Key points

1 Cells

- Eukaryotes (but not prokaryotes) contain a nucleus.
- Tissues are made up of differentiated cells, e.g. epithelial cells, connective tissues, muscles and nerves.
- Control of the cycle cell is tightly regulated to ensure the ordered production of cells.
- The cell cycle: interphase to G1 to S to G2 and M phases.
- Stem cells are undifferentiated cells capable of self-renewal.
- Currently stem cell transplantation is carried out to treat leukaemias.

2 Organisation of cell membranes

- Backbone is made up of phospholipids with a polar head group and a hydrophobic fatty acid chain.
- Cholesterol impacts on the fluidity of the membrane.
- Membrane proteins include:
    - receptors
    - ion channels
    - transporters:
        - uniporter: transport of a specific molecule down its concentration gradient
        - symporter: facilitates the transport of a specific molecule *against* its concentration gradient driven by the co-transport of one or more ions down their concentration gradient
        - antiporter: facilitates the transport of a specific molecule *against* its concentration gradient driven by the movement in the opposite direction of one or more ions down their concentration gradient.
        - enzymes, particularly ATP-hydrolysing enzymes involved in the transport of ions across the cell membrane against the concentration gradient

3 Cell organelles

- Mitochondrial matrix transfers energy present in pyruvate and fats to ATP via the tricarboxylic acid (TCA) cycle and electron transport chain.
- Ribosomes in the cytosol produce soluble proteins for the cytosol.
- Ribosomes associated with the RER are involved in the synthesis of membrane proteins, secretory proteins and proteins of organelles.
- Golgi complexes are associated with glycosylation and protein sorting.
- Cytoskeleton is a network of filaments.
- Cell junctions:
    - tight junctions, which prevent passage between cells
    - anchoring junctions are linked to cytoskeletal structures
    - gap junctions, which provide channels between cells allowing communication.

4 Protein biochemistry

- L-amino acids are linked by peptide bonds to form proteins.
- Primary sequence is the sequence of amino acids.

Medical Sciences at a Glance, First Edition. Edited by Michael D Randall. © 2014 John Wiley & Sons, Ltd.
Published 2014 by John Wiley & Sons, Ltd. Companion website: www.ataglanceseries.com/medicalsciences.

- A single amino-acid substitution leads to abnormal proteins, e.g. abnormal haemoglobin in sickle cell anaemia.
- Secondary structure describes folding, e.g. β-strands are pleated structures that form β-sheets.
- Tertiary structure describes how secondary structures are arranged in space.
- Quaternary structure describes how subunits of polypeptide chains may form functional proteins (e.g. haemoglobin).
- The ubiquitin-proteasome system regulates protein degradation.
- Accumulation of abnormal proteins leads to diseases such as prion diseases and Alzheimer's disease.

5 Lipid biochemistry

- Fatty acids:
  - saturated: no double bonds in hydrocarbon chain
  - mono-unsaturated: one C=C double bond
  - polyunsaturated: two or more C=C double bonds
  - cis-configuration: same side of the double bond
  - trans-configuration: opposite sides of the double bond
  - *de novo* pathway of fatty acid synthesis in the liver where acetylCoA is the building block.
- Triacylglycerol (TAG) contains a glycerol backbone esterified with three fatty acids.
- Cholesterol:
  - component of cell membranes
  - precursor to steroid hormones and vitamin D.
  - precursor to bile acids
- Dyslipidaemias are a risk factor for cardiovascular disease.
- High cholesterol (especially high HDL or low LDL) is a key cardiovascular risk managed by statins.
- Hypertriglyceridaemia is associated with obesity and alcohol consumption and is managed by lifestyle and statins.

6 Carbohydrate biochemistry

- Glucose has the empirical formula $C_6H_{12}O_6$.
- Monosaccharides can be joined via glycosidic bonds.
- Glucose is stored in the liver and skeletal muscle as insoluble glycogen.
- Carbohydrates can also be structural (e.g. glycosaminoglycans).
- Hypergylcaemia is a major risk factor for cardiovascular disease, and leads to renal damage and neuropathy partly via glycation.

