FIRST BM PART I: FIRST YEAR SYLLABUS FOR MEDICAL STUDENTS 2020-21

Content and role of the syllabus
The BM course is intended as a preparation both for clinical work and for the degree course in Medical Sciences. The syllabus is revised annually with the intention of producing a useful and up-to-date guide to the course. Like any syllabus, it summarises the material that is taught and examined, but the organization and level of detail is intended to be helpful to your understanding of the course rather than simply listing topics to be learned. The left-hand side defines the 'Core' that will be covered in university teaching and on which you may be required to answer basic questions in the Part A examinations of subjects 1-3. The Core contains material with which you need to be familiar when you start the clinical part of your course. The topics listed on the right (the 'Extension') will also be taught in the course, but it is expected that you will pursue these further in your own reading and with your college tutors according to your own particular interests. The essay questions in the Part B examination papers for subjects 1-3 will be based on both parts of the syllabus, and you will have a choice of essay questions to answer. Neither part of the syllabus should be treated as a list of facts to learn. You should try and gain an understanding of the topics set out here, and the examiners will set compulsory problem questions (in the Part A papers) to see whether you can apply your understanding of the Core. For Medical Sociology, the syllabus will be covered through lectures and recommended reading: tutorials are not needed. There will be a single examination in this subject. Your approach to all areas of the First BM will be informed through your early clinical experience in the Patient & Doctor course.

Definition of the scope of the courses
Each major section of the syllabus is labelled - [OB], [P&P], [BIOCH] [MS] or [Stats] - as a guide to indicate its primary relevance to one of the four First Year courses and examinations. Do remember, however, that such a division is inevitably artificial. For instance, structure and function should always be considered together: they simply receive different emphasis in the examinations for 'Organization of the Body' and 'Physiology and Pharmacology'. In this respect, notice particularly the cross-referencing between sections.

Drugs: classes of drug and specific names
In the examination, drugs and other pharmacologically active substances will be referred to according to the major classes of drug included in this syllabus. In certain cases, you are required to know a drug or substance by its name, and these names are specifically given in the core syllabus and for convenience summarised in a table at the beginning of the syllabus.

Essay-writing
The examination will additionally test your ability to present material selectively in clearly organised essays to answer precisely the questions set. You will need to develop an integrated understanding of the syllabus, and you will need to develop your written communication skills. Your college tutorial essays and termly college collection exams should provide you with plenty of opportunity for improving these skills.

Experimental evidence and clinical significance
Credit will be given in the examinations for appropriate reference to experimental evidence and to points of clinical significance.

Clinical conditions
Where appropriate, reference has been made to clinical conditions that illustrate the science in the course (this is often distinguished by the use of italics). You will not be expected at this stage to learn clinical details, but you should try to understand the basis for the conditions in the context of the fundamental science you are studying. Remember that you can very quickly read more about any clinical condition that especially interests you by consulting, for instance, the Oxford Textbook of Medicine http://oxfordmedicine.com/view/10.1093/med/9780199204854.001.1/med-9780199204854. Try now to develop the habit of thinking about clinical conditions in a scientific background; then it will be all the easier later on to continue thinking scientifically when you are learning to deal with patients as individuals.

Objectives of the First Year of the BM Course

Outcomes
During your First Year, you should seek to acquire:

- An understanding of the basic principles of structure and function in the healthy human, and of statistics and medical sociology, as set out in the 'core' (the left-hand side of this syllabus).
- An awareness of major issues of clinical significance in the core.
- An ability to apply basic principles to problems based on data from experiments or simple clinical cases.
- An understanding of some related areas beyond the core syllabus and an appreciation of the major supporting evidence (based largely on text-books and reviews rather than on original papers).
- An ability to write clearly about topics in the core syllabus and in selected areas beyond.

Experience
During your First Year, you will gain:

- Laboratory experience in basic medical science: physiology and pharmacology, gross and microscopic anatomy, and biochemistry.
- Experience of the clinical and personal implications of illness, and of patient: doctor interactions, through the Patient and Doctor course and through lecture-demonstrations by clinicians.
- Experience of note-taking in lectures and of recording data in the laboratory.
- Some experience, especially through tutorials, of the issues behind the design and interpretation of experiments.

British National Formulary "BNF"
This is an essential compilation for clinicians and pharmacists of drugs and their uses with advice on prescribing. It is regularly updated and is available on the internet at (http://www.bnf.org/). It also lists adverse effects of drugs and drug interactions. It is therefore a useful reference work for the course, though there is no suggestion that you need to learn clinical details at this stage (see also the note about specific drugs on the cover page of this syllabus). Recent editions of the BNF explain the introduction of standardised drug names in the EU: where a change has been recommended from the old British name, the new name appears in this syllabus. Many textbooks still use the old names (the differences are relatively few and should not be confusing).

Normal Values for Physiologically Important Parameters

Understanding certain areas of the syllabus requires knowledge of some physiologically and clinically important quantities. This list gives 'typical' values in a healthy young adult, and these are regarded as part of the Core. You should, of course, remember that in each case there will be a range of values that are regarded as 'normal' in the clinic; but you need not commit those *ranges* to memory (ranges are commonly printed on clinical laboratory reports, and they will be provided to you should they be needed in an examination). There is no merit in learning the list below as a memory exercise in itself! You will find it easy to learn these figures when you need to, as you progress through the year.

Concentrations	*Extracellular (range)*	*Intracellular*
Sodium	140 mM (135 - 145 mM)	5-15 mM
Potassium	4 mM (3.5 - 5.0 mM)	140 mM
Calcium	2.4 mM (2.12 - 2.62 mM)	0.1 micromolar (n.b. only about one half of the extracellular calcium is present as free Ca^{2+} ions)
Chloride	100 mM (95 - 105 mM)	less than extracellular, but widely ranging according to tissue
Bicarbonate	25 mM (22 - 29 mM)	10-20 mM (according to intracellular pH)
Hydrogen ions	40 nM (pH = 7.4)	50-100 nM (pH = 7.0-7.3)

Values for blood and urine

Plasma glucose (fasting)	4 mM to 6 mM	Systemic arterial blood pressure	120/80 mmHg
Plasma osmolarity	290 mOsM	Pulmonary arterial blood pressure	20/10 mmHg
PaO_2	90 mm Hg [12 kPa] (range 80-100 mmHg [11-13 kPa])	Resting cardiac output	5 L/min
$PaCO_2$	40 mm Hg [5.3 kPa] (range 35-45 mmHg [4-6 kPa])	Basal oxygen consumption	250 mL/min
Blood pH (arterial)	7.4 (7.35 - 7.45)	Ventilation (at rest)	6 L/min
Glomerular filtration rate	125 mL/min	Alveolar ventilation (at rest)	4 L/min
		Normal heart rate (at rest)	60-100 bpm
Urine osmolarity	30 - 1200 mOsM		

Volumes of body fluid compartments in a 70 kg person:

Total body fluid	42 L		
Extracellular:	as plasma 3 L;	as interstitial fluid 10 L;	as transcellular fluid 1 L
Intracellular	28 L		

Blood cells: normal counts	*Cells/L*	*Differential count*
Erythrocytes	5×10^{12}	
(haematocrit 45%)		
Leucocytes	~7×10^9	100%
neutrophils		40-70%
lymphocytes		20-40%
monocytes		~6%
eosinophils		~3%
basophils		<1%
Platelets	1.5M-4.5M	

Named Drugs with which students are expected to be familiar for Part A Examinations in the First BM Part I

It is most important that students are familiar with the classes of drugs (e.g. oral contraceptives) and their actions rather than the individual names. However, drugs are referred to by name, and for each of the drugs listed here students are expected to know the main therapeutic action(s) and adverse effect(s) as pertaining to the left-hand side of the syllabus. It should be noted that some drugs not included in this list are mentioned in the core syllabus primarily as examples of a drug. A further point to note is that drugs in this list, and other drugs, may be mentioned in the extension material on the right-hand side of the syllabus; it is not uncommon for a drug (e.g. aspirin) to have one action that has been deemed core material and a second action that has been included only in the extension material. Also, it should be noted that some drugs included here are used experimentally rather than therapeutically.

Drug	Chapter	Drug	Chapter
acetazolamide	11.3.5.5	salbutamol	6.4.3.2
adenosine	8.6.8	spironolactone	11.3.5.4
adrenaline	2.2.6 & 2.3.4 & 6.2.2 & 6.4.3.2	suxamethonium	6.4.1
amiloride	11.3.5.4	tetrodotoxin	6.3.2
amiodarone	8.6.8	tubocurarine	6.4.1
amphetamines	6.4.4.2	atracurium	6.4.1
aspirin	14.9.4	verapamil	8.6.8
atenolol	6.4.4.2		
atropine	6.4.4.1 & 8.6.8		
bendroflumethiazide	11.3.5.2		
botulinum toxin	6.4.1		
digoxin	8.6.7		
dobutamine	8.6.7		
furosemide	11.3.5.1		
insulin	14.6.1		
isoprenaline	6.4.4.2		
lidocaine	6.3.3 & 8.6.8		
mannitol	11.3.5.3		
neostigmine	6.4.1		
omeprazole	9.5.3.1		
ouabain	8.6.7 & 8.6.8		
penicillin	4.3.3 & 11.3.3		
propranolol	8.6.7 & 8.6.8		
ranitidine	9.5.3.1		

FIRST-YEAR BM SYLLABUS: SUMMARY OF CONTENTS

1. CELLULAR & MOLECULAR STRUCTURE & FUNCTION

1.1 GENERAL PRINCIPLES OF BIOCHEMICAL STRUCTURES [BIOCH]

Macromolecular organization as the basis of biological structure and function.

Concept of stereoisomerism.

1.2 PROTEINS [BIOCH]

1.2.1 GENERAL PRINCIPLES

Functional types: Structural proteins, enzymes, transporters, regulatory proteins.

1.2.2 PROTEIN COMPOSITION AND STRUCTURE

1.2.2.1 Amino Acids and the Peptide Bond

Principles of structure of amino acids (details of structure of functional groups of individual amino acids not required).

The functional types of amino acid side-groups: Basic, acidic, hydrophilic, hydrophobic (with named examples), “structural” (proline).

The peptide bond: Features, significance in secondary structure.

Importance of stereoisomerism in influencing shape of proteins and hence interaction between molecules.

Basic principles and application of protein sequencing.

Difference between mammalian and bacterial use of stereoisomers. Antibiotics as mimics of D-amino acid structures.

Significance of stereoisomerism in drug development.

1.2.2.2 Principles of protein structure

Factors stabilizing protein structure: Van der Waal’s forces, hydrogen bonds, hydrophobic forces, ionic interactions, disulfide bonds.

Levels of organization (primary, secondary, tertiary and quaternary).

Organization and properties of α-helix, β-sheet, and loop/turn

Structural and functional domains.

Hetero- and homo-oligomeric multi-subunit proteins.

Co-operativity and allostery in multi-subunit proteins: Examples including haemoglobin and metabolic enzymes such as phosphofructokinase.

Post-translational modifications:

Disulfide bonding, cross-linking, peptidolysis.

Non-peptide attachments: Glycosylation, phosphorylation, adenylation, farnesylation.

Roles: Regulation, targeting, turnover, structural.

Reversible and irreversible denaturation of protein.

Organization of secondary structural elements into structural and functional domains: Specific examples, e.g. ABC proteins, 2 units of 6 α helices in membrane; nicotinic acetylcholine receptor.

Comparison of the structure and properties of haemoglobin and myoglobin protein–protein regulation: e.g. cAMP-dependent protein kinase.

1.2.3 STRUCTURAL BASIS OF PROTEIN DIVERSITY

1.2.3.1 Collagen

Collagen as an example of a fibrous protein and histones as examples of globular proteins. Details of how structure relates to biological function. Structural protein of tendons and ligaments: Fibrous protein, triple coils of extended helices, assembled staggered and cross-linked for strength (see **5.2**). *Ehlers-Danlos syndrome.*

Repeating amino-acid unit favours left-handed helix formation.
Hydrogen bonding by glycines as the stabilizing force of the triple helix.
osteogenesis imperfecta.

1.2.3.2 Histones

Structural protein of chromatin: Globular, associate in octamers to form nucleosomes around which DNA is wound.

Need for histones: Packaging of DNA (saves space and protects it)
Significance of the cationic nature of histones. Packaging role of H1.

1.2.4 ENZYMES AND ENZYMIC CATALYSIS

1.2.4.1 Concepts of Biochemical Reactions and Enzymes

Definition of catalysis, definition of enzyme.
Details of energy of reaction and reaction intermediates.
Transition state complex.
Classes of biochemical reaction: Hydrolysis, ligation, condensation, group-transfer, redox, isomerisation.
How enzymes catalyse chemical reactions in general terms.

1.2.4.2 Structure and Function of Enzymes

Importance of active site for catalysis and specificity.
Multimeric enzymes:
Ranges of isozymes e.g. LDH.
Multienzyme complexes e.g. pyruvate dehydrogenase (see **2.3.3**).
Regulation of activity by allostery and by subunit dissociation (e.g. cAMP-dependent protein kinase).

Domain organization.
Mechanisms of catalysis illustrated by serine proteases, carboxypeptidase A and lysozyme.

1.2.4.3 Co-Factors

Importance of co-enzymes and trace elements in enzyme action.
Vitamins as precursors of co-enzymes (see **2.6.2.2**).

Examples of co-factors e.g. from glycolysis, TCA cycle, fatty acid oxidation and synthesis.

1.2.4.4 Kinetic Parameters

Dependence of rate of reaction on substrate concentration and amount of enzyme.	Equilibrium assumption for defining kinetic parameters.
Simple steady state reaction kinetics: Michaelis constant K_m, maximal velocity V_{max}, turnover number and specificity constant.	Derivation of Michaelis Menton equation.
The Ki is the concentration of inhibitor at which under saturating substrate conditions the reaction rate is half of the maximum reaction rate Vmax.	
Principles of competitive, non-competitive and irreversible inhibition, plus role in allosteric control (see **1.2.4.5**).	Linking kinetic parameters to reaction mechanism examples, such as proteases.
Transformations of enzyme kinetics graphs inc. double reciprocal plot (Lineweaver Burk plot) for determining kinetic parameters.	

1.2.4.5 Regulation of Enzyme Activity

Allosteric control and mechanisms of cooperativity.	
Effects of allosteric ligands on enzyme kinetics graphs and their transformations.	Molecular details, including discussions on interfacial regions, structural composition of oligomeric proteins and how allosteric effects are propagated through complex macromolecules.
Examples include competitive vs. non-competitive inhibition, cooperativity and mechanisms thereof, including basic principles such as T ‘tense’ and R ‘relaxed’ states. Specific examples, Haemoglobin vs. myoglobin and aspartate transcarbamylase (ATCase).	Role of cell surface receptors in activating kinases for signal transduction. Use in cell cycle, glycogen breakdown, transcriptional activation, cell growth and development.
Mechanisms of catalysis – Induced fit vs. selected fit models.	
Role of drugs as allosteric ligands.	
Mechanisms of enzyme regulation in the body, inc. phosphorylation, phosphorylation cascades and covalent modification. Role of covalent modification as control mechanisms in blood clotting and digestive enzyme activation.	Structural explanation for effects of cooperativity on enzyme kinetic parameters KM and Vmax.
Mevanolin (statin) – HMG-CoA inhibitor	Imatinib (Gleevec) – Tyrosine kinase inhibitor used to treat chronic *myelogenous leukaemia*.

1.2.6 REGULATORY PROTEINS: STRUCTURE AND FUNCTION

Examples: Proteins that regulate gene expression (see **3.1.4**). regulatory subunits of enzymes (see **1.2.4.2**).	Ligand-induced structural changes (illustrated by the steroid hormone receptor) affect binding to DNA.

1.4 LIPIDS [BIOCH]

1.4.1 TYPES OF LIPID IN THE BODY

1.4.1.1 Fatty Acids and Glycerides

General molecular structure of fats, fatty acids, including complex and simple.
Fatty acid nomenclature.
Sources of fatty acids (dietary and de novo synthesis).
Concept of essential fatty acids

Sources of fatty acids in the diet.
Essential vs. non-essential fatty acids.
Examples of linoleic and linolenic acids as EFAs.

1.4.1.2 Phospholipids

Outline molecular structure of phospholipids and phosphatidyl compounds. Including head group differences.
Phospholipid bilayers and role in cellular integrity and organelle function.
Structure and classes of sphingolipid (sphingomyelin, gangliosides, cerebrosides)
Different classes of phospholipids (PA, PE, PC, PS, PI, CL) and roles in the cell.
Phospholipid degradation and role of phospholipases A1, A2 and C. .

Implications of lipid structure for membrane bilayer properties (curvature, rigidity)

Diseases associated with sphingolipid abnormalities. *Niemann-Pick, Gauchers* and *Tay-Sach's*.

Infant respiratory distress syndrome.

1.4.1.3 Sterols

Outline molecular structure of steroid hormones.
Outline molecular structure of cholesterol and its derivatives: bile acids and steroid hormones.
Role of statins in regulating cholesterol biosynthesis (see **1.2.4.5**).

Effect of steroid hormones as transcriptional regulators
Cholesterol as a component of plasma lipoproteins.
Role of LDL cholesterol as marker for increased risk of atherosclerosis (see **46.2.2**).

1.4.2 ROLES OF LIPIDS

Signalling: e.g. steroid hormones (see **14.1.3**).
Signalling molecules derived from arachidonic acid: eicosanoids (see **14.9.4**).

1.5 CARBOHYDRATES [BIOCH]

1.5.1 TYPES OF CARBOHYDRATES

Monosaccharides: e.g. glucose, fructose. galactose. Disaccharides: e.g. sucrose, lactose. Polysaccharides.
Glycogen, starch, cellulose.
Molecular structure of carbohydrates and formation of 1,4 and 1,6 glycosidic bonds.
Formation of pyranose and furanose ring structures.
Lectins as specific proteins that bind to carbohydrates.
Reactions of sugar molecules – Blood tests.

Importance of 1,4 and 1,6 glycosidic bonds in carbohydrate function.

Importance of ring shape (chair vs. boat) for carbohydrate function.

1.5.2 ROLES OF CARBOHYDRATE IN THE BODY

1.5.2.1 Structural

Proteoglycans in the extracellular matrix (see **5.2**).
Roles and functions distinct from other macromolecules in providing compression strength to tissues.
Linkages to proteins, N-linked, O-linked glycan structures.
Synthesis of glycosylation structures in the cell.
Lipid linkages to dolichol phosphate.
Examples and functions of proteoglycans including hyaluronic acid, chondroitin, dermatan, keratan sulphate (see **5.2**).

Role of high mannose groups in regulating glycan synthesis in the ER and Golgi apparatus.

1.5.2.2 Energy Sources

Roles of glycogen, starch, cellulose.
(Details of metabolism as outlined in **2.3**).

Inability of mammals to digest cellulose.

1.5.2.3 As Biosynthetic Precursors

Role of carbohydrates in synthesis of amino-acids, fatty acids and nucleotides.

1.5.2.4 In Conjugates

Structure and function of glycoproteins and glycolipids.
Cell surface carbohydrates in blood groups (see **44.1**), including abnormalities in blood groups (Bombay phenotype).

Role of membrane proteins as sites of attachment for blood group carbohydrate antigens.
Carbohydrate recognition in cell adhesion and signalling.

1.6 STRUCTURE AND FUNCTION OF MEMBRANES [P&P]

1.6.1 SOLUTES, MEMBRANES, AND MEMBRANE TRANSPORT

Principles of solubility, osmosis, and diffusion.
Transmembrane passage of gases and water.
Fick's Law of diffusion (see **8.3.4**).

Passage of charged and uncharged solutes through artificial lipid membranes.

Membrane transport: Pores, channels, carriers and pumps for the passage of ions and substrates such as glucose.
Channels: Voltage-gated e.g. for Na, for K, for Ca.
Ligand-gated e.g. by Ach.
Stretch activated.
Carriers: Primary active transport e.g. Na/K-ATPase.
Secondary active transport e.g. Na/Ca exchange, the Na-glucose symporter.
Facilitated diffusion e.g. glucose transporter (GLUT).
Simple kinetic properties of channels and carriers.

Structure of membrane channels, carriers and pumps (see **1.6.5**).

Cellular ion homeostasis (see also **6.3.1**).
Cellular homeostasis (see also **6.3.1**).
Control of intracellular Na, K, Ca.
Control of intracellular pH; normal intracellular pH and the concept of buffers and acid/base transporters.

The pump-leak model of ion homeostasis.

1.6.2 COMPOSITION OF MEMBRANES

Roles of lipids (including cholesterol), proteins and carbohydrates (including glycoproteins and glycolipids).

Comparison of micelles, bilayers and monolayers.
Variation in membrane properties with different types of lipid constituents.
Biosynthesis of phospholipids and glycoproteins: Involvement of CTP and dolichol.
Structural aspects of membrane proteins: α-helical content and amphipathic nature.
Role of glycocalyx in capillary solute exchange.

