term is used to make a clear distinction between these 'objective' neuronal processes and the 'subjective' sensation of pain. Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential damage, or described in terms of such damage.

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56 Taste and smell

1. The special senses of taste and smell are two closely related sensations which, along with other receptors in the mouth, give us the sensation of flavour. The modalities of flavour are taste (gustation), smell (olfaction), touch (texture), temperature (thermoreception) and common chemical sense (chemoreception).
2. The taste buds are the gustatory end organs found in the tongue, soft palate, pharynx, larynx and epiglottis, and are unevenly distributed around these areas. On the tongue the taste buds are innervated by the glossopharyngeal (IXth) and a branch of the facial (VIIth) nerves.
3. There are five basic or primary qualities of taste: sweet (e.g. sugars), sour (e.g. acids), salt (e.g. sodium chloride), bitter (e.g. quinine) and umami (e.g. monosodium glutamate).
4. The common chemical sense has been defined as the sensation caused by the stimulation of epithelial or mucosal free nerve endings by chemicals. Evidence suggests they are polymodal nociceptors that in the mouth are innervated by the trigeminal (Vth) nerve.
5. The human olfactory organ is in the olfactory epithelium or mucosa situated high in the back of the nasal cavity. This organ responds to airborne, volatile molecules that gain access to the epithelium with the in–out air flow through and behind the nose.
6. The olfactory epithelium contains specialized, elongated nerve cells whose axons run upwards in bundles through perforations in the cribriform plate of the skull. They constitute the olfactory (Ist) cranial nerve. Humans are able to distinguish 10000 or more different odours.

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57 Special sense of vision

1. Vision in humans involves the detection of a very narrow band of light ranging from 400 to 700nm in wavelength. The shortest wavelengths are perceived as blue and the longest as red. The eye contains photoreceptors which detect light that is focused onto the retina (200- μ m thick) by the cornea and the lens.
2. The photoreceptors are divided into rods and cones. The rods respond in dim light and cones respond in brighter conditions, and can distinguish between red, green and blue light.
3. Each eye contains approximately 126 million photoreceptors (120 million rods and 6 million cones).
4. The layers between the retinal and the receptor cells contain a number of excitable cells, the bipolar, horizontal, amacrine and ganglion cells. The ganglion cells are the neurones that transmit impulses to the rest of the central nervous system via axons in the optic (IInd) nerve.
5. The optic nerves from the two eyes join at the base of the skull at a structure called the optic chiasma. Approximately half of each of the optic nerve fibres crosses over to the contralateral side; the other half remains on the ipsilateral side and is joined by axons crossing from the other side. Axons from the temporal region of the retina of the left eye and the nasal region of the retina of the right eye proceed into the left optic tract and vice versa for the other eye.
6. The neurones of the optic tract connect to the first relay stations in the pathway: the lateral geniculate bodies, the superior colliculus and the pretectal nucleus of the brain stem. The bulk of the neurones reach the lateral geniculate nucleus in the thalamus and eventually end in the primary visual cortex via the optic radiation.

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58 Special senses of hearing and balance

1. The young healthy human can detect sound wave frequencies of between 40Hz and 20kHz, but the upper frequency declines with age. When sound waves reach the ear, they pass down the external auditory meatus (the external ear) to the tympanic membrane that vibrates at a frequency and strength determined by the pitch and the magnitude of the sound.
2. The vibration of the tympanic membrane causes three ear ossicles (malleus, incus and stapes) in the middle ear (an air-filled cavity) to move, which in turn, displaces fluid within the cochlea (the inner ear), as the foot of the stapes moves the oval window at the base of the cochlea.
3. The inner ear includes the cochlea and the vestibular organs responsible for balance. The receptors involved in hearing and balance are specialized mechanoreceptors called hair cells.
4. The cochlea comprises a coiled tube about 3cm in length with three tubular canals running parallel to one another, namely the scala vestibule, scala media and scala tympani. The scala vestibule and the scala tympani contain perilymph (similar in composition to extracellular fluid) and the scala media contains endolymph (similar to intracellular fluid).
5. The hair cells of the vestibular system are found in the inner ear close to the cochlea in two otolith organs called the utricle and saccule, and in a structure called the ampulla found in the three semicircular canals. The otolith organs primarily detect linear motion and static head position, and the semicircular canals detect rotational movements of the head.
6. The auditory signals are relayed through a complex series of nuclei to the brain stem and the thalamus. eventually terminating in the primary auditory cortex in the temporal lobe of the cerebral cortex. The vestibular afferent fibres have their cell bodies in the vestibular ganglion and terminate in one of four vestibular nuclei in the medulla. They then project to a number of areas in the central nervous system, the spinal cord, thalamus, cerebellum and oculomotor nuclei, where they are involved in posture, gait and eye movement as well as projecting to the primary somatosensory cortex and the posterior parietal cortex.