7 Basic mechanisms of drug action

- Drugs may act at:
  - G-protein-coupled receptors
  - ion channels
  - intracellular receptors
  - enzymes
  - DNA
  - pumps and transporters.
- Agonists activate receptors to cause a cellular response.
- Agonists have efficacy.

- Competitive antagonists compete with agonists for binding and so oppose the activation.
- Antagonists lack efficacy.
- Non-competitive antagonists oppose the action of an agonist at a separate site and so blockade cannot be overcome by the agonist.
- The affinity of a drug describes how well it binds to receptors. It is described by the K_d value, the concentration that occupies 50% of the receptors.

8 General principles of cellular metabolism

- The oxidation reactions in cells are coupled to the reduction of a small molecule, e.g. NAD^+ to NADH and an electron is transferred from the molecule oxidised to NAD^+.
- Under aerobic conditions NADH is then re-oxidised by the electron transport chain in mitochondria, which pumps protons across the inner mitochondrial membrane.
- The flow of protons back across the inner mitochondrial membrane drives the phosphorylation of ADP to form ATP.
- Metabolism is regulated via enzyme phosphorylation by kinases and dephosphorylation by phosphatases.

9 Enzymes

- Biological catalysts that speed up biochemical reactions.
- Most enzymes are proteins and sensitive to pH and temperature.
- Competitive enzyme inhibitors bind to the active site and compete with the substrate; their actions may be overcome by increasing the concentration of substrate. They do not affect V_{max}.
- Non-competitive enzyme inhibitors bind to a site distinct from the active site and reduce activity; their actions are not overcome by increasing the concentration of substrate. They reduce V_{max}.
- Drugs such as statins (to reduce cholesterol), ACE inhibitors (used in hypertension and heart failure) and a number of antibiotics are enzyme inhibitors.

10 Central metabolic pathways

- Pyruvate dehydrogenase complex is a central enzyme that is responsible for the production of acetylCoA from pyruvate.
- PDH is tightly regulated.
- AcetylCoA undergoes oxidation via the Krebs cycle.
- The flow of electrons through the electron transport chain drives the pumping of protons to create a proton gradient. The inner mitochondrial membrane is impermeable to protons except for Complex V (ATP synthase), and flow of protons is coupled to ATP synthesis.

11 Fat metabolism

- Lipolysis is the breakdown of triacylglycerols to glycerol and free fatty acids.
- The glycerol enters glycolysis or is converted to glucose via gluconeogenesis.
- Fatty acid oxidation yields acetylCoA, which feeds into the Krebs cycle or is used to make ketone bodies.
- Fatty acids are oxidised by β-oxidation, which cleaves two carbons off the fatty acid from the carboxyl end, as acetylCoA, for each round of oxidation.

12 Glucose metabolism

- Glucose levels are controlled by insulin and glucagon.
- Glucose enters glycolysis as glucose-6-phosphate.
- In glycolysis the net yield for each glucose is 2 ATP, and a further 6 ATP can be generated from the oxidation by the ETC of the 2 NADH produced.
- In aerobic conditions, the pyruvate can be converted to acetylCoA, which enters the Krebs cycle.
- Gluconeogenesis is the production of glucose from non-carbohydrate sources.
- In health, plasma glucose is tightly regulated (4–8 mmol/L) by insulin, cellular uptake and counter regulatory systems.

13 Amino acid metabolism

- Non-essential amino acids are made by either *de novo* pathways or conversion from existing amino acids.
- Excess amino acids are broken down with removal of the α-amino group to form an ammonium ion, which is converted to urea via the urea cycle.
- Amino acids are either glucogenic or ketogenic.
- Glucogenic amino acids are those that will form pyruvate, or the TCA cycle intermediates, and primarily be used in gluconeogenesis.
- Ketogenic amino acids form acetylCoA or the ketone body acetoacetate.

14 Principles of molecular genetics

- Restriction enzymes are endonucleases that recognise and cut DNA at specific sequences.
- Plasmids are small circular DNA molecules that can be present in a bacterial cell and replicate along with the bacterial genome.
- Southern blot uses a DNA probe to detect a DNA sequence.
- Northern blot is used to detect RNA sequences.
- Western blot uses an antibody to probe polypeptides.