1.6.3 THE FLUID MOSAIC MODEL OF MEMBRANE STRUCTURE

The fluidity of membranes.
Modes of association of proteins with the lipid phase: Surface proteins, transmembrane proteins, anchored proteins.
Lateral heterogeneity of membranes; lipid rafts; caveolae; multiprotein complexes; signalling domains.

Implications of the model for membrane function and behaviour: e.g. mobility of receptors, recirculation of membrane constituents.
Range of motions for membrane components: rotational and translational; lipid translocation and asymmetry.
Limitations of the fluid mosaic hypothesis and more recent models of membrane dynamics: Restricted lateral diffusion of proteins; part-time protein docking.

1.6.4 FUNCTIONS OF MEMBRANE PROTEINS

1.6.4.1 Transport through Lipid Membranes.

See **1.6.5** and **1.6.1.**

1.6.4.2 Vesicular Transport

Membrane proteins: Promote and regulate vesicle formation.
Determine the destination of vesicles and their contents (see **1.9**).

1.6.5 TRANSPORTERS: STRUCTURE AND FUNCTION

Types of transporters with examples (see **1.6.1)**.
Channels.
Carriers - passive and active (i.e. pumps).
Specificity due to interaction between solute and channel or carrier.
Passive transport in channels: Gated channels undergo conformational change to open or regulate the channel.

Carriers: Undergo cyclical conformational change to transport ligands across the membrane.
Saturation of carriers at high solute concentrations.

Common features: e.g. transmembrane segments and energy-producing domains.
Amphipathic nature of transmembrane segments.
Polar/ionic inner surface of pores.

Flipases, P-glycoprotein.

1.7 SUB-CELLULAR ORGANELLES [BIOCH; OB]

Structure and function of the cell membrane and sub-cellular organelles: Rough and smooth endoplasmic reticulum, ribosomes, Golgi apparatus, mitochondria, lysosomes, endosomes, peroxisomes.
Cytoskeleton: microtubules, intermediate filaments and microfilaments.
Specific intermediate filament proteins in different tissues (see **5.3** & **6.1**).
Metabolic compartmentation (see **2.5**).
Vesicle and protein trafficking (see **1.9**).

1.8 THE NUCLEUS [BIOCH; OB]

Size and structure of nucleus.
Nuclear functions: Gene replication and repair, genetic transcription, ribosome production (see **3**).
The interphase nucleus: Euchromatin and heterochromatin. Histones.
Constitutive and facultative heterochromatin (Barr body).
Concept of condensed chromatin and gene inactivity.

Chromatin structure: the packing of DNA (a long molecule) into a compact structure; solenoids, loops.
Chromatin structure related to functions of DNA.

Nuclear envelope: Defines eukaryotes.
Nuclear pores and two-way communication between nucleus and cytoplasm.
The nucleolus: Site of ribosomal subunit production.

Structure and functions of the nuclear envelope, inner and outer membrane, perinuclear space, nuclear lamina structure of nuclear pores.

1.9 TRAFFICKING [BIOCH; OB]

Vesicle trafficking routes:
From endoplasmic reticulum to the Golgi apparatus, thence to the plasmalemma, or to lysosomes.
Trafficking to the plasmalemma adds material to it or allows secretion into the extracellular space: Constitutive and regulated secretion.

Transport of vesicles: Role of cytoskeleton.

Receptor mediated endocytosis.
Transcytosis.

Ligand–receptor binding. Clustering of receptors.
Coated pits and vesicles: Clathrin.
Low pH in endosomes.

Principle of the targeting of newly synthesized proteins by signal sequences.

Details of protein trafficking in endoplasmic reticulum/Golgi and import of proteins into mitochondria or nucleus.
Role of chaperonins. Autophagy.
Genetic defects of trafficking pathways.

1.10 THE CELL CYCLE : MITOSIS AND CELL DIVISION [OB] [BIOCHEM]

1.10.1 MITOSIS AND CELL DIVISION

Phases of the cycle:
Interphase: G_1, S (nuclear DNA replication), G_2; G_0 non-cycling cells.
Mitosis: M (i.e. nuclear division) appearance of the chromosomes and separation of the chromatids, prophase, metaphase, anaphase, telophase. Cell division.

Demonstration of cell-cycle phases by ^{3}H-thymidine.
Centrosome, centrioles, aster, spindle.
Centromeres and interaction with spindle.
Cyclins.

1.10.2 MEIOSIS

Creation of offspring with new gene combinations by sexual reproduction.
Haploid gametes are formed by two special cell divisions 'meiosis'.
Chromosome abnormalities through faults in meiosis (see **3.3**).
Meiosis I ('reduction division'):
Follows a normal S-phase in primary gametocytes.
Prophase I:
Pairing of homologous chromosomes.
Chromatids 'cross-over' (exchange of maternal and paternal genes).

Role of the synaptonemal complex.
Molecular mechanism of recombination: Concepts of strand invasion, Holliday junction, branch migration.
Reciprocal vs non-reciprocal recombination.

Anaphase I:
Maternal and paternal chromosomes separate at random to form daughter nuclei.
Result: two secondary gametocytes, each with only one chromosome of each pair, and with new combinations of maternal and paternal genes on each chromosome.

Meiosis II:
Follows meiosis I with no intervening S-phase.
Resembles mitosis – chromatids separate to form new nuclei.

One primary gametocyte can thus produce 4 gametes (e.g. spermatozoa).

1.11 NORMAL CONTROL OF CELL GROWTH AND DIFFERENTIATION [OB]

1.11.1 CELL GROWTH AND DIVISION

Growth in development, morphogenesis.

Growth after birth:
Renewing tissues: e.g. skin, gut epithelium - continually dividing stem cells.
Resting tissues: e.g. liver, cells multiply only to repair damage.
Non-dividing tissues: e.g. neurons do not multiply after birth.

Maintenance of normal tissue structure and function:
Cell growth and division, controlled by extracellular growth factors, and balanced by cell loss and cell death.

Apoptosis (programmed cell death).

Characteristics of normal fibroblast growth *in vitro.*

1.11.2 STEM CELLS AND DIFFERENTIATION

Embryonic stem cells; pluripotent and unipotent cells (see **5.1** epithelia, **44.1.3** haematopoietic stem cells).

Induced pluripotent stem cells.

Selective gene expression as the basis for producing cells with different functions.

Principles of the establishment of tissues: Progressive restriction of developmental potential.

Determination of the potency of different types of stem cells.
Mosaic vs regulative decisions in cell type specification.

The stability of cell differentiation.

Regulation of tissue structure and function by hormones and growth factors (affecting gene expression and cell multiplication and turnover).

Role of retinoids in normal and abnormal differentiation (e.g. of epithelia).

1.12 ABNORMALITIES OF GROWTH [OB]

Elementary classification with physiological and pathological examples and their causes.

1.12.1 INCREASED GROWTH

1.12.1.1 Hypertrophy

Increase in a tissue or organ by an increase in cell size.
Characteristics of hypertrophy:
Typical of 'permanent' tissues, e.g. skeletal muscle in exercise.
Cardiac hypertrophy as a pathological example.

Bladder smooth muscle hypertrophy in response to prostatic enlargement.

1.12.1.2 Hyperplasia

Increase in a tissue or organ by combined cell growth & proliferation.
Characteristics of hyperplasia.
Typical of 'renewing' tissues:
e.g. skin (to abrasion), bone marrow (increased erythropoiesis at high altitude).
Also seen in tissues with little obvious renewal ('resting') e.g. endocrine glands.

Range of circumstances leading to thyroid hyperplasia (see also **14.3).**
Regeneration of the liver after liver disease or partial resection.

1.12.1.3 Neoplasia

Definition and characteristics of neoplasia.
Distinction between neoplasia and hyperplasia.
Benign tumours: Growth by expansion.
Malignant tumours: Growth with invasion, metastasis and progression.

(Detailed pathology and genetic basis of cancer are taught and examined in the second year).
Nuclear and mitotic abnormalities especially in malignant tumours.
Abnormal differentiation especially in malignant tumours.

1.12.2 DECREASED GROWTH

1.12.2.1 Developmental

Agenesis:
Complete failure to develop - e.g. renal agenesis in *Potter's syndrome*.
Hypoplasia:
Partial failure to develop - e.g. testes in *Klinefelter's syndrome*; ovaries in *Turner's syndrome.*

1.12.2.2 Progressive

Physiological atrophy (involution) e.g. thymus at puberty.

Pathological:

General: affecting many different tissues or organs - e.g. wasting in starvation, and in malignant disease (“cachexia”).

Tissue-specific: e.g. osteoporosis.

Local atrophy - through various causes:

Disuse — e.g. bone and muscle of an immobilised limb

Ischaemic — e.g. cerebral atrophy

Neuropathic — e.g. muscle wasting after nerve injury or poliomyelitis

Idiopathic — e.g. the neuropathies such as Parkinson's

Atrophy (in neurons and cardiac muscle).

1.13 LIGHT AND FLUORESCENCE MICROSCOPY [OB]

Resolution: can show bacteria and details within nucleated cells such as nuclei, mitochondria, ribosomes and storage 'granules'.

Reveals structures commensurate with one wavelength of light.

Simple appreciation of the steps needed to prepare tissue for light microscopy: fixation, sectioning and staining.

Artefacts of specimen preparation e.g. usually, lipid is dissolved and lost from the specimen during fixation and embedding.

General histological appearance of an 'H & E' stained section: nuclei (and structures rich in nucleic acids) stain purple, most proteins stain pink (in particular the cytoplasm of muscle, red blood cells, epithelial cells).

'Basophilic' structures, such as nucleic acids, bind basic dyes (e.g. purple haematoxylin); 'acidophilic' structures bind pink eosin.

Localisation of specific molecules by immunocytochemistry.

Confocal microscopy.

Localisation of specific nucleic acid sequences by in situ hybridisation.

Green Fluorescent Protein (GFP) and live imaging.

Fluorescence microscopy for imaging labelled antibodies and proteins.

1.14 ELECTRON MICROSCOPY (EM) [OB]

Resolution: Shows structure within organelles, lipid membranes, viruses and macromolecules e.g. DNA and proteins.

Heavy metal salts (uranium, lead) to 'stain' sections for transmission E.M.

Appearance of the main cell organelles as listed in **1.7** in transmission EM.

Scanning EM to study surfaces of cells and organelles.

2. CELLULAR METABOLISM [BIOCH]

2.1 GENERAL PRINCIPLES

The overall strategy and logic of human metabolism:
Partial and complete oxidation, trapping of energy as ATP, coupling of ATP hydrolysis to energy-requiring reactions, CO_2 and water production.

Free energy, entropy.

Structure of ATP and its energy content.

2.1.1 PRINCIPLES OF METABOLIC CONTROL

Short-term controls: Allosteric effects (milliseconds), covalent modification (seconds to minutes).
Long-term controls: Enzyme induction/suppression (hours to days).
Cycles between organs e.g. Cori cycle: Principle that control of metabolism includes (i) delivery i.e., anatomy, functioning circulation and (ii) transmembrane movement i.e. membrane transporters of substrates, as well as enzyme regulation.

2.1.2 OXIDATION–REDUCTION REACTIONS

Oxidation and reduction by NAD^+/NADH, FAD/$FADH_2$, $NADP^+$/NADPH.

Key examples of linked oxidation and reduction: Oxidation of glyceraldehyde-3-phosphate and implications for energy transfer by substrate-level phosphorylation.

2.1.3 ROLE AND CONTROL OF THE TCA CYCLE

Substrates and products of the cycle.

Entry to TCA cycle of carbon skeletons of amino acids. Odd chain length fatty acids.

Significance of a cyclic (as opposed to a linear) pathway.
Connection with other metabolic pathways via substrate (e.g. acetyl CoA) or through intermediates (e.g. α-ketoglutarate).
Use of TCA cycle intermediates for biosynthesis, glucose, fatty acids and some amino acids.

Succinyl CoA as precursor of porphyrins and haem.

Significance of “anaplerotic” reactions to maintain concentrations of TCA cycle intermediates.
Pyruvate carboxylase - reaction and regulation.
Operation related to demand for ATP, not to substrate availability.

Regulation of TCA cycle by calcium: Activation of pyruvate dehydrogenase, isocitrate dehydrogenase and α-ketoglutarate dehydrogenase in response to an increase in intra-mitochondrial calcium concentration.

2.1.4 ATP PRODUCTION AND ITS CONTROL

Near-constancy of intracellular ATP concentration; relative concentrations of ATP, ADP and AMP. Relationship between these compounds. Adenylate kinase.
Signals of ATP utilization: Rising ADP as a signal to mitochondria, rising AMP as a cytoplasmic signal to regulate glycolysis.

2.1.5 PATHWAYS OF MITOCHONDRIAL OXIDATION

2.1.5.1 The electron transport chain

Arrangement of large protein complexes linked by smaller, mobile intermediates.
Organisation of the electron transport chain.
Multiple oxidation/reduction centres allowing sequential oxidation/reduction reactions with increasing redox potential. Examples of oxidation/reduction centres: Haem, iron-sulphur centres, ubiquinone, copper.

2.1.5.2 Re-oxidation of reduced cofactors in the mitochondrion

Re-oxidation of mitochondrial NADH (diffusible in the matrix) and $FADH_2$ (enzyme-bound) in the mitochondrion.
Malate-aspartate shuttle for re-oxidation of cytoplasmic NADH.

2.1.6 MITOCHONDRIAL ATP SYNTHESIS

2.1.6.1 The Chemiosmotic Mechanism

Oxidative phosphorylation: Indirect coupling of energy release from oxidation of energy substrates to the synthesis of ATP.
Flow of electrons down the respiratory chain drives H^+ extrusion from the mitochondrion.
Mitochondrial matrix as a closed environment, with inner membrane impermeable to H^+. Extrusion of H^+ creates a pH and electric potential gradient.
Discharge of proton gradient as regulator of the electron transport chain and hence of substrate oxidation - "respiratory control" coupling.
Uncoupling of substrate oxidation and ATP generation by un-couplers such as 2,4-dinitrophenol.
Flow of H^+ back into the mitochondrion via the F_0F_1 ATP synthase drives ATP production.

Defining Mitchell's chemiosmotic theory
Experimental evidence for the chemiosmotic hypothesis.
Death from dinitrophenols use as a weight loss aid.

2.1.6.2 Uses of the Proton Gradient

ATP synthesis – basic structure and mechanism of the F0F1 ATP synthase. Reversibility of ATP synthase.

ATP/ADP exchange across inner membrane. Examples of other inner membrane transport processes linked to discharge of the proton gradient.

Thermogenesis in brown adipose tissue and its importance in neonates.

2.1.7 BODY ENERGY SUPPLIES

Stores: Relative stores of fat, carbohydrate (as liver and muscle glycogen and as blood glucose), and protein.
Intake (see **2.6**): Relative intake and energy values of fat, carbohydrate and protein.

2.2 FAT AS A METABOLIC FUEL

2.2.1 OVERVIEW

Advantages and disadvantages of fat as a metabolic fuel. Contribution to total energy production. Comparison of glucose and fatty acid energy yields

2.2.2 ASSIMILATION OF DIETARY FAT

Assimilation, emulsification, absorption, packaging as chylomicrons.
Transport in lymphatics to peripheral tissues. Lipoprotein lipase in release of fatty acids from chylomicrons.
Role of insulin in fat distribution and storage.
Uptake of fatty acids and re-synthesis to triglyceride in adipose tissue.
Utilisation of triglyceride by skeletal muscle, heart and renal cortex.
Release and transport of NEFAs. Hormonal regulation of lipolysis.
Plasma NEFA levels under different metabolic conditions.

2.2.3 METABOLIC FUELS AND TISSUES

Use of NEFA and endogenous triglyceride in heart.
Skeletal muscle and use of free NEFAs, glucose and glycogen during different forms of exercise.
NEFA use in renal cortex.

2.2.4 OXIDATION OF FAT

Production of fatty acyl CoA, carnitine “shuttle” and its control.
β-oxidation of fatty acids in the mitochondrial matrix.
Overall pathway - generation of reduced cofactors and acetyl CoA.

Cytoplasmic fatty-acid-binding protein, transport to mitochondrial membrane
Enzymes of fatty acid oxidation: VLCAD, LCAD, MCAD, SCAD.

Oxidation of other fatty acids: Unsaturated fatty acids, very long chain fatty acids, odd-chain-length fatty acids, branched-chain fatty acids.
Defects of fatty acid oxidation - relative frequency, biochemistry and clinical symptoms of MCAD deficiency, carnitine deficiency, *Jamaican vomiting sickness.*

2.2.5 FATTY ACID METABOLISM IN THE LIVER

2.2.5.1 Oxidation

See **2.2.4**

2.2.5.2 Biosynthesis

Production of triglyceride from excess sugars and amino acids.
Key differences between fatty acid biosynthesis and β-oxidation: enzymes, cofactors, subcellular compartments.
Balance between oxidation and synthesis, regulated by substrates availability. Role of malonyl CoA.

Outline of structure and function of fatty acid synthase complex.

2.2.5.3 Ketogenesis and ketolysis

Role in fasting and starvation.
Role in fasting and starvation.
Production in the liver from fatty acid, as an alternative fate for acetyl CoA
Use of ketone bodies in peripheral tissues.
Pathways for ketogenesis and ketolysis
Ketone bodies as a glucose-sparing fuel.

Structures of common NEFA-derived ketones and steps in their synthesis.

2.2.6 INTEGRATION OF FATTY ACID METABOLISM

Effects of insulin, glucagon, adrenaline and thyroxine on synthesis, breakdown, uptake and release of fatty acids.

2.3 GLUCOSE AS A METABOLIC FUEL

2.3.1 OVERVIEW

Storage and availability of glucose. Relative use of glucose by different tissues: brain, skeletal muscle, red blood cells, renal medulla.

2.3.2 GLYCOLYSIS

2.3.2.1 Significance

Overall scheme and importance in generating ATP in different tissues under anaerobic conditions. Production of lactate.

2.3.2.2 Glucose uptake (transport and phosphorylation)

Glucose uptake requires transport and phosphorylation. GLUT1-4-mediated facilitated transport and SGLT-mediated secondary active transport.
Tissue differences:
Uptake dependent on plasma glucose concentration
- in liver (appropriate for glycogen or fat synthesis)
- in endocrine pancreas (to control hormone release)
insulin-independent glucose transport by GLUT2.
Uptake elsewhere (in 'peripheral' tissues) depends on energy needs of tissue and is regulated in tissues that can also use non-carbohydrate energy substrates: Importance of the insulin-dependent glucose transporter (GLUT4).
Phosphorylation: Hexokinase in peripheral tissues, glucokinase in liver, pancreatic β-cells. Physiological significance of differences in their properties (K_m values and inhibition).

2.3.2.3 Trapping energy: formation of ATP in glycolysis

Substrate-level phosphorylation: quantity of ATP per molecule of glucose

Principal points of ATP formation.

2.3.2.4 Control of glycolysis

Glycolysis is regulated by the energy needs of the cell:
Specific importance in type IIb skeletal muscle fibre.
Phosphofructokinase as principal control point of glycolysis: ATP inhibition and role of fructose-2,6-bisphosphate.
Feed forward activation of pyruvate kinase in muscle.

Isozymes of glycolytic enzymes.

Variation of isozyme expression in different tissues; correlation with different metabolic function of different tissues.

2.3.2.5 Utilization of other monosaccharides

Galactose and fructose: importance as fuel, entry into pathways of glucose metabolism.

Galactosaemia - typical pattern of presentation; metabolic problems.
Hereditary fructose intolerance - presentation; metabolic problems.

2.3.3 AEROBIC OXIDATION OF GLUCOSE AND PENTOSE PHOSPHATE PATHWAY

Pyruvate dehydrogenase as key regulatory enzyme.

Control of activity in relation to metabolic state of mitochondrion.

Importance of aerobic glucose oxidation in the brain.

Pentose phosphate pathway:
Significance as a generator of NADPH and for the synthesis of various carbohydrates, including pentoses for nucleic acids.
Role in antioxidant pathways.

Reaction sequence of the pentose phosphate pathway.
Glucose-6-P dehydrogenase deficiency - significance and metabolic consequences; prevalence (common); mechanism of damage to rbc; development of acute haemolytic anaemia.

2.3.4 STORAGE OF GLUCOSE

Glycogen synthesis in liver and muscle.

Cost of synthesis.

Mobilization: phosphorylase and debranching enzyme.

Glycogen storage disorders – metabolic consequences of *Type 1 Von Gierkes disease, Type iii Cori's disease and Type v Mcardles disease*

The "glucose–fatty-acid cycle".

Control of glycogen synthesis and breakdown in muscle and in liver; roles of adrenaline, glucagon and insulin.