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59 Motor control and the cerebellum

1. Motor control is defined as the control of movements by the body. These movements can be both influenced and guided by the many sensory inputs that are received. They can also be triggered by the conscious need to move.
2. With respect to voluntary movement, the exact site from where an idea for movement is initiated is unknown, but it is thought to be in the areas of the cortex other than the primary sensory or primary motor cortices, namely the association cortex or possibly the basal ganglia.
3. The motor cortex, via the lateral corticospinal and corticorubrospinal tracts, initiates the activity of the muscles. The upper motor neurones refer to those neurones that are wholly in the CNS motor pathways.
4. A large group of motor fibres (the corticospinal tract) descends directly from the cortex to the grey matter in the spinal cord but, as it passes through the brain stem, it divides in two.
5. Eighty-five per cent of the fibres of the corticospinal tract cross over the midline (decussate) and descend as the lateral corticospinal tract, terminating directly on the α - and fusi-motor neurones, as well as on interneurons that can be either inhibitory or excitatory in nature. The other 15%, the anterior corticospinal tract, do not decussate and remain ipsilateral, eventually terminating in the upper thoracic spinal cord, and project bilaterally onto the motor neurones and interneurons that innervate the muscles of the upper trunk and neck.
6. The cerebellum is anatomically distinct from the rest of the brain and is connected to the brain stem by three thick strands of both afferent and efferent fibres called cerebellar peduncles. The primary function of the cerebellum is the coordination and learning of movements and it is made up of three functional and anatomical structures: the spinocerebellum, which is involved in the control of muscles and posture; the cerebrocerebellum, which is involved in the coordination and planning of limb movement; and the vestibulocerebellum, which is involved with posture and the control of eye movements.

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60 Proprioception and reflexes

1. Proprioception is the ability to be aware of the orientation of our limbs with respect to one another, to perceive the movements of our joints and to accurately assess the amount of resistance or force that opposes the movement we make. The three qualities of this modality are position, movement and force.
2. The receptors or proprioceptors that mediate proprioception are principally found in the joint capsules (i.e. joint receptors), muscles (muscle spindles) and tendons (Golgi tendon organs).
3. Joint receptors are mechanoreceptors that signal the position of the joint when the joint capsule is compressed or stretched. They also signal the direction and velocity of the movement. They are Ruffini-type (slowly adapting) stretch receptors.
4. Each muscle contains a small number of small muscle fibres called intrafusal muscle fibres that are thinner and shorter than the ordinary extrafusal muscle fibres. Several intrafusal muscle fibres are grouped together and encased in a connective tissue capsule, and contain specialized nerve endings that act as a receptor responding to stretch of the main muscle fibres. These so-called muscle spindles lie in parallel to the extrafusal muscle fibres and effectively measure length changes in the muscle.
5. The Golgi tendon organs are also stretch receptors but are found in the muscle tendons. They are in series with the extrafusal muscle fibres and respond to tension in the muscle as a whole. They can respond both when the muscle contracts and when the muscle is stretched.
6. Joint receptors are most likely involved with mediating the sense of position and movement of the joint. The most likely detectors of force sensation are the muscle spindles and Golgi tendon organs. Stimulation of the muscle spindles leads to a monosynaptic stretch reflex involving excitation of the homonymous α -motor neurones and a reciprocal inhibition of the heteronymous α -motor neurone. Stimulation of the Golgi tendon organs leads to a polysynaptic protective reflex in which there is inhibition of the homonymous α -motor neurone and excitation of the heteronymous α -motor neurone.

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