15 DNA and RNA

- DNA is made up of a double helix of adenine, guanine, cytosine and thymine:
    - adenine pairs with thymine
    - guanine pairs with cytosine.
- DNA polymerases are responsible for DNA replication.
- RNA primases generate the RNA primer.
- DNA ligase joins single DNA strands together.
- Helicases and topoisomerases wind or unwind the helix.
- mRNA is the RNA copy of a gene used to code for proteins.
- rRNA (with proteins) forms the small and large ribosomal subunits.
- tRNA is responsible for delivering the correct amino acid to the ribosome for protein synthesis.

16 Gene expression

- Transcription is the synthesis of RNA on expressed DNA.
- This is a tightly regulated process, involving transcription factors.
- Translation is the decoding of mRNA into proteins.
- Exons are DNA regions that code for the mature mRNA.

- Introns are regions of DNA that are transcribed but removed during post-transcriptional processing.

17 Medical genetics

- Genotype is the genetic make-up of a cell.
- Karyotype is the chromosome content of a cell.
- Mutation is a permanent heritable change in DNA sequence.
- Gene therapy is the introduction of genetic material into a patient to replace absent or damaged genes.

18 Cell excitability

- Extracellular K^+ is the major determinant of resting membrane potential.
- The Nernst equation is key to determining the resting membrane potential.
- The $3Na^+/2K^+$ pump maintains and replenishes the ionic distribution across the cell membrane.
- Plasma K^+ is tightly regulated and is a key electrolyte monitored in patients.
- Hypokalaemia (often due to diuretics) is associated with reduced excitability of nerve and muscle and can lead to cardiac arrhythmias.
- Hyperkalaemis (often due to renal disease or ACE inhibitors) causes cell depolarisation and can lead to cardiac arrhythmias.

19 Nervous conduction

- Resting membrane potential is ~-70 mV
- Once threshold is reached, Na^+ channels open and Na^+ influx leads to depolarisation and initiation of the action potential.
- Depolarisation activates K^+ channels, which contribute towards repolarisation.
- Once activated, Na^+ channel move to the inactive state and this helps repolarisation.
- Following the action potential, the cell becomes refractory.
- Myelination enables the AP to 'jump' and underpins salutatory conduction.
- Local anaesthetics:
    - inhibit voltage-operated Na^+ channels to block transmission of action potential
    - are used to prevent transmission of pain
    - are antiarrhythmics, which are used to control abnormal cardiac rhythms.

20 Synaptic transmission

- Presynaptic depolarisation leads to Ca^{2+} influx coupled to the exocytosis of vesicles of neurotansmitters.
- Excitation leads to an excitatory postsynaptic potential and inhibition leads to hyperpolarisation with an inhibitory postsynaptic potential.
- Neurotransmitters are 'inactivated' by cellular reuptake (e.g. noradrenaline) or extracellular degradation (e.g. acetylcholine by acetylcholinesterase).
- Synaptic transmission may be modulated by presynaptic inhibition.
- Many drugs act synapses, for example:
    - SSRI antidepressants increase levels of 5-HT in central synapses, which lead to changes in receptor populations and antidepressant effects
    - TCA antidepressants inhibit reuptake of noradrenaline and 5-HT
    - benzodiazepines increases GABAergic activity, leading to hyperpolarisation and inhibition of neuronal activity

- opioids can cause pres-synaptic inhibition to impair neurotransmission.

21 Autonomic nervous system

- Parasympathetic system usually involves acetylcholine acting post-synpatically at muscarinic receptors.
- Sympathetic system usually involves noradrenaline acting at α- or β-adrenoceptors.
- At autonomic ganglia acetylcholine acts at nicotinic receptors.

22 Neuromuscular transmission

- Acetylcholine acts at nicotinic receptors at the NMJ, which are ion channels that lead to depolarisation (miniature end plate potentials which summate to form excitatory post-synaptic potentials).
- Non-depolarising blockers are competitive antagonists of acetylcholine at the nAChR.
- Depolarising blockers are agonists at the nAChR and the activation of the nAChR leads to prolonged depolarisation and inactivation of the voltage-operated Na^+ channels.
- Myasthenia gravis involves the production of autoantibodies against the nicotinic receptor.