Hormone receptors on hepatocytes. Role of autonomic nervous system in hepatic metabolism. Calmodulin as subunit of phosphorylase kinase.

2.3.5 GLUCONEOGENESIS

Quantitative importance and sites of synthesis.

Why we can't make glucose from fatty acids.

Common substrates: lactate, alanine, glutamine, glycerol and other sugars

Comparison between glucogenesis and glycolysis.

Allosteric and hormonal control of glucogenesis.

2.4 AMINO ACID METABOLISM

2.4.1 PROTEIN DIGESTION (see also **9.5.4** and **9.5.5**)

Dietary intake; digestion by pepsin, trypsin, chymotrypsin. Uptake of di- and tripeptides by intestinal cells; conversion to amino acids.

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2.4.1.1 Amino acids

Essential and non-essential amino acids.
Positive and negative nitrogen balance.
Incorporation into body proteins or derivatives (e.g., hormones, neurotransmitters), oxidation, conversion to glucose or fatty acids.
Categories of amino acid based on possible metabolic fate: Glucogenic via pyruvate, glucogenic via TCA cycle intermediates, ketogenic via acetyl CoA, mixed.

Arginine as an essential amino acid produced by endogenous synthesis.

2.4.1.2 Amino Acid Metabolism

2.4.1.2.1 Oxidation

Transamination; role of α-ketoglutarate and glutamate.
Significance of glutamate dehydrogenase. Fate of ammonia generated.
Transport of ammonia from peripheral tissues. Metabolism of glutamine in intestinal cells and renal cortex.
Nitrogen excretion as urea or as ammonium ions; implications for pH regulation.

Pyridoxal phosphate in transamination.

2.4.1.2.2 Urea synthesis

Principal steps in formation of urea from ammonia.
Localisation in periportal cells of liver lobule and intra-cellular compartmentation.
Control of the urea cycle:
acute: regulation of enzyme activity; carbamyl-phosphate synthetase as the controlling step.
chronic: induction of urea-cycle enzymes with high protein diet.

2.4.1.2.3 Tissue-specific amino acid metabolism

Branched chain amino acid metabolism in muscle.

Amino acid metabolism in specific tissues: Liver, intestine, skeletal muscle, renal cortex.
The glucose–alanine cycle.

2.5 CELLULAR ORGANIZATION OF METABOLISM

2.5.1 OVERVIEW

The major pathways of metabolism in relation to sub-cellular architecture.

2.5.2 MITOCHONDRIA

Role in energy generation; in generation of NADH and metabolic intermediates; final common pathway of chemical energy production, electron transport chain and oxidative phosphorylation.

Separate mitochondrial genome encodes some components of the electron transport chain complexes.
Mitochondria as “symbionts”.
Mitochondrial biosynthesis. Density of mitochondria in cells (eg high in cardiomyocytes).
Clinical manifestations of mitochondrial disease. Maternal inheritance of mitochondrial DNA. Mitochondrial DNA mutations and their expression (see **3.4**).

2.5.3 ENDOPLASMIC RETICULUM/GOLGI APPARATUS

Outline of role in biosynthesis of lipids, complex carbohydrates and glycoproteins.
Role in detoxification: Significance of cytochrome $P_{450.}$

2.5.4 LYSOSOMES

Outline of role in recycling of building blocks of macromolecules (especially extracellular matrix components) (see **1.9)**.

Range and importance of lysosomal diseases.

2.5.5 PEROXISOMES

Outline of role in substrate processing.

Role in biosynthesis: plasmalogens, bile acids.
Significance of peroxisomes as revealed by peroxisomal diseases.

2.5.6 PROTECTION OF CELLS AGAINST REACTIVE OXYGEN SPECIES

Mechanism of generation of O_2^- and H_2O_2
Existence of specific 'antioxidant' enzymes that remove these toxic species.

Glutathione, vitamins C and E.
Superoxide dismutases, catalase, glutathione peroxidase (need for selenium).
Glutathione reductase, need for NADPH.

2.6 BIOCHEMICAL PRINCIPLES OF NUTRITION

2.6.1 MACRONUTRIENTS

Biochemical basis of nutritional guidelines: Contribution of carbohydrate, protein, fat to dietary intake; the nutritional role of different fatty acids; types of dietary carbohydrate and their effects on metabolism.

Epidemiology of coronary heart disease in relation to nutritional patterns.

Principles of clinical nutrition: energy and nutrient requirements in illness vs. health; means of supplying energy and nutrients in the sick; metabolic effects of parenteral delivery of nutrients. Amino acid supply in the critically ill.

2.6.2 MICRONUTRIENTS

2.6.2.1 Minerals dietary intake, distribution, biological roles.

Zinc. Copper. Iron.

Consequences of zinc deficiency.
Wilson's and Menkes' diseases.

2.6.2.2 Vitamins

Biochemical roles of niacin, riboflavin, pyridoxine and thiamine. Consequences of deficiencies. Folic acid and Vitamin B12. Folic acid and neural tube defects (see **15.3**).

Anti-folate drugs as antibiotics and anti-cancer agents.

2.7 CLINICAL BIOCHEMICAL MEASUREMENT

Measurement of gases, ions, pH, metabolic substrates, hormones and enzymes: Principles and clinical importance.

Uses of enzyme measurement in clinical practice: Assessment of tissue damage. Cardiac enzymes and liver enzymes as examples in the assessment of tissue damage (see **2.3.2.4**).
Recognition of enzyme deficiencies.

Use of enzymes to measure biologically important molecules.

Glucose assays.

3. MOLECULAR AND MEDICAL GENETICS [BIOCH]

3.1 PRINCIPLES OF MOLECULAR GENETICS

3.1.1 DEFINITION OF A GENE

Genes as inherited units of information specifying phenotype at a gross level e.g., morphological characteristics or at a molecular level e.g. particular products – proteins, RNAs.
Mutation: Types of mutation and their consequences. Harmless variants vs disease-causing mutations (see **3.7**).

Identifying amino-acids changed by mutation.

3.1.2 GENES: STRUCTURE AND FUNCTION

Molecular structure of DNA.
Nucleic acid bases, nucleosides and nucleotides.
5'-3' polarity of DNA strands; base pairing rules.
Anti-parallel nature of the DNA double helix.
Semi-conservative DNA replication.
Properties and requirements of DNA polymerases, including proof-reading function.
Enzymes needed for replication.
Role of tRNAs and aminoacyl-tRNA synthase.

Transfer of genetic information to cells in vitro shows that genes can be extracted from cells, making chemical identification possible.
Confirmation that genetic information is carried by DNA and RNA but not by proteins.
Physical evidence for DNA structure. Simple treatment of X-ray diffraction.

Evidence for the nature of genetic code.
Identification of individual codons, stop and start signals.

3.1.3 REGULATION OF GENE EXPRESSION

Control of gene expression at the level of transcription.
Comparison of control mechanisms in bacteria and eukaryotic cells.
Eukaryotic and prokaryotic promoter structures.
General features of eukaryotic transcription factors.
Properties of RNA polymerases.

Epigenetic modifications, chromatin organisation and gene activity (see **1.8**).
DNA methylation, Histone tail modifications.

Essential features of bacterial operons and key genetic experiments which demonstrate them.

3.1.4 TRANSCRIPTION, RNA PROCESSING AND TRANSLATION

Features of the three eukaryotic RNA polymerases and their main products: mRNAs, rRNAs, tRNAs, snRNAs, miRNAs.
RNA bases; relationship between a DNA coding strand and its transcript
Outline of production and processing of mammalian mRNA: Transcription, capping and polyadenylation.
Roles of 5'cap and poly(A) tail.
Introns, exons and outline of the mechanism of splicing.
The importance of alternative pre-mRNA processing.

Assembly of the initiation complex. Recruitment of RNA polymerase.
Termination and release of the transcript.
Discovery of introns.
Ribozymes.
Details of translation at the ribosome; initiation, elongation and termination of protein synthesis.
Translation regulation.
Degradation of the transcripts.

Alternative polyadenylation, alternative splicing
Pre-mRNA processing and disease.
Outline of ribosome structure and translation initiation.
Surveillance mechanisms. Nonsense-mediated decay.
Intracellular sites of protein synthesis and the signal hypothesis (see **1.9**).

3.1.5 ORGANIZATION OF THE GENOME

Nuclear and Mitochondrial genomes.
Coding and non-coding genes.
Functions of non-coding RNAs in controlling gene expression.
Single copy sequences.
Multiple-copy genes (e.g. for histones and the genes for ribosomal RNA).
Highly repeated non-coding sequences.
The Human genome.
Information content of different genomes:
Comparison between simple, non-redundant genomes of bacteria and viruses and the complex genomes of eukaryotes.
Coding/non-coding ratio in the mammalian genome.

3.1.6 CHARACTERISATION OF GENES AND GENE PRODUCTS AT THE MOLECULAR LEVEL

Meaning of 'cloning a DNA sequence'.
Principles of DNA cloning: Use of restriction enzymes & simple cloning vectors; polymerase chain reaction.
Separation of DNA fragments according to size by electrophoresis.
Techniques based on nucleic acid hybridisation: Southern blotting, Northern blotting, Fluorescent in situ hybridisation (FISH).
Assessment of the potential pathogenicity of an identified sequence change.
Use of CRISPR/Cas9 technology to generate or correct sequence changes.
Enzyme based techniques: PCR, RT-PCR, DNA sequencing.
Use of antibodies in protein detection – Western blotting, Elisa, Imaging, Immunoprecipitation.
Principle of DNA sequencing (Sanger).
High throughput sequencing methods use different techniques to Sanger.
Concept of sequencing depth in exome/whole genome sequencing.
Examples of uses for cloned genes and probes in fundamental research, and for diagnostic and therapeutic applications.

3.2 GENERAL CONCEPTS OF MEDICAL GENETICS

Impact of genetic disease on public health.
Relationship of genes and environment.
Mendelian fundamentals: Character, gene (locus), allele, genotype, phenotype, dominant and recessive traits.

3.3 CHROMOSOMES

Chromosome structure and the normal chromosome complement.
Sex determination and abnormalities of the sex chromosomes.
Analysis of chromosome complement – array CGH as the standard tool.
Chromosomal abnormalities, with examples of their occurrence and effects
Recognition of the clinical features and karyotypes for the following conditions: Down Syndrome, Patau Syndrome, Edwards Syndrome, Turner Syndrome, Klinefelter Syndrome
Numerical: Aneuploidy, monosomy, trisomy.
Structural: Balanced and unbalanced translocations, Robertsonian translocations, duplications, deletions, inversions.

3.4 GENETICS OF DISEASE

Single gene disorders: With examples of their occurrence and effects.
Knowledge of Clinical Genetics Syndrome List (supplied with lecture handouts)
Autosomal dominant: Segregation, expression in heterozygotes, penetrance, expressivity, risk to offspring.
Autosomal recessive — transmission, expression in homozygotes, carrier status, risk to siblings. Consanguinity.
Basis of rare occurrence of X-linked disease in females.
Mitochondrial disorders: heteroplasmy.
X-linked — transmission, hemizygous males, carrier females.
Mitochondrial inheritance.
Polygenic disease: Concordance in twin studies, relative risk, susceptibility genes.
Prenatal diagnosis and Pre-implantation Genetic Diagnosis – techniques and ethical considerations.

3.5 GENES IN POPULATIONS

Hardy-Weinberg equilibrium.
Assortative mating, genetic drift, selection and mutation.
Polymorphism and heterozygote advantage.
Ethnic differences in disease frequencies.

3.6 IDENTIFYING GENES FOR SINGLE GENE DEFECTS AND GENETIC CHANGES ASSOCIATED WITH MULTIFACTORIAL DISEASES

Identification of candidate genes responsible for single gene defects.
Exome and whole genome sequencing approaches to gene identification.
Concept of genetic linkage and the principle of its use in genetic mapping.
Use of genome browsers.
Understanding of current NHS developments in Whole Genome sequencing.

Identifying genetic factors conferring susceptibility to common multifactorial conditions Heritability. Affected sib-pairs.
Population-wide statistical association.
Genome-wide association studies (GWAS).
Relative risk assessment.

Polygenic Risk scores.

3.7 MUTATION AND HUMAN DISEASE

Effects of single-base changes, deletions and unstable repeat units (anticipation); with examples of some resultant genetic diseases.

Molecular basis of mutant phenotypes with examples.

3.8 CANCER GENETICS

'Double hit' hypothesis (Knudson).
Assessment of a family history of cancer to estimate the likelihood of a genetic predisposition.

Genes predisposing to cancer development:
Hereditary breast and ovarian cancer (BRCA1/2 mutations).
Familial adenomatous polyposis (APC mutations).
Lynch syndrome (MLH1, MSH2, MSH6 mutations).

Li-Fraumeni syndrome (P53 mutations).
Multiple Endocrine neoplasia.

Genetic testing: Diagnostic versus predictive testing.

Cancer surveillance. Risk reducing surgery.

Consent issues (ethical considerations).
Chromosomal abnormalities in cancer.
Genetic stratification approach in cancer medicine.
Ethical considerations.

4. PRINCIPLES OF DRUG (& HORMONE) ACTION [P&P; BIOCH]

4.1 TYPES OF PHARMACOLOGICALLY ACTIVE AGENTS [P&P; BIOCH]

Acting via receptors:
- Endogenous agents: e.g. hormones (see **14**); neurotransmitters (see **6.4**); growth factors; vaso-active factors (such as endothelin).
- Exogenous agents, 'drugs', that modify the effect of endogenous agents: Agonists or antagonists acting at the receptor for the endogenous agent; drugs that act indirectly (e.g. by physiological antagonism, by effects on release, metabolism, or reuptake of endogenous agent).

Enzymes and enzyme inhibitors.

Drugs acting on membrane transporters or ion channels e.g. calcium channel blockers, potassium channel blockers.

(Other endogenous factors e.g. those regulating inflammation and immunity will be studied in the second year).

4.2 RESPONSE [P&P; BIOCH]

4.2.1 LIGAND-RECEPTOR INTERACTIONS [P&P; BIOCH]

Proteins as receptors.

Three types of cell surface receptor: ion-channel-linked, G-protein-linked, enzyme-linked receptors.

Ligand-receptor interactions.

Efficacy: Affinity; types of agonist and antagonist.

Types of enzyme-linked receptors (e.g. tyrosine kinases, guanylate cyclases).

Kinetics of ligand-receptor interactions.

Schild Plot. Inverse agonists.

4.2.3 RECEPTOR–EFFECTOR COUPLING [P&P; BIOCH]

Concept of second messengers: Principle of amplification; G-proteins.

Control of adenylate cyclase by G-proteins, including inhibition of adenylate cyclase e.g. by muscarinic receptor activation.

Cyclic 3',5'-AMP (cAMP).
- Produced in response to e.g. β-adrenoceptor stimulation
- Action: cAMP-dependent protein kinase (Protein Kinase-A; PK-A) regulates specific enzymes.
- Degradation: Phosphodiesterase (inhibited by methylxanthines)

Intracellular calcium:
- Raised by release of Ca^{2+} from intracellular stores (e.g. α_1- adrenoceptor stimulation) or by opening of Ca^{2+}-channels in cell membrane.
- Coupling of receptor stimulation to production of inositol trisphosphate (IP3) and diacylglycerol (DAG); IP3 releases intracellular calcium, DAG activates protein kinase-C; Role of calmodulin; Action: Activates specific enzymes. Lowered by reuptake to stores or extrusion from the cell.

Other cyclic nucleotides as second messengers: cGMP for atrial natriuretic peptide (ANP).

Gap junctions: Connexin subunits, for passage of ions and small molecules (second messengers) between adjacent cells e.g. linking epithelial, cardiac and some smooth muscle cells.
Desensitization (tachyphylaxis).

4.3 PRINCIPLES OF DRUG ADMINISTRATION, AVAILABILITY AND ELIMINATION (PHARMACOKINETICS); DRUG DISCOVERY [P&P]

4.3.1 ROUTES OF DRUG ADMINISTRATION

Main routes of administration:
oral, sublingual, rectal, topical (skin, eye, by sniffing), inhalation, and injection (intravenous, subcutaneous, intramuscular, intraspinal).
Factors governing choice of route:
rate of absorption of drug from site of administration & transport to site of action
desire to administer drug close to its desired site of action (see **6.3.3*)***
susceptibility of drug to degradation by digestion or metabolism
desired time-course of action (see also **4.3.3**)

Concept of bioavailability.

'Enteric coated' preparations.
Drug discovery.

4.3.2 DISTRIBUTION OF DRUGS IN THE BODY: FACTORS AFFECTING THE CONCENTRATION OF A DRUG AT ITS SITE OF ACTION

Concept of the Volume of Distribution of a drug.
Lipid solubility:
Needed for simple diffusion across epithelia; effect of pH differences across epithelia on the distribution of ionisable drugs (e.g. absorption of weak acids from the stomach; renal effect (see **4.3.3**); Henderson-Hasselbalch equation; partition into body fat.

Drug transfer across the blood-brain barrier, and the placenta.

Binding of drugs to plasma proteins:
Reduces free drug able to diffuse into tissue fluid; reduces renal clearance of drugs.

Drug interactions through competitive displacement from plasma proteins.

Binding of tetracyclines to calcium (effect on absorption from gut, discolouration of teeth).

Carrier-mediated transport:
Uptake of some drugs from the gut, and excretion into bile and urine.

4.3.3 DRUG METABOLISM AND EXCRETION

Concepts of the Clearance of a drug (see also **11.3.2**) and of the Half-Life of a drug in the plasma.
Principles of drug metabolism.
Chemical modification usually abolishes activity:
Hydrolysis e.g. acetylcholinesterase (see **6.4.4.1**).
Oxidative deamination e.g. Monoamine oxidase (MAO) (see **6.4.4.2**);
Introduction of functional groups by mixed-function oxidases (cytochrome P_{450} system) - inducible in liver.

Metabolism may activate some agents - concept of 'pro-drugs'.
Drug interactions through induction of hepatic cyt. P_{450} system.

Drug metabolites may be toxic e.g. severe hepatotoxicity in paracetamol overdose
Conjugation: Addition of polar groups hastens excretion.
Pharmacogenetic considerations.

Renal excretion of drugs.
Glomerular filtration: Most drugs are freely filtered (unless bound to serum proteins); filtered drugs may be passively reabsorbed or trapped in urine according to their lipid solubility and tendency to ionise.
Tubular secretion and reabsorption (e.g. secretion of penicillin).

Factors governing the half-life of a drug (distribution and clearance).
Time profiles of drug concentrations after a single oral dose (absorbed rapidly or slowly), a repeated oral dosage regimen, and continuous intravenous infusion.

Adjustment of urinary pH to regulate the renal elimination of some drugs.
Secretion of conjugated drugs into bile, deconjugation in gut, reabsorption; enterohepatic recirculation.

Effect of physical form of drug on its absorption and distribution (particle size, crystalline form, e.g. long-acting insulin formulations).
Depot formulations e.g. oily suspensions of antipsychotic drugs.

5. TISSUE TYPES: STRUCTURE & FUNCTION [OB]

5.1 EPITHELIAL TISSUES

Classification by cell shape and organization:
Simple (squamous; cuboidal; columnar; pseudostratified).
Stratified.
Urothelium (transitional) (see **11.2**).
Classification by function: Secretory, absorptive, mechanical.
Stem cells and differentiated cells (see **1.11**).
Basement membranes: Structure and function in epithelial anchorage, polarity and differentiation.
Functions of intercellular junctions:
Desmosomes: Mechanically linking intermediate filaments of adjacent cells.
Adherens junctions: Linking actin microfilaments.
Gap junctions: Allowing intercellular communication by ions and small molecules (see **4.2.3**).
Junctional complexes: Determining trans-epithelial transport. Leaky and tight epithelia (see **11.3.3**).
Polarity. Apical and basolateral surfaces.
Functions: Trans-epithelial transport; synthesis and secretion; protection; generation of movement over the apical surface (ciliated epithelia).
Disorders of junctional complexes: pemphigus.

EM appearance of intercellular junctions.

Epithelial morphogenesis in the embryo (e.g. neurulation - see **15.3**) and later (e.g. mammary gland).

5.2 CONNECTIVE AND SKELETAL TISSUES

Types of macromolecules making up the extracellular matrix (ECM), a simple appreciation of their nature and properties:
e.g. collagen (see also **1.2.3.1**), elastin, proteoglycans.
Cell types and their functions in soft connective tissues:
Fibroblasts - synthesis of ECM.
Macrophages – phagocytosis and degradation of ECM. (see **44.1.2.2**).
Mast cells, lymphocytes (see **44.1.2.3**).
Adipocytes - triglyceride storage.
Structure, mechanical properties and functions of tendons, ligaments, aponeuroses, fascia, cartilage and bone.
Adipose tissue: Storage and thermal insulation.
Cartilage: Chondrocytes as sole cell type (chondroblasts as stem cells) secretion and degradation of ECM.
Classification of cartilage: Hyaline, elastic, fibrocartilage; mechanical properties and examples.
Collagen disorders: osteogenesis imperfecta; Marfan's syndrome; Ehlers-Danlos syndrome.