23 Structure of the respiratory system

- Airways are lined by the respiratory epithelium.
- The trachea leads to the main bronchus, bronchioles and then alveoli.
- Large pulmonary artery supplies blood to the lung and two pulmonary veins draining blood from the lung.
- The serous pleural sac is composed of two membranes.
- The diaphragm is the main muscle of respiration.

24 Respiratory physiology

- Breathing is tidal with a dead space.
- Compliance is the change in volume for a unitary change in pressure, and may limit inhalation.
- Ventilation-perfusion matching matches blood flow to ventilation of the alveoli.

25 Gas transport

- Four O_2 molecules are carried by haemoglobin, which has four subunits.
- Allosteric modulation means that the affinity of haemoglobin increases as the first O_2 molecule binds. This leads to a sigmoidal O_2 dissociation curve.
- The Bohr effect means that H^+, CO_2 and temperature all promote O_2 delivery.
- CO_2 is carried as carbamino compounds, as HCO_3^- or is dissolved.

26 Control of breathing

- Respiratory centres in the brainstem maintain an optimum minute-to-minute control of respiratory volume.
- The basic ventilatory rate and rhythm is produced by the dorsal respiratory group in the medulla oblongata.
- The duration of inhalation is prolonged by the apneustic centre.
- Central chemoreceptors in the medulla oblongata respond to increases in $[H^+]$ to provide fine control.

- Peripheral chemoreceptors in the aortic arch and carotid arteries respond quickly to significant hypoxia.
- Type I respiratory failure is hypoxia without hypercapnia, e.g. ascent to altitude.
- Type II respiratory failure is hypoxia with hypercapnia, e.g. lung disease.

27 Acid-base physiology

- Normal extracellular pH is maintained at 7.4.
- The lungs can lead to rapid control of pH.
- Hyperventilation causes hypocapnia, e.g. to correct hypoxia. So plasma pH rises = respiratory alkalosis. This can be compensated by hypoventilation or by the kidneys increasing [HCO_3^-] excretion.
- Hypoventilation causes hypercapnia, e.g. when ventilation is impaired by disease. Plasma pH falls = respiratory acidosis. This can be compensated by hyperventilation or by the kidneys increasing [H^+] excretion.

28 Respiratory pathophysiology

- FVC is the maximum volume exhaled.
- FEV_1 is the volume exhaled in the first second and is decreased with increased airways resistance.
- Asthma is associated with reversible decreases in FEV_1 and is primarily managed with β_2-agonists as bronchodilators and inhaled steroids to reduce the inflammatory response.
- COPD is a spectrum of emphysema (destruction of alveoli) and chronic bronchitis with remodelling of the airways. It is associated with increased airways resistance that shows little variation. It is primarily managed by β_2-agonists and muscarinic receptor antagonists.

29 Structure of the cardiovascular system

- Conduit arteries lead to arterioles, which lead to capillaries then to venules and then veins, and blood is returned to heart.
- Blood vessels are made up of tunica intima, tunica media and tunica adventitia.

30 Cardiac physiology

- Cardiac output the volume pumped by each ventricle per minute and is normally 5 L in man.
- The sinoatrial node is the normal pacemaker with intrinsic activity due to I_f.
- The action potential jumps across the atrioventricular node and is conducted throughout the ventricles.
- The ECG records the electrical activity; in lead II:
    - P wave is atrial depolarisation
    - P-Q interval is conduction across the atrioventricular node
    - QRS complex reflect ventricular depolarisation
    - T wave is ventricular repolarisation.
- Frank-Starling relationship means that the force of contraction is proportional to preload.
- Sympathetic control leads to positive inotropic and chronotropic effects.
- Parasympathetic control leads to negative chronotropic effects.

31 Cardiovascular physiology

- Sympathetic control via α-adrenoceptors leads to vasoconstriction.
- Sympathetic control via β-adrenoceptors (mostly skeletal muscle) leads to vasodilatation.
- The endothelium releases NO and other vasodilators.
- Fluid exchange at the capillary bed is due to the balance of hydrostatic and osmotic pressures.