Types of collagen and their distribution.

ECM of hyaline cartilage: Proteoglycans and type II collagen (plus elastin in elastic cartilage; or type-I collagen in fibrocartilage).

Bone: ECM - collagen, hydroxyapatite, proteoglycans.
Cells: Osteoblasts, osteocytes (bone formation), osteoclasts (bone removal).
Adaptations for strength and lightness: Compact and trabecular (cancellous, spongy) bone.
Lamellar structure of mature bone; Haversian system, blood supply.
Marrow cavities (fat storage and haematopoiesis).
Bone as a highly vascular living tissue, constantly being remodelled
Growth of long bones: Remodelling; epiphyseal and appositional growth (accretion).
Bone as a store of calcium and phosphate.
Joints: Structure & function of fibrous; cartilaginous; synovial joints (see **7.2**).
Osteoporosis

ECM of bone: osteoid, type I collagen.

Repair of fractures; early development; 'woven' bone.

Overview of endocrine effects on bone: STH, PTH, vitamin D metabolites, calcitonin, estrogens, androgens.
(detailed endocrine regulation of calcium & phosphate in second year).

5.3 SKIN

Functions: Protective (water, infection, UV); Sensory; Thermoregulation.
Epidermis: Cell types and functions (keratinocytes, melanocytes, Langerhan's, Merkel cells); epidermal layers; nails and hair.
Keratin sub-types, keratinocyte maturation.
Dermis: Composition, sweat glands, sebaceous glands. Blood supply of skin; nerve endings (see **6.1**).
*Psoriasis; Disorders of junctional complexes (see **5.1**); Basal cell cancer; Melanoma; albinism.*
Keratin disorders e.g. epidermolysis bullosa simplex.

6. EXCITABLE CELLS: NEURAL COMMUNICATION

6.1 TISSUES OF THE PERIPHERAL NERVOUS SYSTEM [OB]

Structure of “typical” neuron: Cell body, dendrites, axon and terminal arbors.
Structural and functional polarity.
Cytoskeleton: Microfilaments; Neurofilaments; Microtubule transport system. Kinesins and dynein molecular motors.
Myelin sheaths, nodes of Ranvier; Schwann cells unmyelinated axons.
Structure of a peripheral nerve: Fascicular arrangement of axons.
Epineurium, perineurium, endoneurium.
Ganglia: Dorsal root, sympathetic, parasympathetic and enteric ganglia. Ganglion structure
Structure and distribution of nerve endings: Sensory terminals, motor end-plate, sympathetic varicosities.
Types of sensory nerve endings in skin and specific adaptations relating to function: Hairs, Meissner corpuscle (touch), Ruffini endings (stretch), Merkel discs (touch), Pacinian corpuscle (vibration), free nerve endings (thermal and nociceptive).

6.2 DIVISIONS OF THE PERIPHERAL NERVOUS SYSTEM [OB]

Principles of the peripheral organization of the somatic motor and sensory nervous systems, and of the autonomic nervous system.

6.2.1 SOMATIC NERVOUS SYSTEM

Segmental organization of somatic nervous system (see **6.2.1**).
Somatic motor fibres (efferent): Cell bodies in spinal cord, terminate directly on muscle fibres at motor end plates.
Weakness, paralysis from loss of motor fibres.
Somatic sensory fibres (afferent): Sensory endings in tissues, cell bodies in dorsal root ganglia, synapse to other neurons inside central nervous system, convey information from receptors e.g. in skin (touch, pain, temperature), in joints (position sense, pain), in muscle and tendons (reflex control of movement).
Pain from irritation of sensory fibres, loss of sensation from damage to sensory fibres. Local anaesthetics (see **6.3.3**).
Visceral afferents: Cell bodies in dorsal root ganglia, often run with autonomic nerves (see **6.2.3**).
Motor and sensory fibres typically run in the same peripheral nerves – "mixed nerves".
Fibres of the somatic nervous system are mostly myelinated with fast to medium velocity (see **6.3.2**); slow 'C-type' pain fibres unmyelinated.

Effects of nerve compression and damage*: neuropraxia; axonotmesis; neurotmesis.*
Wallerian degeneration.
Degenerative disorders: Axonal death as a cause of disease. *Motor Neuron Disease. Amyotrophic Lateral Sclerosis, Charcot-Marie Tooth Disease, Spinal Muscular Atrophy.*
Vincristine neuropathy as an effect of degeneration of cytoskeleton.
Diseases of myelination (autoimmune and genetic). *Multiple sclerosis.*

6.2.2 AUTONOMIC NERVOUS SYSTEM (ANS)

Efferent system for involuntary control of body functions. Two major efferent divisions: Sympathetic and parasympathetic.

Cell bodies in CNS send pre-ganglionic fibres (mostly myelinated, slow to medium velocity) to synapse on ganglion cells outside CNS. Pre-ganglionic transmitter Ach.

Parasympathetic outflow: Cranial (oculomotor, facial, glossopharyngeal vagus) and sacral.

Vagus (X) nerve to thoracic & most abdominal viscera.

Sacral nerves to lower gut & urogenital tract.

Sympathetic outflow: Thoracic and lumbar (T1-L2) to all viscera.

Ganglion cells send post-ganglionic fibres (non-myelinated slow) to cardiac and smooth muscle and glands.

Parasympathetic ganglion cells typically within end-organ, release Ach.

Sympathetic ganglion cells typically in discrete ganglia with long post-ganglionic fibres paravertebral chain.

Midline ganglia, coeliac, superior, and inferior mesenteric ganglia; most release noradrenaline.

*Horner's syndrome (**8.5.5**)*

Adrenal medullary cells are modified sympathetic ganglion cells that secrete adrenaline into the blood.

Peptides in ANS (see **6.4.4.3**).

Visceral afferents (from stretch and chemoreceptors) often run with autonomic nerves: May elicit involuntary autonomic reflex (e.g. baroreceptor reflex) or may give sensation and mixed autonomic and voluntary somatic effects (e.g. micturition).

Referred pain from viscera.

Enteric nervous system: Sensory, motor and secretomotor neurons in plexuses in the gut wall, Coordinates activity of gut; Modulated by pre-ganglionic parasympathetic fibres and post-ganglionic sympathetic fibres.

See also specific sections on e.g. autonomic transmission, and nervous control of thoracic and abdominal viscera.

Drugs and the autonomic nervous system (see **6.4.3**).

Effects of lesions of ANS.

Non-adrenergic, non-cholinergic autonomic neurons – role in penile erection.

6.3 NERVE CONDUCTION [P&P]

6.3.1 MEMBRANE POTENTIAL

General ion distribution across membranes.
Role of Na/K pump in generating Na^+ and K^+ distribution.
Role of differential membrane permeability to K^+ and Na^+ in generating the membrane potential.
Concept of ion equilibrium potential (Nernst equation).
Effects of varying external K^+, Na^+, or Cl^- on membrane potential.

Double-Donnan distribution (osmotic-equilibrium).
Constant field equation (Goldman equation), conductance equation.

6.3.2 ACTION POTENTIAL

Ionic mechanism of the action potential.
Conduction of action potential.
Factors influencing conduction velocity, (e.g. fibre diameter, myelination, temperature).
Role of myelination in saltatory conduction.
Range of nerve fibre sizes (non-myelinated and myelinated) and their conduction velocities: Compound action potential in a peripheral nerve.
Effects of ion-channel blockers e.g. tetrodotoxin (TTX) and tetraethylammonium ions (TEA).
Passive electrical constants of membranes (length constant, time constant).

Experimental evidence for the Hodgkin-Huxley model. Explanation of voltage-clamp, patch-clamp and gating currents. State-diagrams for Na^+ and K^+ channels.
Electrical circuit model of membrane potential.

6.3.3 LOCAL ANAESTHETICS

Examples of local anaesthetics e.g. lidocaine, mechanisms of action.
Duration of action: Dependence on lipid solubility, use of vasoconstrictors.
Sequence of blockade: Pain first, then general sensory, motor last.

Cocaine.
Local, regional, spinal, epidural anaesthesia.
Risks of accidental systemic administration.

6.4 SYNAPTIC TRANSMISSION [P&P]

6.4.1 NEUROMUSCULAR TRANSMISSION

Morphology and function of neuromuscular junction (NMJ).
Synthesis, storage, release and action of Ach. Hydrolysis of Ach.
Mechanisms of action of neuromuscular blocking drugs: Competitive non-depolarising (tubocurarine, atracurium), depolarising (suxamethonium), vesicular release (botulinum toxin).
Methods of reversing neuromuscular block.
Examples and effects of anti-cholinesterases. (neostigmine)
Therapeutic use of anticholinesterases in *myasthenia gravis.*

Structure of ACh-activated cation channels; two ACh receptor sites per channel. High signal-to-noise ratio of synapse. Choline recycling.
Pseudocholinesterase deficiency.

6.4.2 AUTONOMIC SYNAPSES

Synapses on cardiac and smooth muscle (en passant junctions, varicosities): Structure and function in comparison with NMJ.

6.4.3 AUTONOMIC TRANSMISSION

6.4.3.1 Cholinergic

Nicotinic and muscarinic receptors: Distribution, function and sub-types

Local and systemic actions of agonists (nicotine, muscarine) and of antagonists (atropine).

Therapeutic use of antimuscarinics in e.g. asthma, urinary incontinence.

Acetylcholinesterase.

Existence of receptor subtypes M_1, M_2, M_3: ganglionic vs. neuromuscular nicotinic receptors.

Hexamethonium vs. decamethonium as evidence for structural differences between N_1 and N_2 subtypes.

Autonomic effects of anti-cholinesterases.

6.4.3.2 Catecholaminergic

Synthesis, storage and release of catecholamines (dopamine, noradrenaline, adrenaline).

Actions of experimental toxins to interfere with synthesis.

Effect of reserpine.

DA as a transmitter in brain, gut and kidneys.

Use of L-DOPA second year LHS.

Adrenoceptors: $\alpha 1$, $\alpha 2$, $\beta 1$, $\beta 2$; distribution and function.

Relative potency of noradrenaline, adrenaline, and isoprenaline on $\alpha 1$, $\beta 1$, $\beta 2$.

Local and systemic effects of agonists and antagonists.

Therapeutic use of selective agonists and antagonists e.g. salbutamol

$\beta 2$-agonists in asthma.

$\beta 1$-blockers (e.g. atenolol) in cardiovascular disease.

Reuptake of transmitter and subsequent degradation: MAO, Catechol-O-methyl transferase (COMT).

Inhibitors of reuptake (amphetamines) and of degradation (MAO inhibitors).

Therapeutic applications of selective antagonists: in asthmatics.

Role of β3 receptors on adipocytes.

6.4.3.3 Purinergic, gaseous, and neuropeptide signalling

Other transmitters and neurotransmitters e.g. nitric oxide (NO), ATP and neuropeptides e.g. Neuropeptide Y (NPY) and Vasoactive intestinal peptide (VIP).

Concept of co-transmission.

Putative functions of co-transmitters.

6.5 MUSCLE AND INNERVATION [OB; P&P]

6.5.1 STRUCTURE AND FUNCTION: [OB; P&P]

Relationship between ultrastructure and function in all three muscle types: Comparisons between types; limitations on regeneration and repair following damage.

Muscle proteins: Actin, Myosin, Troponin, Tropomyosin, Dystrophin, Alpha-actinin, Titin.
Dystrophin-associated glycoprotein complex.
Muscular dystrophy

Functional and metabolic characteristics of different fibre types in skeletal muscle. Distribution of fast and slow fibre types between muscles.

Skeletal muscle:
Gross structure: Striated appearance; fascicular arrangement; myofibres controlled in groups (motor units) by somatic nerves ending at motor end plates (neuromuscular junctions) (see **6.4.1**).
Connective tissues: Epimysium, perimysium and endomysium
Multinucleate with satellite regenerative cells.
Ultrastructure: Sarcomere; sarcolemma, sarcoplasm, sarcoplasmic reticulum, myofibrils, myofilaments.
Organisation of muscle proteins in sarcomere: Z-line; thin and thick filaments), T-tubules and triads.
Development – mesodermal progenitor, myoblasts, myotubes, myocytes (fibers).

Rigor mortis – myosin remains bound to actin as contraction requires energy – used to estimate time of death.

Cardiac muscle:
Cardiomyocytes: Branching mesh of mononuclear striated cells joined and electrically coupled by intercalated discs (desmosomes and gap junctions: electrically a 'functional syncytium').
Purkinje fibres specialised myocardial fibres enabling heart contraction in co-ordinated manner.
Autonomic innervation (see **6.5.3**).

Smooth muscle:
Distribution: Found in lining of viscera in most organs; structural and functional relationships – different types; loose or densely arranged.
Gross structure: Elongated, spindle shaped, non-striated mononucleate, fusiform non-striated cells.
Microscopic structure: Filaments not aligned in parallel regular arrays, actin and myosin arranged as lattice, cell-cell; mechanical and communicating.
Focal densities, dense bodies, caveola. Autonomic innervation (see **6.2.2**).

6.5.2 SKELETAL MUSCLE [P&P]

Muscle action potential as the trigger for muscle fibre contraction.
Grading of contraction depends on motor unit recruitment and frequency of nerve (and, therefore, muscle) action potentials.
"One-to-one transmission"; twitch summation; tetany.
Cross-bridge cycling and sliding filament theory of contraction.
Role of sarcoplasmic reticulum and Ca^{++}: E/C coupling and muscle relaxation (SR Ca^{2+}-ATPase).
Troponin/tropomyosin inhibition of cross-bridge cycling: Disinhibition by a rise of intracellular Ca^{++}.

Length–tension curve of muscle (active and passive).
Relation of sliding-filament theory to length-tension relationship.
T-tubules and triads in e/c coupling:
link between t-tubules and sarcoplasmic reticulum - Ca^{2+}-release.

6.5.3 CARDIAC MUSCLE [P&P]

Heterogeneity, roles, and basic ionic mechanisms of the cardiac action potentials (differences in sino-atrial node cells vs ventricular myocytes; sub-epicardial cells vs sub-endocardial cells).
Role of Ca^{2+} entry (during the long AP) and SR Ca^{2+} release in E/C coupling
Mechanism of relaxation.
Regulation of contraction:
The Frank-Starling mechanism.
Role and mechanisms of autonomic input in controlling the amplitude and frequency of the heartbeat.
Inotropic effect of cardiac glycosides (see **8.6.7**).
Role of sinoatrial node (SAN) (see **8.6.1**).

Effects of methyl-xanthines.
Possible cellular basis of the Frank-Starling mechanism.

6.5.4 SMOOTH MUSCLE [P&P]

Neurogenic and myogenic activity.
Role of the action potential (when present).
Role of Ca^{2+} entry and SR Ca^{2+} release in activating contraction.
L type calcium channels.
Role of cAMP and cGMP in inhibiting contraction.
Regulation of contraction:
Excitatory and inhibitory autonomic innervation.
Stimulation or inhibition by a variety of hormones and locally produced compounds.
Vascular smooth muscle: Role of the endothelium; see **8.6.5.**
Control of contraction by the actions of myosin light chain kinase (Ca^{2+} activates, PK-A and PKG inhibit) and myosin light chain phosphatase (PK-C inhibits).

Types of smooth muscle:
(i) electrically excitable: driven entirely through nervous activity e.g. vas deferens, arterioles.
(ii) spontaneous electrical activity *modulated* by nervous activity: pacemaker depolarizations and spikes e.g. bladder, some gut muscle or basic slow wave activity e.g. most gut, uterus.
(iii) electrically inexcitable: Regulated through receptors acting via second messengers (not via E_m) e.g. respiratory tract, many blood vessels.
Patterns of innervation of these types of smooth muscle.

7. MUSCULOSKELETAL ANATOMY [OB]

Basic principles of living, gross and imaging anatomy, (including CT and MRI) of the principal features of the musculoskeletal system. You should be able to identify specified major named structures on the living body, a dissection, or a clinical image, and define their principal functions.
In general, muscles should be learned as functional groups.

7.1 BONES OF THE LIMBS

Principles of skeletal organization; bone as a tissue (see **5.2**).
Long, flat, and short bones; adaptations to strength and force transmission.
As examples, the bones of the upper limb, their functional adaptations; comparisons with bones of the lower limb.
Shoulder girdle: Clavicle; scapula (glenoid fossa; acromion)- comparison with pelvic girdle (pubis, ischium, ilium, acetabulum).
Arm: Humerus (head, neck, shaft) - comparison with femur (head, neck, shaft).
Forearm: Ulna and radius - comparison with tibia and fibula.
Small bones of hand (carpals; metacarpals; phalanges) - comparison with foot (tarsus, metatarsals, phalanges).
Principles of development of limb bones (see **15.4**).

Scapula: Coracoid, spine.
Humerus: Lesser and greater tuberosities; epicondyles

Femur: Greater and lesser trochanters; linea aspera, epicondyles.

Scaphoid in force transmission.
Specialisations of the thumb.

Stages of ossification and principles of timing of ossification.
Major palpable bony landmarks (especially around shoulder, elbow, wrist).

7.2 JOINTS OF THE LIMBS

Principles of the structure and function of fibrous, cartilaginous, synovial joints.
Relationships between stability and mobility.
Principles of attachment of capsule, strengthening ligaments, synovial membrane.
For each specified joint, you should know its structural and functional classification, the type and range of movements, and main muscle groups acting at the joint.
Compare the movements and structural specialisations of the shoulder girdle (sterno-clavicular and acromio-clavicular joints) and pelvic girdle; shoulder and hip; elbow and knee.
Role of the rotator-cuff muscles to provide active stabilisation for the shoulder joint.
Compare the structural specialisations of the hand (dexterity and grip) with foot (stability and support).

Comparison of forearm (radio-ulnar) and wrist with the leg (tibio-fibular) and ankle.

7.3 MUSCLES AND MOVEMENTS OF THE LIMBS

Principles of the organization, function and innervation of functional muscle groups.

Functional grouping and movements of the muscle groups of the upper limb; comparisons with the lower limb: Shoulder adduction and abduction, flexion and extension; elbow flexion and extension; hip flexion and extension, abduction and adduction; knee flexion and extension; rotation of shoulder and hip.

Principles of attachments of muscles to bones: 'origins' and 'insertions'.

Principles that determine muscle power, degree of shortening, and action(s)

Control of tendons at joints by retinacula, tendon sheaths.

Muscles groups acting on the shoulder girdle and shoulder compared with those acting at the hip.

Muscles groups of the flexor and extensor compartment of the arm (acting on the elbow) compared with those acting at the knee.

Pronation and supination of the forearm; joints and muscles involved.

Movements of the hand compared with the foot.

Examples of individual muscles functioning within a group.

Muscles groups acting to produce flexion and extension at the ankle, inversion and eversion of the foot.

Muscles groups of the forearm involved primarily in flexion and extension of wrist and fingers compared with ankle and toes.

7.4 BLOOD SUPPLY TO THE LIMBS

Basic principles and general organization of arterial supply and venous and lymphatic drainage, structural adaptation of blood vessels (see **8.5.2**).

Upper limb arterial tree compared with lower limb arterial tree;

Upper limb arteries: subclavian, axillary, brachial, radial, ulnar, palmar arches

Lower limb arteries: external iliac, femoral, popliteal, anterior and posterior tibial, dorsalis pedis, plantar arch.

Arterial anastomoses around joints.

Superficial and deep veins draining the upper and lower limbs.

Valves in extra-abdominal veins below the heart.

Communicating veins: normal flow from superficial to deep. Effects of gravity on venous return from legs, roles of muscle pump, fascial compartments.

Varicose veins

Lymphatic drainage follows venous drainage; valves in lymph vessels; superficial and deep nodes; principles of drainage via successively more central nodes, axillary lymph nodes - role in drainage of breast.

Principal arterial pulse points. Measurement of systemic arterial pressure (see **8.6.4**).

Upper limb veins: Axillary, subclavian, cephalic, basilic.

Lower limb veins: Superficial – long and short saphenous; deep - venae comitantes, popliteal, femoral.

Effects of arterial insufficiency in limbs.

Points of access to veins for venepuncture.

Examples of specific groups of nodes to illustrate a route of lymphatic drainage.

7.5 NERVE SUPPLY OF THE LIMBS

Division of spinal nerves into primary rami: Posterior (to extensors of spine and overlying skin); anterior (to limbs and ventral trunk).
Principles of organization of limb plexuses in relation to limb development.
Principles of origin and distribution of motor nerves; Spinal levels of origin for nerves involved in limb movements.
Sensory nerves -dermatomes and their overlap.
Variation in density of sensory innervation in different body areas; motor innervation in different muscle groups.
Nerve supply to flexor and extensor compartments of the limbs; specified nerves to muscle groups:
Upper limb: Musculocutaneous and radial nerves.
Lower limb: Femoral and sciatic nerves.
Anatomical basis of biceps and knee jerk reflex arcs: significance in mapping injuries to spinal nerve roots.
Effects of damage to major limb nerves.
Common nerve injuries as examples to illustrate principles of organization.

Brachial and lumbosacral plexuses.
Upper limb: Median and ulnar nerves.
Lower limb: Gluteal and obturator nerves.

Autonomic nerve supply to limbs.

Electromyogram.

7.6 SPINE

Major features of the development of the segmental structure of the body (see **15.2**).
Basic principles of development of the spine; sclerotome formation; segmentation.
Basic principles of spine structure sufficient to understand its functions as the central, flexible, controllable, weight-bearing axis of the body.
Structures of a typical vertebra; Body, pedicle, canal, lamina, transverse and spinous processes; articulation facets.
Regional specializations for function at cervical, thoracic, lumbar and sacral levels; the atlas and axis; fused vertebrae in sacrum and coccyx; attachments of ribs, pelvis, skull.
Intervertebral joints: Movements possible at different regions of the spine; intervertebral discs.
Disc herniation lesions ("slipped disc"); sciatica.
Curvatures of the spine: Lumbar and sacral lordosis.
Transmission of weight through the spine.

Determination of spinal level from vertebral prominences.
Imaging of spinal levels using MRI.

7.7 IMAGING

The techniques in current clinical use and their ability to demonstrate morphology and tissue function.
Radiography: Principles of radiography and x-ray attenuation.

Computer Tomography (CT): Principles and applications for imaging different body systems.
Magnetic Resonance Imaging (MRI): Principles and applications for imaging different body systems, including a basic understanding of imaging protocols and different appearance of scans.

Spiral CT.
Nuclear medicine techniques: Basic principles and scan types.

Radiographic Contrast agents: Applications to show body cavities and tissues, including blood and lymphatic vessels.
Ultrasound: Principles and applications of clinical ultrasound imaging.

Arthrograms.

8. BREATHING AND CIRCULATION

8.1 THORACIC ANATOMY [OB]

Principal features of the living, gross and radiographic anatomy, including CT and MRI appearance of the thorax. You should be able to identify specified named structures on the living body, a dissection, or a clinical image, and to define their major functions.

8.1.1 THORACIC CAGE

Structure of thoracic cage in relation to movements of respiration and protection of thoracic contents.

8.1.1.1 Living anatomy of the thorax

Surface markings on the chest of the apex beat and borders of the heart, the diaphragm, the apices of the lungs.
Relative expansion of the upper and lower chest in anteroposterior and lateral dimensions; descent of diaphragm on inspiration.
Percussion of the chest wall to detect dullness due to heart and liver, or resonance of gas-filled cavities i.e. lung fields and gas in stomach.
Auscultation: Heart sounds; breathe sounds over trachea, lung fields.

Surface markings of the lung fissures

8.1.1.2 Skeletal and soft-tissue framework of the thorax

Sternum, ribs and costal cartilages.
Diaphragm attachments; innervation by phrenic nerves (origins C3,4,5).
External & internal intercostal muscles; segmental intercostal nerves & vessels.
Movements of the ribs: Expansion of transverse diameter by movement of the lower ribs; expansion of anterior-posterior thorax by movement of the upper ribs.
Role of intercostal muscles and diaphragm in shallow breathing.
Rib fractures, flail segments – movement on respiration.
Pneumothorax

Sternum components: manubrium, body, xiphisternum, sternal angle
Accessory muscles of respiration
Narrow costophrenic angle and its importance

8.2 RESPIRATORY SYSTEM MORPHOLOGY [OB]

Structure of the airways, lungs and pleural cavity in relation to respiration.

8.2.1 UPPER AIRWAY

Role of the nose: Olfaction, and warming, cleaning, and humidifying inspired air.
Bones forming the facial skeleton; paranasal sinuses.
Conchae and meati of the nose.
Airway components of pharynx; naso-, oro-, and laryngopharynx.

Sites of impaction of inhaled bodies
Airway protection during swallowing
Muscles involved in phonation

Principles of movements of mouth, tongue, soft palate, pharynx, epiglottis, and larynx during breathing.
Protection of airway during swallowing.
Principles of movements of the vocal cords in phonation.
Innervation of nose, nasopharynx, larynx, trachea.

8.2.2 PLEURA AND PLEURAL CAVITIES

Pleural sac. Parietal and visceral layers of pleura.

Somatic innervation of parietal, and autonomic innervation of visceral pleura

8.2.3 INTRATHORACIC AIRWAY AND LUNGS

Airway: Trachea left and right main bronchi; division into lobar bronchi.
Anatomy of bronchial bifurcation - left right differences in relation to inhaled foreign bodies **(see 8.3.9.1**)
Principles of lobar organization and bronchopulmonary segmentation
Structural features of the lungs in relation to gas exchange.
Pulmonary arterial supply to gas-exchange tissues; bronchial arterial supply to non-exchange tissues.
Venous drainage of the lungs and bronchi.
Afferent and efferent autonomic innervation of airways and lungs.
Principles of lymphatic drainage of airway.
Appearance of trachea, lungs, pulmonary vessels on radiographs and CT.

Individual bronchopulmonary segments: Apical segment of lower lobe

Effect of bronchial constriction on airflow, *asthma* (covered in detail in second year)

Principle of CT settings for normal or soft (e.g. lung) tissue

8.2.4 TISSUES OF THE RESPIRATORY SYSTEM

General structure of mucous and serous membranes; the mucous membranes of the respiratory tract.
Epithelial cell types and their functions in the airways: Ciliated cells, goblet cells.
Development and cellular structure of alveoli: Surfactant production.
Type I and type II pneumocytes; alveolar macrophages; alveolar capillaries elastic fibres.
*Cystic fibrosis (see **9.5.5**)*

Accumulation of viscous secretion in cystic fibrosis

Brush cells, Clara cells, small granule-containing cells

Respiratory distress of the new-born
Effects of smoking on respiratory epithelia
Role of growth factors in differentiation and morphogenesis

8.3 RESPIRATORY PHYSIOLOGY [P&P]

Note: Integrative aspects of the control of breathing and blood gas transport will be studied and examined in the second year.

8.3.1 OVERVIEW OF PULMONARY FUNCTION

Total ventilation. Respiratory dead space and alveolar ventilation.
Concept of partial pressure and its units of measurement.
Resting oxygen consumption and carbon dioxide production.

Respiratory quotient (R).

Normal alveolar partial pressures of oxygen (P_AO_2) and carbon dioxide (P_ACO_2) as being close to normal arterial values (see **8.3.5** and **8.3.6**).

The alveolar gas equation: $P_AO_2 = P_IO_2 - P_ACO_2/R$.

8.3.2 RESPIRATORY MECHANICS - STATICS

Tidal volume, vital capacity, functional residual capacity, and their measurement.

Other lung volumes and their measurement

Negativity of intra-pleural pressure: Pneumothorax.

Measurement of intra-pleural pressure and lung compliance

Concepts of compliance, surface tension.

Regional ventilation

Surfactant.

Laplace's equation

Atelectasis in Respiratory Distress Syndromes

8.3.3 RESPIRATORY MECHANICS - DYNAMICS

Concept of airways resistance.

Distribution of airways resistance

Turbulence of airflow leading to wheeze.

Relation of airways resistance to lung volume

Measurement of airways resistance

Peak expiratory flow and its measurement.

Forced expiratory volume in one second (FEV1)

Work of breathing

Pathologies affecting airways resistance e.g. *asthma, chronic obstructive pulmonary disease* (*emphysema & chronic bronchitis*).

Distinction between obstructive *(e.g. asthma)* and restrictive *(e.g. pulmonary fibrosis)* lung disease.

8.3.4 DIFFUSION OF RESPIRATORY GASES

Concept of diffusion and of the diffusing capacity of the lung.

Fick's law of diffusion (see also **1.6.1**).

Factors influencing the speed of diffusion.

Perfusion limitation and diffusion limitation of gas transfer.

Pathologies affecting diffusion e.g. *pulmonary fibrosis, pulmonary oedema, emphysema.*

Measurement of diffusing capacity using carbon monoxide.

8.3.5 OXYGEN TRANSPORT

Normal value for systemic arterial partial pressure of oxygen (P_aO_2).

Measurement of arterial partial pressure of oxygen.

Role of haemoglobin in oxygen transport.

Contribution of dissolved oxygen to oxygen transport.

Concept of oxyhaemoglobin saturation.

Measurement of arterial oxyhaemoglobin saturation by pulse oximetry.

Shape of the oxyhaemoglobin dissociation curve.

The Hill equation and cooperative binding.

Myoglobin: Role of myoglobin and comparison with haemoglobin,

Shift of the curve by CO_2 and pH (Bohr effect).

Varieties of haemoglobin: e.g. fetal, sickle cell (see **44.1.1**).

Effect of temperature and 2,3-DPG concentration on oxyhaemoglobin dissociation

Delivery of oxygen to the tissues and factors affecting it.

Body oxygen stores and the effect of apnoea.

hypoxic hypoxaemia, cyanosis.

Cyanide and carbon monoxide poisoning, oxygen therapy.

8.3.6 CARBON DIOXIDE TRANSPORT

Normal value for systemic arterial partial pressure of carbon dioxide (P_aCO_2)
Role of bicarbonate in carbon dioxide transport.
Concept of buffering and its importance in carbon dioxide transport.
Role of haemoglobin in buffering H^+ from dissociating H_2CO_3.
The Henderson-Hasselbalch equation.
Additional role of haemoglobin in CO_2 transport by formation of carbamino compounds.
Role of carbonic anhydrase in red cells; the chloride shift.

Contribution of dissolved carbon dioxide to oxygen transport.
The CO_2/blood dissociation curve: Haldane effect.
The Davenport diagram showing the interdependence of plasma bicarbonate, pCO_2, and pH in oxygenated and deoxygenated blood.
Body stores of CO_2 and the effects of apnoea.

8.3.7 PULMONARY PERFUSION AND VENTILATION/PERFUSION (V/Q) MATCHING

The pulmonary circulation as a low-pressure circulation.
Normal values for pulmonary arterial blood pressures (systolic and diastolic).
Effect of regional mismatch of perfusion to ventilation on pulmonary gas exchange (including consequences of the shape of the oxyhaemoglobin dissociation curve).
Concept of pulmonary shunt.
Normal increases in both regional perfusion and regional ventilation from top to bottom of the lung arising due to gravity
Hypoxic pulmonary vasoconstriction and acute pulmonary hypertension.

Measurement of regional distribution of perfusion and ventilation.
Regional differences in ventilation/perfusion ratios and alveolar gas composition.
The three-compartment model of the lung: Shunt, ideal alveolus and dead-space.
Hypercapnic pulmonary vasoconstriction.
Pathological examples of V/Q mismatch: Pulmonary embolism, pneumonia.
Prominence of shunt as a cause of hypoxaemia in Covid-19

8.3.8 CONTROL OF BREATHING

Generation of breathing rhythm within brainstem.
Central chemoreceptors - location and role of normal stimulants.
Peripheral chemoreceptors, (including carotid and aortic bodies) - location, innervation, and normal stimulants.
Response of ventilation to arterial blood gases (P_aO_2 and P_aCO_2) mediated by the respiratory control system.
Effect of ventilation on alveolar pressures of oxygen and CO_2 (P_AO_2 and P_ACO_2) brought about by the ventilation of the alveoli (the concept of the metabolic hyberbolae).
Pulmonary stretch receptors.
Autonomic innervation of the bronchi.

Identification of Pre-Bötzinger complex as a centre of rhythm generation.
Theories of pacemaker and network origins of respiratory rhythm.
Hering-Breuer reflex. Pulmonary irritant and J receptors.

8.3.9 ACUTE AIRWAYS OBSTRUCTION

8.3.9.1 By Foreign Bodies

Consequences of acute airway obstruction (upper and lower) by foreign bodies.

8.3.9.2 In Unconsciousness and Sleep

Consequences and relief during basic resuscitation of upper airways obstruction.

8.5 CARDIOVASCULAR SYSTEM: MORPHOLOGY [OB]

8.5.1 THE HEART

Structure of the heart in relation to its action as two pumps, left and right. You should be able to identify specified major named structures on the living body, a dissection, or a clinical image, and to define their major functions. Cardiac muscle (see **6.5.1**).

8.5.1.1 Exterior of heart

Normal position of heart, borders, apex, in chest.
Situs inversus.

Fibrous & serous pericardium; Fluid accumulation in pericardial cavity.

Pericardial sac.
Principal venous structures draining to the heart (superior & inferior venae cavae, pulmonary veins; coronary sinus).
Principal arterial structures leaving the heart: Aorta & pulmonary trunk.

8.5.1.2 Interior of heart

Atria and ventricles: Structural adaptation to function.
Valves: Structure and positions of the atrioventricular, pulmonary, and aortic valves.

Relation of intra-atrial features (fossa ovalis, crista terminalis) to development (see **16.5**).
Damage to papillary muscles, valve replacement.

8.5.1.3 Blood supply of heart: Distribution of supply

Principles and morphology of coronary vascular supply.
Principles of blood supply to myocardium: coronary arteries as functional end arteries, coronary perfusion during diastole.
Angina. Myocardial ischaemia; consequences of occlusion of the major coronary arteries.

Example of a specific coronary artery and its importance.
Coronary venous sinus.

8.5.1.4 The Conducting System (see **8.6.1**)

Principles of conducting system of the heart.
Sinu-atrial and atrioventricular nodes. Atrioventricular bundle: right and left branches.
Innervation of heart from vagus parasympathetic and sympathetic systems (see **6.2.2**).
Referred pain from the heart to central chest, neck and left arm (male), from diaphragm to shoulder (C4)

8.5.2 HISTOLOGY OF BLOOD VESSELS

Structure and functions arteries, arterioles, capillaries, venules and veins: Endothelium; tunica intima, media, vasa vasorum, adventitia; elastic and non-elastic vessels.
Portal systems in liver and pituitary gland.
Structure and function of different types of capillaries: Non-fenestrated and fenestrated capillaries, sinusoids, 'tight' capillaries.

Arterio-venous anastomoses.
Atherosclerosis - degenerative process narrowing arterial lumen and weakening walls (details to be covered in second year).

8.5.3 THE GREAT VESSELS

Major arteries and veins carrying blood to and from, the heart.

Aorta: Ascending, arch, descending thoracic and abdominal aorta *Aortic aneurysm.*
Brachiocephalic artery: Subclavian to upper limb and common carotid arteries; carotid bifurcation.
Common iliac: External iliac to lower limb; internal iliac (to pelvis, buttock, perineum.
Pulmonary artery. Ligamentum arteriosum (relation to development see **15.5**).
Superior vena cava draining head and upper limbs; inferior vena cava draining abdomen pelvis and lower limbs.

Coronary and large artery arteriography.

8.5.4 MEDIASTINUM

Position and function of the major structures within the chest, and their relationship to the heart and lungs.

Organization and divisions of the mediastinum; superior; anterior; middle (heart); posterior.
Position of heart, great vessels, trachea, oesophagus, phrenic and vagus nerves and sympathetic trunks; lymph nodes at hilum of lung.
Thoracic duct draining lymph into left subclavian vein.

Thymus.

8.5.5 AUTONOMIC INNERVATION OF THORACIC VISCERA (see **6.2.2**)

Sympathetic system: origin of preganglionic fibres from T1 - L2 of cord. Thoracic splanchnic sympathetic nerves to abdominal viscera.
Sympathetic chain of ganglia; effects on heart and airways.
Parasympathetic system; preganglionic fibres in vagus nerves; effects on heart and airways.
Visceral afferent (sensory) fibres with vagus and sympathetic nerves.
Horner's syndrome (damage to sympathetic trunk at head of first rib affecting sympathetic innervation of the head)

8.6 CARDIOVASCULAR PHYSIOLOGY [P&P]

8.6.1 ELECTRICAL ACTIVITY IN THE HEART: THE ELECTROCARDIOGRAM

Pacemaker and conducting system (see **6.5.3**),
relative conduction velocities in parts of the conducting system.
Key components and origin of the 3-lead ECG. The heart as a dipole in a volume conductor.
P, QRS, T waves. Historical appreciation of the contributions of Waller, Einthoven and others to understanding the ECG. The12-lead ECG.

8.6.2 THE HEART AS A PUMP

Role of papillary muscles in valve function.
1st and 2nd heart sounds. 3rd and 4th heart sounds.
Cardiac cycle: Pressure and volume changes in relation to the ECG.
Jugular venous pulse in relation to the cardiac cycle.
Physiological significance of the Frank-Starling mechanism. Historical appreciation of the Frank–Starling Mechanism.
Concept of pre-load (CVP) and after-load (aortic pressure). Concept of cardiac work.
Determinants of cardiac output. Measurement of cardiac output: dye dilution and thermodilution; Doppler-echocardiography.
Measurement of cardiac output using the Fick principle applied to oxygen uptake.
Neural and chemical factors affecting the inotropic and chronotropic state of the heart.

8.6.3 PROPERTIES OF THE VASCULAR SYSTEM

Functions of the circulation: systemic and pulmonary divisions.
Distribution of cardiac output to main organs of the body.
Structure and roles of arteries, arterioles, capillaries, & veins (see **8.5.2**). Arterio-venous anastomoses.
Relation between flow velocity and total cross-sectional area of vessel bed. Laplace's law: the importance of elastic tissue in maintaining the stability of resistance vessels.
Blood volume and its distribution with respect to vessel type.
Effect of vessel radius on its resistance to flow.
Anomalous viscosity of blood.
Fluid balance across capillaries (Starling forces).

Production of vasoactive substances by endothelium.

8.6.4 HAEMODYNAMICS

Units of measurement of blood pressure: mmHg.
Normal systemic arterial pressure: Systolic (120 mmHg), diastolic (80 mmHg), mean (MAP) and pulse pressures.
Measurement of arterial blood pressure; sphygmomanometry and Korotkoff sounds.
Central venous pressure (CVP).
Measurement of CVP; jugular venous pressure (JVP).
Normal central venous pressure: 5 mmHg (7 cmH_2O).
Normal cardiac output at rest (CO; 5 litre/min).
Relationship between arterial and venous pressures, cardiac output and systemic vascular resistance (SVR): MAP-CVP = CO x SVR.
Net flow of liquid across the capillary wall: lymph flow returning to the circulation via the thoracic duct.

Dependence of local hydrostatic pressure (P) at the bottom of a free column of blood on height (h), blood density (ρ), and the acceleration due to gravity (g) ($P=h\rho g$); implications for variation in pressure between head and feet in a standing person.
Use of cmH_2O as a unit of blood pressure.
Appreciation of the history of the circulation (e.g. Harvey).
Bernoulli's equation for the steady flow of a frictionless liquid: $(P + \rho u^2/2 + h\rho g) = \text{constant}$, where u is blood velocity (m/s).
Poiseuille's equation for steady flow (Q) of liquid with friction (viscosity μ) through a uniform horizontal vessel of radius r and length L: the pressure drop $\Delta P = 8QμL/(\pi R^4)$.
Laminar and turbulent flows.
Lymphoedema.

8.6.5 THE CONTROL OF REGIONAL BLOOD FLOW

Autoregulation.
Factors affecting local vascular control: temperature, metabolic, myogenic, autacoids, nitric oxide.
Role of the endothelium.
Reactive hyperaemia.
Neural and hormonal control.
Distinguishing features and the control of circulation in the major organs: Skeletal muscle, coronary, pulmonary, cutaneous, cerebral, renal.

Stretch-activated ion channels.
Evidence for role of nitric oxide.

Measurement of blood flow in specific organs.
Use of venous occlusion plethysmography to measure blood flow in a limb.

8.6.6 SENSORY RECEPTORS AND REFLEXES

The integrative processes involved in long term blood pressure regulation will not be taught or examined until the second year.

Arterial baroreceptors: Aortic arch baroreceptors innervated by vagus nerve (X); Carotid sinus baroreceptors innervated by glossopharyngeal nerve (IX) and function.
Afferent and efferent pathways.
Low pressure cardiopulmonary receptors.

Classes of baroreceptor fibre and their thresholds for firing.

Effect of arterial chemoreceptor stimulation on the circulation.
Significance of blood pressure regulation.

8.6.7 PHARMACOLOGY OF CARDIAC CONTRACTILITY

Principles of influence of drugs on cardiac contractility: Direct effects on heart, indirect effects through changing vascular tone.
Cardiac glycosides (e.g. digoxin, ouabain): Possible mechanism of action.

Effects on cardiac contractility of coronary and peripheral vasodilators (e.g. ACE inhibitors, hydralazine, nitrates).

Positive effect of adrenoceptor agonists e.g. dobutamine ($\beta 1$-agonist).
Negative effect of adrenoceptor antagonists e.g. propranolol.