32 Blood pressure

- Blood pressure is the product of cardiac output and total peripheral resistance.
- Blood pressure is regulated via autonomic control and volume control.
- The renin-angiotension-aldosterone system is important in controlling resistance and volume.
- Baroreceptors help to maintain a constant blood pressure.
- Hypertension is often defined as sustained increases in systolic (>140 mmHg) and/or diastolic (>90 mmHg) blood pressures.
- Hypertension is treated via lifestyle changes and drugs (ACE inhibitors, calcium channel blockers and diuretics).

33 Blood 1

- Iron deficiency anaemia is usually secondary to chronic blood loss and is characterised by reduced haematocrit and is microcytic.
- Meglaloblastic anaemia is often due to vitamin B_{12} or folate deficiency and is macrocytic.

34 Blood 2

- Clotting involves the coagulation cascade leading to fibrin production and platelet aggregation.
- Coagulation is inhibited by warfarin as a vitamin K antagonist and by heparins, which activate antithrombin III.
- Antiplatelet drugs (e.g. low-dose aspirin and clopidogrel) have a major role in the prevention of cardiovascular events.
- Leukaemias and lymphomas are haematological neoplasias.

35 Cardiovascular pathophysiology

- Risk factors are: gender, smoking, ethnicity, diabetes, dyslipidaemia, obesity, family history.
- Ischaemic heart disease is due to impaired coronary flow and may manifest as angina or myocardial infarction.
- Statins are HMG CoA reductase inhibitors that reduce cholesterol synthesis and reduce cardiovascular risk.
- Chronic heart failure is the inability of the heart as a pump to meet the circulatory needs of the body.
- Left-sided heart failure leads to breathlessness due to pulmonary oedema.
- Right-sided heart failure leads to peripheral oedema.
- Chronic heart failure is managed by diuretics, ACE inhibitors and β-blockers.

36 Structure of the renal system

- Ultrafiltration occurs at the Bowman's capsule leading to the formation of tubular fluid.

- The proximal convoluted tubule feeds into the loop of Henle, then distal convoluted tubule and then the collecting duct.
- Urine passes down the ureters to the bladder for storage before passing down the urethra.

37 Renal physiology: filtration and tubular function

- Renal blood flow and GFR are regulated by autoregulation.
- In the proximal convoluted tubule 65% of filtered water, Na^+, K^+, Cl^- and other solutes (almost all of the glucose and amino acids) is reabsorbed.
- Weak acids and bases are secreted by non-specific transporters.
- The distal convoluted tubule finely tunes Na^+ levels under the control of aldosterone.
- Renal function is measured by determining serum creatinine levels and then determining creatinine clearance and/or estimated GFR.

38 Renal physiology: loop of Henle

- Essential for the production of concentrated urine.
- The hyperosmotic interstitium is set up for countercurrent multiplication.
- The descending limb is very permeable to water so that tubular fluid becomes concentrated by equilibrating with the hyperosmotic interstitium.
- The ascending limb is impermeable to water, so solute reabsorption occurs in the absence of accompanying water reabsorption.
- The water permeability of the late distal tubule and the collecting duct is dependent on ADH.
- The countercurrent multiplier of the loop of Henle sets up the hyperosmotic interstitium to promote the reabsorption of water from the collecting ducts.
- Loop diuretics (e.g. furosemide) inhibit the $Na^+/K^+/2Cl^-$ triporter in the loop of Henle and impair its ability to set up a hyperosmotic interstitium.

39 Regulation of body fluids

- ADH is released from the poster pituitary under the control of osmoreceptor cells in the anterior hypothalamus.
- ADH promotes the translocation of aquaporin-2 water channels to the apical membrane of collecting duct cells.
- The renin-angiotensin-aldosterone system is activated by low blood pressure, sympathetic activity and low Na^+.
- Aldosterone acts on the principal (P) cells of the late DCT and collecting duct to increase the expression of apical Na^+ channels and basolateral Na^+/K^+-ATPase pump.
- Diuretics are key cardiovascular drugs (hypertension and congestive heart failure) and reduce circulating volume and oedema.