Risk that drugs increasing cardiac contractility may precipitate ischaemia and dysrhythmia.
Role of after-depolarizations.
Positive effect of phosphodiesterase inhibitors (eg milrinone).
Calcium sensitizers as positive inotropes (e.g. Levosimendan, cardiac myosin activators).

8.6.8 CARDIAC DYSRHYTHMIAS AND HEART BLOCK

Examples of common dysrhythmias e.g. atrial fibrillation, complete heart block, ventricular fibrillation and ventricular tachycardia.
Basic examples of dysrhythmias on ECG recording.

Possible causative mechanisms:
Effects of ischaemia, electrolyte imbalance, autonomic nervous system.
Structural causes, e.g. hypertrophic cardiomyopathy, aberrant conducting pathways as in Wolff-Parkinson-White syndrome, atrioventricular nodal re-entrant tachycardia (AVNRT).

Examples of anti-dysrhythmics, e.g. lidocaine, propranolol, amiodarone, verapamil, adenosine; brief outline of possible principles of action.

Pro-arrhythmogenic effects of anti-dysrhythmic drugs.

Use of cardiac glycosides (ouabain).
Types of heart-block.
Secondary pacemakers.
Therapeutic use of anti-muscarinic drugs (atropine).

Possible iatrogenic origins of heart-block.

Vaughan Williams Classification of drugs.

9. ABDOMEN & DIGESTIVE SYSTEM

9.1 ABDOMINAL ANATOMY [OB]

Principles of the living, radiological & gross anatomy, including CT & MRI appearance of the principal features of the abdomen and pelvis. You should be able to identify specified major structures as appropriate on the living body, a dissection, or a clinical image, and to define their functions.

9.1.1 ANTERIOR ABDOMINAL WALL

Basic structure of the anterior abdominal wall in relation to its function.
Surface projections of the major organs.
Consequences of deficiencies in the abdominal wall e.g. the inguinal canal
Inguinal hernias

Individual muscles of the anterior abdominal wall*, femoral hernia, congenital umbilical hernias*

9.1.2 POSTERIOR ABDOMINAL WALL

Basic structure of the posterior abdominal and pelvic walls.
Muscular floor of the pelvic cavity, levator ani.
Distribution of vessels and nerves to organs and the lower limbs.
Midline arteries to alimentary tract and its derivatives (liver, pancreas). (see **9.3.2**).
Paired lateral arteries to derivatives of intermediate mesoderm; kidneys, adrenals, gonads.
Segmental paired arteries to body wall.

Individual muscles of the posterior abdominal and pelvic walls.

9.1.3 PERITONEAL CAVITY AND PERITONEUM (see **11.1.1**)

Peritoneal cavity in relation to abdominal organs.
Peritoneum: visceral and parietal layers.
Pelvic cavity.

Innervation of peritoneum. Greater sac, lesser sac.
Spread of infection and fluid within the abdomen.

9.1.4 SPLEEN

Position of the spleen in the peritoneal cavity.
Arterial supply to spleen.
Roles of spleen: Turnover of red blood cells. (Role in immunity studied in 2nd year).

Enlargement of the spleen in infection and leukaemia.

9.2 MOUTH, PHARYNX AND OESOPHAGUS [OB]

Mandible and temporo-mandibular joint; muscles of mastication.
Mouth and tongue; innervation; mechanism of chewing.
Hard and soft palate; functions of soft palate to protect airway.
Salivary glands: Parotid, submandibular, sublingual; autonomic regulation
Pharynx and its division: Naso-, oro-, & laryngopharynx. Oesophagus.

Types of teeth, their functions.
Trigeminal nerve anaesthesia.

Position of salivary gland ducts draining into mouth: *duct blockage.*
Gag reflex.

Movements of mouth, tongue, soft palate, pharynx, epiglottis during swallowing.
*Developmental defects of palate and lip (clefts see **15.9**)*

9.3 THE GASTRO-INTESTINAL TRACT [OB]

Principles of the structure, vascular supply, innervation of the abdominal alimentary tract in relation to its movements, secretions and absorptive functions.

9.3.1 MORPHOLOGY OF GASTRO-INTESTINAL TRACT

Abdominal oesophagus; gastro-oesophageal junction and 'sphincter' mechanism.

Imaging techniques using barium contrast.

Stomach: Fundus, body; pyloric region (sphincter); greater and lesser omentum.
Pyloric stenosis. Gastric ulceration.

Duodenum; Entry of biliary and pancreatic ducts; sphincter of Oddi.

Duodenal ulcers.

Jejunum, ileum, attachment to small bowel mesentery

Caecum; appendix; ascending, transverse, descending and sigmoid colon; rectum, anal canal. Mechanisms of continence, role of sphincters (see **9.5.2**). *Appendicitis.*

Colon cancer.
Causes of faecal incontinence.

9.3.2 VASCULATURE OF ALIMENTARY TRACT

Distribution of major arteries to the gut and associated organs, venous drainage to hepatic portal vein, and portal/systemic anastomoses.
Major features of organization related to development.

Coeliac artery to foregut derivatives; abdominal oesophagus, stomach, proximal half of duodenum to entrance of bile & pancreatic ducts.

Superior mesenteric artery to midgut derivatives; distal duodenum, small intestine, colon to splenic flexure.

Inferior mesenteric artery to hindgut derivatives; splenic flexure to recto-anal junction.

Arrangement of arterial supply to gut; marginal vessels; arcade anastomoses.

Volvulus, intussusception, and consequences of ischaemia.

Control of gut arterial supply by sympathetic nerves.

Drainage of veins to hepatic portal vein; sites of portal-systemic venous anastomosis.

Consequences of portal hypertension.

Venous drainage of the rectum. *Haemorrhoids.*

Principles of lymphatic drainage.

9.3.3 AUTONOMIC INNERVATION OF ABDOMINAL VISCERA (see **6.2.2**)

Sympathetic and parasympathetic (vagus) to fore- and mid-gut and sacral S2-4 to hind gut., supplies to abdominal organs.
Effects on motility, sphincters and secretion.
Visceral afferent (sensory) fibres with vagus and sympathetic nerves.

9.3.4 HISTOLOGY OF THE DIGESTIVE TRACT

Basic structure of gut wall and its regional modifications: mucosa (i.e. epithelium, lamina propria, muscularis mucosae). submucosa; submucosal nerve and vascular plexus; muscle layers; myenteric plexus; gut-associated lymphoid tissue. serosa.
Types, functions and turnover of the various epithelial cells (enterocytes, goblet cells, enteroendocrine cells - see **15.6**). Stem cells (see **11.1**).
Oesophagus: Stratified squamous epithelium; smooth and skeletal muscle; Langerhans (dendritic) cells.
Stomach: Structural, functional and cellular specializations of the fundus, cardiac and pyloric regions.
Gastric pits and glands, rugae.
Parietal cells (see also **19.5.3.1**) and Chief (zymogenic) cells
Small intestine: Structure of epithelium, villi, lacteals, brush border of absorptive enterocytes, crypts - replacement of epithelial cells by division, migration and differentiation of stem cells, plicae circulares, Peyer's patches.
Large intestine: Crypts, no villi, predominance of goblet cells, taeniae coli.

Mucosal immune system: M cells, dendritic cells, gut-associated lymphoid tissue (role studied in second year).
Paneth cells.

Coeliac disease (autoimmune).
Inflammatory bowel disease.

Colorectal cancer (mutations in APC)

9.4 LIVER AND PANCREAS [OB]

Principles of organization of the liver in relation to its processing of venous drainage of the bowel, secretion of plasma proteins etc., production of bile and its storage and transport to the intestine
Principles of organization of the pancreas and drainage of its exocrine and endocrine secretions

9.4.1 LIVER AND BILIARY TRACT

Position of liver.
Porta hepatis.
Liver blood vessels: Hepatic portal vein, hepatic artery, hepatic veins.
Portal-systemic venous anastomoses.
Peritoneal attachments of liver, falciform ligament, lesser omentum.
Biliary system: Hepatic ducts, gall bladder and cystic duct, common bile duct, drains with pancreatic duct into the duodenum, Sphincter of Oddi. (see **9.4.3**)

Spread of cancers via portal system from gut to liver.
Named lobes and segments of the liver.

9.4.2 HISTOLOGY OF LIVER AND BILIARY SYSTEM

Liver: major functions; histological structure in relation to function - hepatocytes, sinusoids, space of Disse, bile canaliculi, portal triads, structural and functional subunits (lobules).

Kupffer cells as an example of the mononuclear phagocyte system.

Biliary system: bile-resistant epithelium, the gall bladder.

Gallstones

Regenerative capacity of the liver (see **1.12.1.2**)

Stellate cells: pericyte-like cells involve

Cirrhosis

9.4.3 PANCREAS

Position of pancreas on posterior abdominal wall; relation to duodenum.

Exocrine role: Main pancreatic duct, drains into duodenum with common bile duct. Sphincter of Oddi. (see **9.4.1**)

Endocrine role (see **14.6).**

Principles of vascular supply; develops at junction of fore- and mid-gut so supplied by both celiac and superior mesenteric arteries.

Head, uncinate process, neck, body, tail of pancreas; relation to development.

*Developmental abnormalities (see **15.7**).*

9.4.4 HISTOLOGY OF SALIVARY GLANDS AND PANCREAS

Microscopic anatomy of the salivary glands and pancreas in relation the secretion of saliva and pancreatic juice; zymogen granules.

Salivary glands: Myo-epithelial cells, serous cells, mucous cells; ducts; control of secretion.

Exocrine and endocrine components of pancreas:
Exocrine acini and ducts, endocrine islets (see **14.6**).

9.5 GASTROINTESTINAL PHYSIOLOGY [P&P]

9.5.1 ACTIVITY OF THE ALIMENTARY TRACT FOLLOWING A MEAL

Cephalic, gastric, intestinal phases of activity.

Integration of intrinsic and extrinsic neural control and local hormones in regulation.

9.5.2 ALIMENTARY TRACT MOTILITY

Movements of different parts of the alimentary tract and their co-ordination. Relationship to abnormal bowel movements. Effects of drugs.

Swallowing (see **9.2**).

Oesophageal sphincters (see **9.3.1**).

Gastric motility and emptying — its control.
Importance of stomach as a storage organ; formation of chime.

Gall bladder motility.
Small intestinal motility: segmentation and pendular activity.
Large intestinal motility: peristalsis (stimulated by distension via enteric nervous system).
Role of enteric nervous system.
Influence of drugs on motility: anti-emetics, laxatives, anti-diarrhoeal drugs parasympathomimetics, opiates.
Influence of diet on motility.
Defaecation: Voluntary and autonomic control.

Gut motility controlled according to contents by:
(i) hormones released by specialised epithelial cells.
(ii) stretch receptors acting via the enteric nervous system.

Electrical slow waves, migrating motor complex (MMC).
NANC (non-adrenergic, non-cholinergic nerves).

Importance of dietary fibre.
Common motility disorders: e.g. constipation, *irritable bowel syndrome.*

9.5.3 GASTROINTESTINAL SECRETION

Salivary secretion: mechanisms and regulation. Components of saliva.
Gastric secretions:
Acid (see **9.5.3.1**); enzyme (pepsinogen); mucus.
Intrinsic factor - role in vitamin B_{12} absorption.
Pancreatic secretion: enzyme, chloride and bicarbonate components.
Biliary secretion; entero-hepatic recirculation of bile salts.

Experimental pouches, innervated and vagally denervated.
Sham feeding experiments.
Pernicious anaemia.
Abnormalities of chloride secretion in cystic fibrosis.
Entero-hepatic recirculation of drugs.

9.5.3.1 Gastric Acid Secretion and Peptic Ulceration

Mechanism and regulation of gastric acid secretion:
parietal cells, role of the H^+-K^+ ATPase in maintaining a large pH gradient.
Interactions of vagal stimulation, histamine and gastrin in control of gastric acid secretion.
Peptic ulcer: Possible causes and therapy with antacids.
direct antacid agents e.g. aluminium hydroxide.
histamine antagonists e.g. ranitidine.
blockers of H^+-K^+ ATPase e.g. omeprazole.
Evidence for association of *Helicobacter pylori* with peptic ulceration:
Chemotherapy for *Helicobacter.*

Adverse effects of antacid therapy.
Also used, but rarely for peptic ulcer: Anti-muscarinic agents e.g. pirenzepine.
Zollinger–Ellison syndrome.

9.5.4 DIGESTION IN THE ALIMENTARY TRACT

Contributions of saliva, gastric secretion, pancreatic secretion and bile to the digestion of protein (see **2.4.1**), carbohydrate and lipid (see **2.2.2**)
Pepsin, Trypsin, Chymotrypsin.
Enterokinase as an activator of intestinal peptidases.

Diversity of proteases, amylases and lipases.
Use of pancreatic enzymes in substitution therapy in pancreatic malabsorption.

Role of brush border peptidases.
Role of brush border disaccharidases.
Composition, concentration and secretion of bile.
Emulsion and micelle formation and the role of bile salts.

Inability of humans to digest cellulose.

9.5.5 ABSORPTION BY THE ALIMENTARY TRACT

Integration of nutrient digestion and absorption.
Role of active and passive epithelial transfer.
Absorption of amino acids and peptides in the small bowel.
Intracellular peptidases.
Active absorption of D-glucose and D-galactose by Na-dependent secondary active transport; hexose exit from the epithelium.
Oral rehydration solutions: Notably isosmotic salt/glucose solution.
Fate of unabsorbed carbohydrate.
Intracellular triglyceride re-synthesis. Chylomicron formation and passage via lymph.
Absorption of water-soluble and fat-soluble vitamins.
Absorption of water and minerals, especially calcium and iron (see **44.2.1.3**).
Intestinal electrolyte transport:
Tight and leaky epithelia and segmental variation apical and basolateral transporters for Na+, Cl-, K+, HCO3- , and short-chain fatty acids regulation of ion transport.
*Cystic fibrosis (see **8.2.4**)*

The unstirred layer.

Minor passive components:
uptake of fructose by facilitated diffusion.
Role of glutamine as an intestinal fuel.
Osmotic diarrhoea due to carbohydrate malabsorption; Lactase deficiency.

Toxin-induced diarrhoeas.

9.5.6 DEFENCE MECHANISMS IN THE ALIMENTARY TRACT

The role of the different components of the alimentary tract in protecting the body**.**

Taste as a protective mechanism.
Gastric acid as a protective mechanism; sterility of small bowel contents.
Epithelial barrier functions; protective role of mucus.
Concepts of mucosal immune system (details covered in second year).

Achlorhydria: bacterial overgrowth as a cause of fat malabsorption.

10. BIOCHEMISTRY: INTEGRATIVE ASPECTS, DEFENCE AND DISEASE [BIOCH]

10.1 METABOLIC INTEGRATION

Integration of different pathways.
Central hubs in metabolism e.g acetyl CoA and glucose 6 phosphate.
Subcellular compartmentalisation within and between pathways.
Regulation of pathways from both intracellular and hormonal signals.
Integration between different tissues to give whole body metabolic control in different states eg fed vs fasting/starvation.

Glucose-fatty acid cycle.
Avoiding futile cycling in metabolism.

10.2 DIABETES MELLITUS

Diabetes mellitus type 1 and 2.
Mechanisms of Type 1 and Type 2 diabetes mellitus: Insulin deficiency (from b-cell destruction) vs. insulin resistance.
Major metabolic disturbances in diabetes mellitus (Types 1 and 2): Polyuria, polydipsia, dehydration, fatty acid mobilisation, ketoacidosis, hyperglycaemia.
Glucose tolerance test.

Comparison between starvation and type 1 diabetes.
Biochemical principles underlying the treatment of type 1 diabetes.

Complications of diabetes mellitus.
Future treatment and diagnosis developments.

10.3 BIOCHEMICAL DEFENCE MECHANISMS

10.3.1 HEPATIC DETOXIFICATION MECHANISMS

Conversion of toxic, lipophilic compounds to polar, more water-soluble derivatives for excretion, by oxidation, reduction and conjugation.

Oxidation/reduction reactions: Significance of oxidation/reduction reactions in detoxification, activation of xenobiotics (to carcinogens), activation of prodrugs.
Conjugation: Functional groups introduced by oxidation/reduction subsequently used to increase water-solubility by conjugation, esp. with glucuronic acid.

Dehydrogenases (e.g. alcohol dehydrogenase), reductases, oxidases.
Mono-oxygenases – cytochrome P_{450}; function as electron donor.
Flavin-containing mono-oxygenases.
Conjugation with sulphate, acetyl groups, amino acids.

10.3.2 METABOLISM OF ALCOHOL

Role of the liver in alcohol metabolism.
Alcohol dehydrogenase and Cytochrome P450 mono-oxygenase.
Aldehyde dehydrogenase.
Resultant susceptibility of liver to alcohol-induced damage.
Metabolic effects of alcohol: Hypoglycaemia, lactic acidosis, hyperuricaemia.

Major pathways of hepatic ethanol metabolism. Roles of alcohol dehydrogenase, cytochrome P_{450} mono-oxygenase, peroxisomal catalase. Effects of ethanol metabolism on NADH levels. Significance of differing rates of alcohol metabolism in different individuals, and their possible relation to alcohol tolerance.

Concept of modification of drug metabolism by alcohol.

Significance and subtypes (I–IV) of acetaldehyde dehydrogenase; recognition of variations of acetaldehyde dehydrogenase between races; significance for alcohol tolerance.

Cellular effects of acetaldehyde; acetate; metabolic consequences of increased NADH on fatty acid metabolism and gluconeogenesis. Effect on collagen synthesis (hepatic fibrosis in alcoholism).

A consequence of induction of the cytochrome P_{450} system; increased metabolism and decreased activity (e.g. phenobarbital, warfarin) and increased activation with risks of hepatotoxicity (e.g. paracetamol).

10.3.3 REACTIVE OXYGEN SPECIES

Formation of superoxide, hydrogen peroxide and derivatives.
Superoxide dismutase, peroxidise.
Vitamins C and E as anti-oxidants.

10.4 INBORN ERRORS OF METABOLISM

Importance of these individually relatively rare diseases in the population. A logical scheme for understanding any individual disease: Site of the enzyme defect and an understanding of the relevant biochemistry. Rational approach to treatment.

Examples of common conditions, e.g. *phenylketonuria*, urea cycle defects.

11. URO-GENITAL SYSTEM

11.1 URINARY TRACT MORPHOLOGY [OB]

Principles of the living, radiological and gross anatomy, including CT and MRI appearance of the uro-genital tract in both male and female. You should be able to identify the specified major structures on the living body, a dissection, or a clinical image (radiograph, endoscopic image etc.), and to define their functions.

11.1.1 ANATOMY OF THE PELVIS AND PERINEUM

Bones forming the pelvic walls & bordering pelvic inlet and outlet; muscular floor (levator ani) of the pelvis.
Position of the pelvic organs in male and female.
Perineal membrane and perineal body.
Urogenital triangle in the male and female.
Position of urethra, vagina, anal canal in perineum.
Internal iliac arterial supply to pelvic viscera, to perineum and to buttock;
Sympathetic and parasympathetic (S2-4) supply to pelvic organs; sacral nerve somatic nerve supply to perineum and lower limb.

Prolapse of pelvic organs after damage to pelvic/perineal floor; incontinence.

11.1.2 KIDNEY AND URETER

Position of kidneys in abdomen; relationship peritoneum and with adrenal glands.
Asymmetry of left and right kidneys.
Cortex & medulla; hilum, renal arteries and veins, pelvis of ureter,
Ureter: Position, retroperitoneal course, function of oblique entry to bladder.

renal capsule; major and minor calyces;
Kidney "ascent"; ectopic renal arteries.
*Pelvic (horseshoe) kidney (*see **15.7**)*; polycystic kidneys.*

11.1.3 URINARY BLADDER AND URETHRA

Position of bladder in abdomen, trigone forming bladder base
Internal involuntary and external voluntary sphincters.
Autonomic and somatic innervation of bladder and sphincters (see **11.4**)
Urethra. Male urethra; prostatic, membranous and penile (see also **19.1.2**).

11.2 HISTOLOGY OF THE URINARY TRACT [OB]

Structure of the renal corpuscle (vascular and renal poles); glomerulus; Bowman's capsule.
Filtration barrier: Podocytes, basement membranes, capillary fenestrations.
Afferent and efferent arterioles.
Structure and relationship to function of epithelium of proximal and distal convoluted tubules, and associated vasculature; component parts of the loop of Henle, collecting ducts.
Blood supply to the cortex and to the medulla: Vasa recta.

Significance of proteinuria.

Cortical and juxtamedullary nephrons.

Juxtaglomerular apparatus: macula densa, juxtaglomerular cells, extraglomerular mesangial cells. (see **11.3.3**).
Structure of the ureter, bladder, and urethra. Detrusor muscle and parasympathetic innervation
Urothelium ('transitional epithelium') of lower urinary tract; plaques in plasma membrane (see **5.1**).

Specializations of bladder epithelium for distension.
Hypertrophy of detrusor in prostatic enlargement (see **1.12.1.1**).

11.3 RENAL PHYSIOLOGY [P&P]

11.3.1 ROLE OF THE KIDNEY

Overall functions of the kidney eg regulatory, excretory, and endocrine (erythropoietin secretion, vitamin D activation).
General mechanism of urine formation, glomerular filtration, tubular reabsorption and secretion.
Renal blood flow relative to cardiac output, glomerular filtration rate (GFR), variable reabsorption of majority of filtrate.
Distribution of hydrostatic pressure along renal vasculature.
Role of the kidney in salt and water homeostasis.

Absolute values for key parameters of normal renal function.
Consequences of renal failure: Loss of ability to deal with volume and salt loading; disturbances of electrolyte balance (e.g. hyperkalaemia) and mineral metabolism; metabolic acidosis; uraemia; loss of endocrine functions.

11.3.2 GLOMERULAR FILTRATION

Concept of ultrafiltration and components of filtration barrier; driving (Starling) forces for filtration and determinants of GFR; concept of filtration fraction.
Definition of renal clearance and use of inulin and creatinine clearance to measure GFR. Units of measurement of clearance.
Autoregulation of GFR: myogenic response, tubulo-glomerular feedback.

Experimental evidence for ultrafiltration.
Concept of filtration pressure equilibrium.

Para-amino hippurate (PAH) clearance to measure Effective Renal Plasma Flow (ERPF).
Differential regulation of the afferent and efferent arterioles (e.g. by angiotensin II and by atrial natriuretic peptide 'ANP').

11.3.3 TUBULAR TRANSPORT

Principles of epithelial transport.
Active versus passive transport processes; relevance of Starling forces; leaky and tight epithelia; transcellular versus paracellular route.
Importance of basolateral Na/K-ATPase in driving solute and water reabsorption.
Mechanisms of apical sodium entry (coupled transporters and channels)
Main functions and transport mechanisms of the different parts of the nephron
Proximal tubule:
Isotonic reabsorption of the bulk of filtrate. Concept of Tm and glucose "overspill".

Composition of the tubular fluid along the nephron.

Secretion of endogenous and exogenous organic cations and anions (e.g. uric acid, penicillin).

Loop of Henle: Urine concentration (see **11.3.4**).

Distal tubule and collecting duct, fine regulation of renal electrolyte and water output.

Juxtaglomerular apparatus.
Renin-angiotensin-aldosterone system.
Action of aldosterone on Na^+ re-absorption and K^+ and H^+ secretion; Sympathetic control

Consequences of hyper- and hypoaldosteronism on renal tubular transport and body electrolyte balance.

11.3.4 FORMATION OF DILUTE AND CONCENTRATED URINE

Range of urine osmolarity.

Establishment of cortico-papillary interstitial osmotic gradient by counter-current multiplication in loops of Henle (role of NaK2Cl co-transport and role of urea).

Regulation of tubular water permeability by ADH (i.e. antidiuretic hormone, vasopressin) to concentrate urine (site and mechanism of action)

Role of the vasa recta in counter-current exchange.

Renal V2 receptors (vasopressin2 receptors – cAMP); aquaporins.
V1 receptors (IP_3, DAG) in blood vessels.
Diabetes insipidus: Central and nephrogenic.
Effect of ADH/vasopressin on urea permeability in the inner-medullary collecting duct.

11.3.5 DRUGS AND THE KIDNEY

11.3.5.1 Loop diuretics *(e.g. furosemide)*

Mechanism of action: Inhibition of the NaK2Cl transporter in the thick ascending limb disrupts the osmotic gradient needed for urine concentration.

Secretion of furosemide by the proximal convoluted tubule, and acts on the loop of Henle from within the lumen.
Inhibition of tubulo-glomerular feedback, via *macula densa* cell inhibition.
Treatment of oedema e.g. in congestive heart failure.

Adverse effects: e.g. K^+ loss, hypokalaemia and volume depletion.

Peripheral vasodilator effects.

11.3.5.2 Thiazide diuretics *(e.g. bendroflumethiazide)*

Mechanism of action: Inhibition of NaCl transporter in the distal tubule.
Comparison with loop diuretics: Less potent, smaller loss of K^+.

Treatment of hypertension and oedematous conditions.
Can precipitate gout through competitive inhibition of uric acid excretion.

11.3.5.3 Osmotic diuretics *(e.g. mannitol)*

Mechanism of action: Osmotic activity in tubule diminishes fluid reabsorption.

Treatment of cerebral oedema and prophylaxis of acute renal failure: adverse effects: e.g. volume-overload.

11.3.5.4 Potassium- sparing diuretics

Aldosterone antagonists e.g. spironolactone.

Adverse effects: e.g. hyperkalaemia.

Inhibitors of the epithelial Na^+ channel in the collecting duct e.g. amiloride.

11.3.5.5 Carbonic anhydrase inhibition *(e.g. acetazolamide)*

Mechanism of action: Inhibition of bicarbonate reabsorption in the proximal tubule.

Acetazolamide not considered useful as a diuretic but used to treat glaucoma and as prophylaxis against mountain sickness.
Adverse effect: e.g. hypokalaemia and acidosis.

11.4 BLADDER CONTROL AND URINARY CONTINENCE [P&P]

Nervous control of bladder (parasympathetic) and of internal and external urethral sphincters (sympathetic and voluntary control: see **6.2.2**).

Muscarinic antagonists for incontinence due to overactive bladder.

α_1-antagonists for outflow obstruction.

12. BODY FLUIDS [P&P]

12.1 VOLUME, ELECTROLYTE COMPOSITION, OSMOLARITY

Body fluid compartments and their volumes:
- Total body water.
- Extracellular fluid 'ECF' (plasma and interstitial fluid).
- Intracellular fluid 'ICF'.
- Transcellular fluid e.g. exocrine secretions into gut *(and, for study in the second year eg, cerebrospinal fluid and intra-ocular fluid)*

Measurement of the volumes of body fluid compartments.

Approximate normal daily intake and loss of water.

Electrolytes. Reference values in ECF for the concentrations of sodium, chloride, bicarbonate, potassium, calcium, and for pH. Approximate intracellular values for sodium, potassium, calcium and pH

Approximate normal daily intake and loss of sodium and potassium.

Serum osmolarity and its determinants.

Causes and consequences of water and electrolyte depletion (e.g. diarrhoea).

Causes of salt and water overload (e.g. iatrogenic fluid overload, drugs).

12.3 ACID–BASE BALANCE

12.3.1 MAINTENANCE OF INTRACELLULAR AND EXTRACELLULAR PH

Definition of pH as $-\log_{10}[H^+]$. Normal arterial $[H^+]$ = 40 nM and pH of 7.4.

Importance of the maintenance of constant intracellular and extracellular pH.

The Henderson-Hasselbalch equation (see **8.3.6**)

Three lines of defence against acidosis/alkalosis:
(i) buffers; (ii) ventilatory mechanisms; (iii) renal mechanisms

Concept of a buffer.

Main intracellular and extracellular buffers.

Role of Na^+-H^+ exchange, HCO_3^- transporters, and other membrane transporters (e.g. H^+-ATPase) in controlling intracellular pH with respect to extracellular pH.

12.3.2 RENAL CONTRIBUTION TO ACID-BASE BALANCE

Renal regulation of plasma HCO_3^- concentration by:

(a) reabsorption of filtered HCO_3^-.

(b) generation of new HCO_3^-.

(c) distal tubular secretion of HCO_3^-.

Sites, mechanism and regulation of H^+ secretion and HCO_3^- re-absorption/secretion.

Urinary buffers (e.g. phosphate).

Adaptive changes (e.g. in NH_4 synthesis) to maintain acid-base balance.

Concept of $[Cl^-]$ playing a role in determining HCO_3^- concentrations (this will be explored in the second-year course).

Metabolic acidosis in chronic renal failure.

Clinical usefulness of adjusting urinary pH to hasten drug excretion e.g. alkalinise the urine to remove salicylate from the body.

13. REPRODUCTIVE SYSTEM [OB]

Reproductive function is covered in the second year Applied Physiology and Pharmacology course.
For perineum and pelvic cavity (see **11.1.1)**.

13.1 REPRODUCTIVE SYSTEM

13.1.1 REPRODUCTIVE TRACT DIFFERENTIATION AND DEVELOPMENT

Source and migration of primordial germ cells.

Teratoma.

Role of the Y-chromosome and SRY gene in sex determination.

Formation of female and male gonads; intermediate mesoderm forms genital ridge; gonad “migration” – the gubernaculum.

Maldescent of testis.
Torsion of ovary, ovarian cysts.

Mesonephric (Wolffian) and paramesonephric (Mullerian) ducts.
Formation of female and male internal reproductive tracts and external genitalia.

Imperforate hymen, recto-vaginal fistula.

Effects of androgens and of Müllerian inhibiting factor (MIF) on sexual differentiation (e.g. testosterone on mesonephric duct, dihydrotestosterone on external genitalia, MIF on paramesonephric ducts).

Genetic disorders affecting sexual differentiation.
Testicular femininisation syndrome.
5-α-reductase deficiency.
Absence of Müllerian inhibiting factor.

13.1.2 MALE URO-GENITAL SYSTEM

Testis in scrotum, seminiferous tubules, vasa efferentia, epididymis, vas deferens passage through inguinal canal.
Arterial supply, testicular artery from aorta, and venous drainage of testis (to IVC.
Control of testis temperature; dartos and cremaster muscles.

Pampiniform plexus of testicular veins;
Torsion of testis, torsion of appendix of testis.

Dual function of the testis: production of gametes and sex hormones.
Spermatogenesis: Spermatogonium to spermatid; the significance of meiosis; maturation of spermatids to produce spermatozoa.
Functions of Leydig cells (androgen synthesis) and Sertoli cells (support function, blood-testis barrier). Control of testis function by gonadotrophins Luteinising Hormone and Follicle Stimulating Hormone (LH, FSH) and testosterone (see **14.2.2.3**).
Gonadal hormone feedback to pituitary, hypothalamus.

Infertility caused by abnormalities of sperm.

Prostate, seminal vesicles, common ejaculatory duct; relations to pelvic peritoneum.
Functions of the epididymis in sperm maturation, and seminal vesicles and prostate as sources of seminal fluid components.

Penis - erectile tissue; corpus spongiosum and cavernosum; urethra; prostatic, membranous and penile

Effects of testosterone on genital tract, secondary sexual characteristics.

Neural control of sexual function: erection parasympathetic; emission sympathetic; ejaculation somatic.

Non-cholinergic non-adrenergic innervation of erection. Erectile dysfunction, sildenafil (viagra); priapism.

13.1.3 FEMALE URO-GENITAL SYSTEM

Ovary: Intraperitoneal position on posterior aspect of broad ligament.
Fallopian tubes, fibria.
Uterus: Body, fundus, cervix. Vagina
Relation to peritoneum; broad 'ligament'. Pelvic floor and supports of uterus and cervix.
Arterial supply and venous drainage of ovary: Ovarian artery from aorta, drainage to IVC.
Arterial supply and venous drainage of uterus: Internal iliac artery and vein.

Anastomotic arterial supply to uterus.

Dual function of the ovary: Production of gametes and sex hormones.
Maturation of primordial follicles to pre-ovulatory follicles; follicle 'rescue', selection, atresia.
Functions of granulosa and theca interna cells.
Control of ovarian function by gonadotrophins (LH, FSH) and estrogen. (see **14.2.2.3**).
The hypothalamo-pituitary axis; Puberty. Endocrine control of menstrual cycle; gonadal hormone feedback (see **14.2.2.3**).

The ovum and its covering layers at ovulation; process of ovulation.
Formation of corpus luteum; secretion of progesterone, estrogen; luteolysis.
Oogenesis:
Primary oocytes arrest in prophase I during fetal life, build up stores of RNA and protein and then rest until puberty.
After puberty, in each cycle cohorts of oocytes mature by completing meiosis I (giving one secondary oocyte and a polar body and reach metaphase II); ovulation occurs. Meiosis II (with the production of another polar body) is completed on fertilisation.

13.2 HISTOLOGY OF THE REPRODUCTIVE TRACT

Testis: Germinal epithelium; Sertoli cells, stages of development of the male germ cells; interstitial (Leydig) cells.
Structure of epididymis; seminal vesicles and prostate.

Ovary: Ovarian follicles in various developmental stages: primordial, antral, pre-ovulatory, atretic.
Theca interna and externa; granulosa cells; oocyte and zona pellucida; corpus luteum.

Corona radiata.

Corpus albicans.

Fallopian tube: Epithelium and muscle coat.

Uterus: Myometrium, endometrium in different stages of the menstrual cycle - endometrial glands, spiral arteries, endometrial stroma. (see also **14.2.2.3**)
Cervix and vagina.
Correlation of the structure of the female tract with the endocrinological status.

14. ENDOCRINOLOGY

Note that the details of hypothalamic control of the pituitary and integrative aspects of endocrine systems in whole body homeostatic mechanisms are examined after further study in the second-year course 'Applied Physiology and Pharmacology'. In the first year you will be examined, as set out in his section, on the structure and function of the endocrine glands and in the principle actions of their hormones**.**

14.1 PRINCIPLES OF ENDOCRINOLOGY [OB, P&P, BIOCH]

These principles (section 14.1) are relevant to all three first year courses: by its nature, Endocrinology is interdisciplinary. Note that structure is neither taught nor examined separately from function. Examining of Endocrinology has been allocated, where possible, to individual subject papers**.**

14.1.1 PRINCIPLES OF HORMONE ACTION

For any particular hormone, you will be expected to know:

The chemical class & broad structure; site and mechanism of production & release.
Stimuli that cause or inhibit its release; pattern of secretion into the blood/extracellular fluid.
Mechanism of transport in the blood/extracellular fluid (general principles of half-life, distribution and clearance (see **4**).
Distant action: Endocrine (or local action: Paracrine and autocrine).
Principal target tissue(s) & receptors; mechanism of action in target tissue(s) (see **4.2**).
Principal effects of normal hormone levels, excess and deficiency and hormone resistance in target.

Some specific endocrine disorders are suggested for further study.
*Endocrine tumours; multiple endocrine neoplasia MEN1, MEN2 (see **3.8.2**).*

14.1.2 MAIN REGULATORY ROLES OF HORMONES

Homeostasis, including anticipatory responses; stress responses.
Control of reproduction.
Development, growth and differentiation.

14.1.3 CHARACTERISTICS OF MAIN CLASSES OF HORMONE

Hormones synthesized and stored in endocrine glands: Protein, peptide, bioactive amine, steroid, thyroid.
Structure of cells that synthesize and store these hormones.
Order of normal concentration in plasma: Protein and polypeptide hormones, typically nanomolar; steroids, typically sub-micromolar.
Secretion may be in pulses, rhythms (diurnal, reproductive).
Hormones produced enzymatically as they are needed: Prostaglandins; nitric oxide (see **8.6.5**); angiotensin II (see **11.3.3**).

Methods of assay: distinction between free and total (including protein bound) hormone.

14.2 PITUITARY [OB]

14.2.1 COMPONENTS OF PITUITARY [OB]

Development of pituitary gland.

Gross and microscopic structure of pituitary and component parts:
Adenohypophysis, neurohypophysis.

Adenohypophysis: Anterior part — Tuberal and intermediate (vestigial) parts. Folliculo-stellate cells.

endocrine cells: Thyrotrophs, corticotrophs, gonadotrophs, lactotrophs, and somatotrophs.

control of adenohypophysis:
(a) by CNS: Neurosecretion of specific releasing factors from hypothalamus via hypothalamo-hypophysial portal vessels;
(b) by negative feedback of target hormones at pituitary and hypothalamic levels.

Tumours of the adenohypophysis: local and systemic effects.

Neurohypophysis: Nerve endings of hypothalamic neurosecretory neurons. — Concept of neurosecretion.

14.2.2 HORMONES OF THE ADENOHYPOPHYSIS [OB]

Symptoms of excess or insufficiency mostly resemble those of over- or under-activity of the target endocrine organs

14.2.2.1 TSH = thyroid stimulating hormone (thyrotrophin) (from thyrotroph cells)

Glycoprotein. — Two subunits: α common to TSH, LH, FSH; β specific.

Promotes thyroid gland growth and synthesis and secretion of thyroid hormones. — Acts by raising cAMP in thyroid; effects on various aspects of thyroid gland metabolism.

Negative feedback by T3 and T4; hypothalamic control. — Danger of withdrawal of thyroid hormone therapy.

Released in pulses: Diurnal rhythm.

14.2.2.2 ACTH = corticotrophin (from corticotroph cells)

Polypeptide. — Produced by cleavage from a protein precursor (pro-opiomelanocortin 'POMC').

Promotes adrenal cortical steroid secretion and growth. — Acts by raising cAMP in adrenal cortex.

increases mostly glucocorticoid production (some increase in adrenal sex steroids).

Negative feedback by glucocorticoids; hypothalamic control (hypoglycaemia, stress); released in pulses: diurnal rhythm. — Danger of sudden withdrawal of glucocorticoid therapy.

Nelson's syndrome increased pigmentation (melanocyte stimulation by high ACTH).

14.2.2.3 LH = luteinising hormone; FSH = follicle-stimulating hormone (gonadotrophins from gonadotroph cells)

Both are glycoproteins.

Actions on ovary in female:
FSH stimulates follicle development and ovulation.
LH stimulates progesterone production.

Actions on testis in male:
FSH acts to initiate and maintain spermatogenesis.
LH stimulates secretion of testosterone.

Released in pulses: Hypothalamic control and feedback from gonadal hormones.

Cyclical variation in LH and FSH in menstrual cycle.

Infertility, precocious puberty as examples of abnormal secretion.

Both act by raising cAMP.

14.2.2.4 Prolactin = mammotrophin (from lactotroph cells)

Protein.

Promotes growth and development of breast and milk production.

Control: Only pituitary hormone whose principal control is inhibition by the hypothalamus.

Inhibitory to gonads; lactational amenorrhoea.

Receptor - tyrosine kinase.

Inhibition of release is by DA.

Prolactinomas. Dopamine agonists (e.g. bromocryptine) suppress lactation.

14.2.2.5 Growth hormone = somatotrophin (STH: somatotroph cells)

Protein.

Actions on growth: Direct and indirect via IGFs; metabolic actions.

Release (pulsatile) controlled via hypothalamus by metabolites; stress, sleep, exercise.

Short or excess stature resulting from abnormal juvenile secretion.

Acromegaly resulting from increased adult secretion; diabetes insipidus.

Receptor - tyrosine kinase.

Wide-ranging metabolic effects - promotes protein synthesis, but raises blood glucose.

14.2.3 HORMONES OF THE NEUROHYPOPHYSIS [OB; P&P]

14.2.3.1 Antidiuretic hormone (ADH) = vasopressin *[OB; P&P]*

Affects body fluid volume and osmolarity by regulating water reabsorption in the kidney (see **11.3.4**).

Diabetes insipidus: Hypothalamic and nephrogenic types.

14.2.3.2 Oxytocin [OB]

Role in parturition, milk-ejection.

Role in social and parental behaviour.

14.3 THYROID GLAND AND IODOTHYRONINES, CALCITONIN [OB]

Development, gross and microscopic structure of thyroid; vasculature; colloid.

Structure of thyroid hormones.

Synthesis and storage of thyroglobulin, secretion of thyroid hormones; iodine economy of the thyroid; action of TSH.

Plasma transport, long half-lives of T4, T3.

Peripheral metabolism of T4 to T3 and rT3 by liver, kidney; clearance of iodothyronines.

Different deiodinases; interactions with autonomic nervous system; *euthyroid sick syndrome.*

T3 as the metabolically active hormone; T3 receptors.

Action on gene transcription by intracellular receptor.

Actions of T3 on basal metabolic rate (protein, carbohydrate & lipid metabolism), development and growth.

Catabolic versus anabolic effects; negative feedback of T3, T4 on pituitary and hypothalamus.

Control: TSH, iodide.

Excess – thyrotoxicosis; deficiency - cretinism, myxoedema.
Thyroid enlargement (goitre), Thyroid resistance.

Calcitonin production by parafollicular C cells.

Lack of endocrine effect of calcitonin secreting tumours (see year 2).

14.4 PARATHYROID GLANDS

Note (calcium regulation is dealt with primarily in Applied Physiology & Pharmacology in year 2; see **14.8**).

Development of superior and inferior parathyroid glands; relation to thymus.

Secretion of parathyroid hormone in response to low plasma calcium.

Effects of parathyroid hormone-secreting tumours.

14.5 ADRENAL GLAND [OB; P&P]

Development of cortex and medulla; fetal zone of cortex.