40 Bladder control and urinary incontinence

- Parasympathetic control (M_3 receptors) leads to contraction and micturition.
- Sympathetic control (β_2- and β_3-adrencoeptors) leads to relax of the detrusor muscle, resulting in the bladder relaxing and storing urine.
- Noradrenaline acts at α_1-adrenoceptors to contract the neck of the bladder and urethra and to enable the storage of urine.
- UTIs are common infections and trimethoprim is a first-line antibacterial.
- Overactive bladder is managed by antimuscarinic drugs.

- Benign prostatic hypertrophy commonly affects males over 50 and can be managed with α_1-blockers.

41 Structure of the gastrointestinal system

- Bolus of food passes down the oesophagus to the stomach for retention, before passing to the duodenum then to the jejunum and ileum and finally the large intestines.

42 Upper gastrointestinal physiology

- Salivation is under autonomic control with parasympathetic innervation via M-receptors leading to salivation.
- Gastric secretion is under cephalic, gastric and intestinal control.
- Gastric acid secretion (proton pump) is stimulated via gastrin (CCK_2 receptors), histamine (histamine H_2 receptors) and ACh (M-receptors), and inhibited by prostanoids.
- Dyspepsia is a common clinical condition and is managed by antacids, histamine H_2 receptor antagonists and proton pump inhibitors.
- Peptic ulceration is largely due to *H. pylori* infection and can be cured with 'triple therapy'.
- NSAID-induced ulceration is the one of the most common adverse drug reactions.

43 Lower gastrointestinal physiology

- Monosaccharide uptake is coupled to specific transports on the apical membrane.
- Di- and tri-peptides from protein degradation are transported across the apical membranes and broken down intracellularly to amino acids.
- Lipids are emulsified by bile salts and broken down by lipases to free fatty acids and monoglycerides, which form micelles for delivery of lipids to the microvilli. Fats are then formed intracellularly.
- Parasympathetic activity increases motility.
- Acute diarrhoea is secretory and managed by oral rehydration.
- Drugs (e.g. opioids, antimuscarinic agents) reduce motility and lead to constipation.
- Irritable bowel syndrome is a common condition characterised by altered motility.
- Inflammatory bowel diseases, including Crohn's disease, involve severe inflammation and are managed by anti-inflammatory agents, including steroids and 5-aminosalicylates.

44 The liver

- Key metabolic organ: protein synthesis, cholesterol synthesis, glycogen storage, gluconeogensis, bile production, detoxification.
- Cholestasis is the inability to excrete bile.
- LFTs are used to determine altered liver function. Increased ALT suggests cellular damage; increases in ALP and γGT suggest cholestasis and decreased albumin; and increased INR indicates impaired synthetic activity.

45 Hypothalamus and pituitary

- The anterior pituitary secretes growth hormone, prolactin, LH, FSH, ACTH and TSH.
- The hypothalamus produces ADH and oxytocin, which are secreted by the posterior pituitary.

- Acromegaly is caused by excessive release of GH in adults. In children, excessive release of GH leads to gigantism.
- Pituitary diabetes insipidus is due to the absence or low levels of ADH.

46 Endocrine pancreas

- Insulin secretion is stimulated by glucose, incretins, amino acids, fatty acids and parasympathetic control.
- Insulin causes autophosphorylation of its receptor via intrinsic tyrosine kinase activity, which leads to:
  - increased glucose uptake in adipose and skeletal muscle
  - increased glycogen synthesis, inhibition of glycogenolysis
  - increased protein synthesis, inhibition of protein breakdown
  - increased lipogenesis, inhibition of lipolysis
  - inhibition of gluconeogenesis.
- Glucagon increases blood glucose levels by stimulating hepatic glucose output.
- DM type I is due to the absence of insulin and requires treatment with insulin.
- Diabetes mellitus is a major cardiovascular risk and also associated with nephropathy, neuropathy and retinopathy.
- DM type II is due to reduced insulin sensitivity and/or secretion and is managed by lifestyle and drugs to improve insulin sensitivity (e.g. metformin or pioglitazone) or increase secretion (sulphonylureas).

47 Thyroid gland

- T4 is the prohormone to T3.
- Thyroid hormones are key metabolic regulators.
- Hyperthyroidism: Graves' disease is the most common and is due to antibodies, which activate the TSH receptor. It is managed by β-blockers for symptomatic relief and anti-thyroid drugs (e.g. carbimazole).
- Hypothyroidism: associated with reduced metabolism and can be managed by levo-thyroxine.

48 Adrenal glands and steroid hormones

- Outer cortex secretes steroid hormones:
  - glucocorticoids (e.g. cortisol) oppose those of insulin and at high levels, anti-inflammatory/ immunosuppressive
    - cortisol is regulated by the hypothalamus and pituitary
  - mineralocorticoids (aldosterone) act on the kidneys to retain sodium.
- Inner medulla secretes adrenaline and noradrenaline.
- Cushing's syndrome is associated with excessive levels of glucocorticoids.
- Conn's syndrome is associated with increased levels of the mineralocorticoid aldosterone.
- Addison's disease is associated with adrenal failure and low levels of glucocorticoids and aldosterone.

49 The genital system

- External genitalia (male): penis and scrotum.
- External genitalia (female): mons pubis, labia (majora and minora) and vestibule.
- Internal genitalia (male): testes, epididymides, seminal glands and prostate gland.
- Internal genitalia (female): vagina, uterus and uterine tubes.

50 Reproductive physiology

- In males, LH acts on Leydig cell to stimulate the release of testosterone and FSH acts on sertoli cells to stimulate spermatogenesis.
- In females, LH and FSH promote maturation of primordial follicles in the follicular phase of the menstrual cycle.
- In mid-menstrual cycle an increase in oestrogens leads to a surge in LH and ovulation.
- After ovulation the ruptured follicle becomes the corpus luteum.
- If ovulation is followed by fertilisation then the corpus luteum is retained to maintain pregnancy. This is achieved by hCG.
- Combined oral contraceptives prevent follicular development, ovulation and luteinisation by suppressing the release of LH and FSH.
- Progestogen-only-containing pills increase the viscosity of cervical mucus.

51 Human embryology

- First 8 weeks from fertilisation.
- Early embryo is the blastocyst surrounded by trophoblast cells.
- Gastrulation is the establishment of three germ cell layers.
- Organogenesis occurs in weeks 3–8.
- The first trimester is a period that is highly vulnerable to the teratogenic effects of drugs.
- Fetal period starts at week 9.

52 Structure of the central nervous system

- The cerebral hemispheres form the largest component of the brain.
- Brainstem: composed of the midbrain, pons and medulla oblongata.
- Cerebellum: posterior to the pons and medulla.
- Meninges: membranous layers.
- Ventricular system: two lateral ventricles and midline third and fourth ventricles.

53 The sensory system

- Sensory receptors are sensitive to chemicals, temperature, pain, mechanical forces and photons, and send afferent fibres.
- Two main somatosensory pathways: spinothalamic and medial lemniscus.
- Specialised sensations are conducted directly to the brain. All except smell are communicated to the cerebral cortex via the thalamus.

54 The motor system

- Many brain regions work together to coordinate motor activity.
- The major descending pathways are the corticospinal, vestibulospinal and reticulospinal tracts.
- Motor neurones: *Alpha:* large and rapid conducting neurones which innervate muscle fibres; *Gamma:* control the length and tension of the muscle spindle fibres.

55 Hypothalamus and thalamus

- The diencephalon is involved in maintaining higher order cognition and homeostasis.
- The hypothalamus is at the centre of the limbic system.

- The hypothalamus is involved in homeostasis via the neuroendocrine system.
- The thalamus relays information; it integrates and regulates the transfer of information in a complex way. The thalamus is also believed to be involved in higher functions, such as regulating consciousness.

56 Central nervous system function

- Neurones may form up to 10 000 synapses, creating immensely complex neural networks.
- Long-term potentiation at synapses may provide a mechanism of learning and memory.
- Neurotransmitter function can be gleaned from anatomical location, pathophysiology and pharmacological effects.

57 Disorders and treatments

- Broadly, neurological conditions involve altered function and psychiatric conditions involve altered mood and/or behaviour.
- Epilepsy: abnormal electrical activity and is managed by drugs that reduce excitability.
- Depression: associated with reduced monoamine function and managed by SSRIs or TCAs, which increase levels of monoamines, leading to complex alterations in neurotransmitter control.
- Schizophrenia: associated with overactivity of dopaminergic function and managed by dopamine D_2 receptor antagonists.
- Parkinson's disease: decreased dopaminergic activity in basal ganglia and managed with L-dopa.
- Multiple sclerosis: inflammation leading to demyelination of neurones.
- Stroke: may be ischaemic (most common) or haemorrhagic.

58 Pathogens 1

- Infection involves: (a) attachment and entry; (b) dissemination and multiplication: (c) evasion; (d) exit; (e) damage.
- Bacteria are prokaryotes.
- Lipopolysaccharide (LPS), a component of the outer membrane of Gram-negative bacteria, and lipoteichoic acid (LTA), a component of the cell wall of Gram-positive bacteria, are potent activators of immune and inflammatory responses.

58 Pathogens 2

- Viruses are either single- or double-stranded DNA or RNA surrounded by structural proteins, enzymes and nuclear binding proteins (the capsid). Once inside the cell the biochemical processes of the cell become co-opted to make more viral particles.
- Fungi are eukaryotic. In most cases fungal infection is opportunistic and requires a breakdown of host defences.
- Medical parasitic infections are due to protozoans and helminths.
- Prions are transmissible aberrant proteins, e.g. associated with Cruetzfeld-Jakob disease (CJD).

59 Recognition of pathogens

- Innate immunity: general response to microbes triggered by the recognition of both complement proteins that have opsonised the pathogen, as well as chemical structures that are characteristic of microbes.
- Adaptive immunity: recognition of antigens specific to each type of microbe, which are recognised by antigen-receptors that are clonally expressed by lymphocytes.

60 Defence against pathogens

- Extracellular microbes: innate immune defence is mediated by various cell types, including leucocytes (e.g. neutrophils) and epithelial cells. These cells produce antimicrobial peptides called defensins.
- Intracellular microbes: production of chemicals, e.g. interferons, to neutralise the viral activity.
- Extracellular parasites: removed by generating an inflammatory response through the actions of eosinophils, mast cells and basophils.

61 Integration of the immune response

- Innate response provides an initial rapid response to infection.
- Adaptive immunity is more slowly activated by the invading pathogen, but once activated it provides specific responses tailored to each individual type of pathogen.

62 Immunopathology

- Type I hypersensitivity: allergy is the inappropriate activation of adaptive immunity by allergens (e.g. hay fever).
- Type II hypersensitivity: antibodies to cell membranes, e.g. haemolysis associated with transfusion reactions.
- Type III hypersensitivity: immune complexes can activate complement and neutrophils, leading to tissue damage, e.g. allergic alveolitis.
- Type IV hypersensitivity: cell mediated as seen in graft vs host reactions; autoimmune diseases such as autoreactive T cells leading to autoimmune destruction of the adrenal cortex as occurs in Addison's disease.

63 Immunodeficiency disorders

- An impaired immune response leading to increased susceptibility to infections.
    - Hereditary: Kostmann's disease, a genetic disorder associated with neutropenia.
    - Acquired: e.g. HIV infection leading to depletion of CD4 T cells; toxic effects of drugs leading to myelosuppression and reduced production of white cells.

64 Cancer biology

- Uncontrolled cell division of abnormal cells. Cancer cells may spread via metastasis and this often leads to death.
- Oncogenes: can be responsible for initiating the cell transformation. Different gene products: they can activate cell division or inhibit apoptosis.
- Tumour suppressor genes: oppose the action of oncogenes, acting to regulate passage through the cell cycle; can help maintain DNA integrity.
- Normal cells accumulate mutations and deletions in oncogenes and tumour suppressor gene until they are sufficient to transform the cell.

65 Chemotherapy

- Cytotoxicity targets rapidly dividing (normal and cancer) cells by attacking:
  - DNA synthesis, e.g. antimetabolites
  - structure and function, e.g. alkylating agents, intercalating agents, topoisomerase inhibitors
  - mitosis, e.g. vinca alkaloids
- Myelosuppression is a key side effect.
- Often carried out in cycles.
- Targeted therapy may attack specific receptors associated with tumour growth, markers or signalling systems.