Gross and microscopic structure of adrenal cortex and medulla; vasculature, innervation.

14.5.1 ADRENAL MEDULLA

Catecholamine receptors and their distribution in tissues (see **6.4.4.2**).

Actions on cardiovascular system, respiratory system, gastrointestinal tract, metabolism (see appropriate sections). Mediation of effects: cAMP, or IP_3/calcium (see **4.2.3**).

Control by autonomic nervous system.

Pheochromocytoma.

14.5.2 ADRENAL CORTEX

14.5.2.1 General principles

Synthesis of glucocorticoids and mineralocorticoids from cholesterol (details not needed).
Steroid action: Intracellular receptor controls gene transcription.
Plasma transport of corticosteroids; clearance by liver.

Inherited disorders of steroid synthesis (general principles).
Congenital adrenal hyperplasia.

14.5.2.2 Cortisol

Widespread action on many tissues: Induces enzymes, favours fat mobilisation, protein catabolism, gluconeogenesis (i.e. opposes insulin).
Adrenal insufficiency (Addison's) and excess (Cushing's).
Immunosuppression (at therapeutic doses).

Other effects:

some mineralocorticoid effect (adverse effects of therapy).

14.5.2.3 Aldosterone

See **11.3.3.**

14.5.2.4 Adrenal androgens

At most times a very minor component of secretion.

Route for synthesis of sex steroids: Action of adrenal androgens in fetus and at puberty.
Adrenal sex steroid production in inherited disorders.

14.6 ENDOCRINE PANCREAS [OB; BIOCH]

Development and microscopic structure of islets of Langerhans (see **15.7**)

Blood and nerve supply of islets.

14.6.1 INSULIN

Metabolic effects of insulin and diabetes mellitus see also Biochemistry (**10.3**)

A protein synthesized in β-cells.

Synthesis as proinsulin with C-peptide.
Receptor: Tyrosine-kinase.

Secretion stimulated by: Raised blood glucose, amino acids, hormones e.g. GLP (glucagon-like peptide - sensitises β-cells to glucose), nervous inputs.

Mechanism of stimulus-secretion coupling: Role of ATP-inhibited K^+ channels; action of sulphonylureas.
GIP: Glucose-dependent insulinotrophic peptide hormone secreted by cells in small intestine in response to glucose - sensitises β-cells to glucose.

Widespread actions to promote anabolism; lowers raised plasma glucose.
Diabetes mellitus: Type I and type II.
Treatment of type I and type II diabetes: Diet; insulin; sulphonylureas.

+ other type II diabetic drugs.

Islet transplantation; thiazolidinediones ('glitazones').

14.6.2 GLUCAGON

Metabolic effects of glucagon to be examined in more detail in Biochemistry (see **2.2.6; 2.3.4; 2.3.5)**

Polypeptide hormone synthesized in α-cells.
Released in response to hypoglycaemia.
Acts on liver via cAMP to promote glycogenolysis and gluconeogenesis.
Synergism of actions with catecholamines, glucocorticoids, growth hormone.

Somatostatin, pancreatic polypeptide.

14.6.3 SOMATOSTATIN

Paracrine peptide produced in δ-cells; inhibits insulin release.

Negative paracrine modulator in the gut, salivary glands and pituitary.

14.6.4 ENDOCRINE TUMOURS OF PANCREAS

Effects of insulinoma (rare).

Multiple endocrine neoplasia.

14.7 GASTROINTESTINAL HORMONES [OB; P&P]

Endocrine cells scattered in gut epithelium sense contents of lumen
Peptide hormones released by exocytosis.
Integrated role of gut endocrine and nervous systems to control motor, digestive, vascular activity of gut.
Concept of two families of gut hormones:
Gastrin-like (includes CCK).
Secretin-like (includes glucagon).

Origin of gut endocrine cells from endoderm.

gastrin-like hormones act via intracellular calcium.
secretin-like hormones act via cAMP.

14.7.1 GASTRIN

Produced in gastric antrum.
Stimuli for gastrin secretion; H^+ negative feedback.
Actions: Pepsin secretion; gastric acid secretion (see **9.5.3.1**).

Gastrinoma (ectopic gastrin production - no feedback from stomach acid to limit gastrin secretion: Zollinger-Ellison syndrome.
Pancreatic gastrinoma much more common than gastric gastrinoma

14.7.2 HISTAMINE

Secreted by ECL cells of stomach in response to stretch or vagal stimulation.
Paracrine action to stimulate gastric acid via H2 receptors on oxyntic cells (see **9.5.3.1**).

14.7.3 CCK (CHOLECYSTOKININ = PANCREOZYMIN)

Produced in duodenum and jejunum.
Stimuli for secretion: Protein and fat products in duodenum.

Actions: Stimulation pancreatic enzyme secretion and gall bladder contraction.

14.7.4 SECRETIN

Produced from duodenum to ileum.
Stimuli for secretion: Acid in duodenum.
Actions: Stimulation of HCO_3^- secretion from pancreas and liver.

Action of secretin via cAMP and CFTR on Cl^- conductance stimulates Cl^-/HCO_3^- exchange.

14.7.5 OTHER GASTROINTESTINAL HORMONES

Somatostatin (see **14.6.3**). Pancreatic polypeptide.
Ghrelin – produced by stomach – released in fasting to stimulate appetite
PYY (peptide YY) released by small bowel when food is present to inhibit feeding (NB control of appetite is covered in the second year).
Motilin, vasoactive intestinal peptide, neurotensin.

14.8 HORMONES INFLUENCING CALCIUM, PHOSPHATE, BONE [OB]

These are dealt with briefly in the first year in terms of their actions on bones (see **5.2)**. They will be studied in detail in the second year in the context of the integrated regulation of body calcium.

14.9 OTHER HORMONES

14.9.1 KIDNEY

Erythropoietin: stimulates erythropoiesis in response to hypoxia or anaemia
Renin-angiotensin-aldosterone system. [P&P see **11.3.3**]

Erythropoietin replacement therapy (and dialysis) needed after severe renal damage; EPO abuse by athletes.

14.9.2 HEART [P&P]

Atrial natriuretic peptide (ANP)
Produced in atrial myocytes, released by atrial distension
Reduces salt and water content of body (see **11.3.2**)

14.9.4 EICOSANOIDS: PROSTAGLANDINS, PROSTACYCLIN, THROMBOXANES

Widespread production from arachidonic acid; different types.
Roles: e.g. prostaglandins and contraction of uterus (see **14.3.3**), prostacyclin and vasodilation.
Prostaglandin synthesis inhibitors e.g. aspirin.

15. EMBRYONIC DEVELOPMENT [OB]

Subjects for study are chosen to provide (i) an essential understanding of the principles of developmental biology, (ii) a background with which to understand some congenital abnormalities (including genetic and non-genetic conditions), and (iii) a knowledge of the embryonic origins of adult gross anatomy. Key developmental principles to be covered include: multipotentiality and restriction of potential; inductive tissue interactions; the concept of organisers, signalling centres, and pattern formation.

15.1 DEVELOPMENT OF EMBRYONIC AND EXTRA-EMBRYONIC STRUCTURES, AND IMPLANTATION

(see **1.10**; **1.11)**

Zygote, cleavage of blastomeres, totipotency, formation of blastocyst (inner cell mass and trophoblast). Implantation, bilaminar germ disc (epiblast and hypoblast). Amniotic cavity & amnion. Formation of placenta; components of cord.

Specific maternal and paternal contributions to development.

15.2 FORMATION OF THE BASIC BODY PLAN

Axis/primitive streak formation, gastrulation, tissue interactions leading to formation of definitive germ layers (ectoderm, mesoderm, endoderm), from the epiblast; formation and derivatives of the notochord, somites, intermediate and lateral plate mesoderm.
Somites -sclerotome, dermatome, myotome and their derivatives.
Role of somites in body segmentation.
Teratogenesis, sensitive periods.
Asymmetric body plan – *situs inversus.*

Hemivertebrae.
Kyphoscoliosis.

15.3 MORPHOGENESIS AND INITIATION OF THE ORGANS

Embryonic folding, formation of the gut foregut, midgut, hindgut and coelomic cavities pericardial, pleural, peritoneal cavities; septum transversum formation of the diaphragm; formation of lung buds (see also **8.2.4**).

Diaphragmatic hernia, oesophageal atresia/tracheo-oesophageal fistula

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15.4 DEVELOPMENT OF THE NERVOUS SYSTEM

Formation of nervous system from neuroectoderm.
Neurulation, neural patterning and segmentation, neural crest.
Origins of somatic sensory (Dorsal Root Ganglia and cranial ganglia) and motor neurons (ventral horn spinal cord and cranial nerve nuclei).
Role of somites in segmentation of peripheral nervous system.
Neural crest derivatives Dorsal Root Ganglia; Autonomic ganglia; Cranial nerve ganglia; Enteric nervous system; Schwann cells.
Neural tube closure defects e.g. *spina bifida*

15.5 LIMB DEVELOPMENT: AN ILLUSTRATION OF KEY PRINCIPLES AND CONCEPTS

Induction of limb buds at specific axial levels; outgrowth and patterning in proximo-distal, anteroposterior and dorsoventral axes. Apical ectodermal ridge (AER), Zone of polarising activity (ZPA), dorsal ectoderm.

Development of long bones: Endochondrial ossification; epiphyseal plate organisation; control of cell proliferation; local and endocrine.
Abnormalities of long bone growth *dwarfism, giantism.*
Migration of myotome into the limb to form muscles.
Segmental innervation of skin and muscles (see **15.4**).

Polydactyly, syndactyly.
Thalidomide.
FGFs in control of limb development; Shh from ZPA as morphogen; hox genes and limb patterning.

15.6 DEVELOPMENT OF THE CARDIOVASCULAR SYSTEM

15.6.1 THE EARLY HEART TUBE & CONNECTIONS TO DORSAL AORTA

Formation and fusion of left and right heart tubes.
Structure of early heart tube; myoepicardium, cardiac jelly, endocardium.
Asymmetric morphogenesis to form atria, ventricles, conus cordis, truncus arteriosus.
Onset of contractile activity.
Aortic arches joining truncus to dorsal aorta.

Hand 1/Hand 2 expression and left right asymmetry in heart development

15.6.2 DEVELOPMENT OF THE FETAL AND POSTNATAL HEART AND CIRCULATION

Development of the endocardial cushions
Septation of the atria septa and foramina.
Septation of the ventricles and outflow tract; the role of haemodynamic forces, deformability of the heart wall and cell proliferation
Development of the venous system: Bias of venous inflow into the right atrium prior to septation
The definitive fetal circulation and changes at birth
Congenital abnormalities of the heart, especially septation defects eg Tetralogy of Fallot

15.7 DEVELOPMENT OF THE GUT AND ASSOCIATED STRUCTURES

The endodermal epithelial lining of the gut and its derivatives.
Buccopharyngeal and anal membranes.
Septum transversum formation of diaphragm. *Hiatus hernia.*
Foregut/midgut/hindgut formation and their blood supply.
Stomach and liver expansion. *Pyloric stenosis.*

Atresia and diverticuli of the gut; *Meckel's diverticulum*.
Bi-lobular pancreas.

Greater and lesser sac.

Gut diverticula undergo branching morphogenesis to form liver, pancreas (and lungs - see **8.2.4**). Pancreas dorsal and ventral buds; rotation. *Annular pancreas.*
Rotation and fixation of the gut in relation to peritoneum.
Epithelial-mesenchymal interactions leading to region-specific differentiation and morphogenesis of the gut wall;
Neural crest origin of enteric neurons. *Hirschsprung's disease.*
Spleen from mesoderm only.

15.8 DEVELOPMENT OF THE URINARY SYSTEM

Formation of definitive kidney from metanephros of intermediate mesoderm.
Formation of metanephros (the definitive mammalian kidney) from ureteric bud and surrounding mesenchyme.
Branching of ureteric bud to form ureter, pelvis, major and minor calyces, collecting tubules.
"Ascent" of kidneys.
Formation of bladder from caudal ends of mesonephric ducts, lower allantois, urogenital sinus.
Wilm's tumour.

Pronephros, mesonephros, metanephros form from intermediate mesoderm in craniocaudal sequence.
Congenital abnormalities including polycystic kidney, oligohydramnios, hydronephrosis, kidney agenesis, horseshoe kidney.

Urachus.

15.9 DEVELOPMENT OF THE GENITAL SYSTEM

See **13.1.1** Reproductive tract differentiation and development.

15.10 DEVELOPMENT OF HEAD AND NECK

Cranial neurulation and neural crest migration.
The embryonic pharynx: Pharyngeal (branchial arches), pouches and clefts, and their derivatives.
The nerves, muscles, arteries and skeletal elements of each arch.
1st arch: Trigeminal nerve; muscles of mastication; maxilla and mandible, malleus and incus.
2nd arch: Facial nerve; muscles of facial expression; styloid process, stapes.
3rd arch: Glossopharyngeal nerve; stylopharyngeal muscle; hyoid bone.
4th arch: Vagus nerve; pharyngeal and laryngeal muscles; laryngeal cartilages.
Development of the facial processes and secondary palate.
Clefts of lip, palate and face; DiGeorge syndrome.

(Development of the eye and ear are studied in the second year).
Branchial cysts and fistulae.
Hox genes and patterning of rhombomeres and pharyngeal arches.

44. BLOOD [OB, BIOCH]

44.1 BLOOD CELLS

You should know the roles and normal abundance of erythrocytes, neutrophils, eosinophils, basophils, monocytes, lymphocytes and platelets; and the appearance of these cells in blood films. See normal physiological values.

44.1.1 RED BLOOD CELLS: ERYTHROCYTES

Shape, size and contents of erythrocytes in relation to their function in oxygen and carbon-dioxide transport.

Deformability for passage through capillaries; role in anomalous viscosity of blood.

Erythrocyte cytoskeleton. Crenated erythrocytes.

Normal turnover time 120 days.

Recognition and destruction of 'aged' erythrocytes by macrophages in the spleen.

Anaemia through insufficiency of iron, or vitamins (folate, or vitamin B12).

Pernicious anaemia in the elderly through lack of intrinsic factor.

Use of exogenous EPO.

Megaloblastic anaemia in folate deficiency.

Blood groups Abo and Rh systems.

Bone marrow hyperplasia e.g. in response to prolonged hypoxia, or haemolytic anaemia. (see **44.2.1.3** Iron transport and storage).

Changes in erythrocyte characteristics in globin diseases *e.g. sickle-cell anaemia* (see **8.3.5**).

Role of folate and B12 in erythropoiesis.

44.1.2 WHITE BLOOD CELLS: LEUCOCYTES

44.1.2.1 Granulocytes

Neutrophils (PMNs; polymorphonuclear leucocytes, 'polymorphs').

Reserve stores, growth factors specific for each type of leucocyte.

Increased production in acute bacterial infection.

Adhere to vascular endothelium and migrate into tissues at sites of acute inflammation (details of inflammation in second year).

Phagocytic: Ingest, kill and digest micro-organisms, particularly bacteria. form pus (see **44.2.4.1**).

How to measure neutrophil turnover in vivo. Factors affecting neutrophil abundance and turnover.

Eosinophils

Increased production in chronic allergic conditions or parasitic infection.

May protect against damaging effects of long-standing allergic reactions.

Basophils

Granules contain vasoactive substances including histamine.

Related to tissue mast cells which release histamine (increases blood flow and vascular permeability) in one type of allergic response (details in second year).

44.1.2.2 Monocytes

Blood cells that can give rise by migration into tissues to *macrophages.*

Note that in many tissues, resident macrophages (e.g. Kupffer cells in liver (see **9.4.2**), Langerhan's cells in skin (see **5.3**),) are probably seeded in development and replaced by proliferation in tissues.

Macrophages phagocytose and kill organisms; remove tissue debris (they secrete enzymes e.g. collagenase) allowing effective repair; and are involved in tissue homeostasis and remodelling – they phagocytose apoptotic bodies.

Macrophages may cause tissue damage known as 'chronic inflammation' e.g. in TB (details in second year).

44.1.2.3 Lymphocytes

Stem cells in bone marrow, primary development along two lineages, 'B' cells and 'T' cells. 'T cells' mature in thymus, self-sustaining in the periphery.

Key experiments showing the presence of haematopoietic stem cells in bone marrow (Till & McCullogh and others).

Proliferate in secondary lymphoid organs - lymph nodes, Peyer's patches and spleen (details of production in immune response in second year).

'B cells' e.g. mature into antibody producing cells, plasma cells (see **44.2.4.1**).

'T cells' play a role in regulating the immune response, or else act to kill cells directly (e.g. virus infected cells).

Third type of lymphocyte: Natural Killer (anti-viral and anti-tumour roles).

Small lymphocytes: Quiescent, non-dividing, awaiting activation by antigens.
Re-circulate continuously through tissues by migration through post-capillary venules and via tissue-fluid, lymphatics and lymph nodes back into the blood, thus monitor tissues for presence of antigens.
Respond to specific antigens (presented by antigen-presenting cells) by mounting a specific immune response.

Large lymphocytes (lymphoblasts): Activated, dividing, developing to effector cells.

Immunological memory resides in lymphocytes.

44.1.3 HAEMOPOIETIC STEM CELLS (see **1.11.2**)

As classic example of well-studied cellular differentiation lineage.

Markers of differentiation: Proteins (e.g. cell surface markers); mRNA (= cDNA) profiles.

Specialised protein synthesis, e.g. globin, immunoglobulin.

Self-renewal of stem cells in adult red bone marrow.

Sensitivity to ionising radiation and to cytotoxic drugs, e.g. those used in chemotherapy of cancer.

Experimental basis of determination of haemopoietic function.

44.2 PLASMA PROTEINS

44.2.1 GENERAL FUNCTIONS OF PLASMA PROTEINS IN OSMOTIC BALANCE BETWEEN CIRCULATION AND INTERSTITIAL COMPARTMENTS, TRANSPORT, DEFENCE, HAEMOSTASIS.

44.2.1.1 Albumin

Significance in osmotic balance between vascular and interstitial compartments; origins of oedema and ascites as signs of severe (usually chronic) liver disease.

Role in transport of hormones, fatty acids and drugs.

Example of another transport protein: Transferrin (see **44.2.1.3**)

Oedema of malnutrition.

44.2.1.2 Catabolism of Haem

Origin from red cells; conversion to bilirubin; transport to liver bound to albumin; conjugation in liver to render it water-soluble; excretion of bilirubin.

Competition with drugs for binding sites on albumin.

Bacterial metabolism of gut bilirubin to urobilinogen; some oxidized to urobilins.

Significance of colour of faeces and urine in bile-duct obstruction (see **9.4.1**).

Jaundice as a sign of hyperbilirubinaemia.

Significance of conjugated and unconjugated bilirubin in liver function tests in investigation of causes of jaundice.

Common causes of elevated levels of conjugated and unconjugated bilirubin.

Toxicity of bilirubin.

Kernicterus. Effects of light on bilirubin: significance for phototherapy of neonatal jaundice.

44.2.1.3 Transferrin, Ferritin and Iron Homeostasis

Iron: major roles of iron in the body, including haemoglobin. Size of dietary intake and absorption in relation to whole body stores. Hepcidin and the iron cycle (see **2.6.2.1**).

Control of absorption at gut mucosal cells; loss of iron via menstruation and cell shedding from gut and skin.

Consequences of iron deficiency.

(Iron Homeostasis covered in second year)

Causes of iron deficiency.

44.2.1.4 Vitamin-K-dependent clotting factors

Proteases that, when activated, act on one another sequentially: Ultimate product is insoluble fibrin.
Action of these and other plasma proteases is inhibited by other proteins produced in the liver e.g. the protease inhibitor a-1-antitrypsin.
See also 'Haemostasis' (see **44.2.3**).

Identity: Prothrombin (Factor II), and Factors VII, IX, X.
Significance of clotting defects in liver disease.
γ-carboxyglutamate residues:
role in metal-ion binding
made by a vitamin K-dependent post-translational modification of clotting factors.
Inhibition of that process by coumarin anticoagulants.

44.2.1.5 Serum anti-proteases.

α1-antitrypsin and defence against lung damage.

44.2.2 LIPOPROTEINS

Lipoproteins as transport vehicles for lipids: Major lipoprotein fractions.

Metabolism (origin and fate) of chylomicrons, VLDL, LDL and HDL.

The LDL receptor and its regulation.

Examples of single-gene inherited dyslipidaemias: Familial hypercholesterolaemia, type I hyperlipoproteinaemia.
Possible significance of HMG CoA reductase in atherosclerosis; inhibition of cholesterol synthesis in the management of atherosclerosis.
Treatment of inherited dyslipidaemias.

44.2.3 HAEMOSTASIS

Haemostasis:
Vasospasm; formation of haemostatic plug by platelets
coagulation of the blood; subsequent clot resolution and repair.
Structure of vessel walls (see **8.5.2**).
Platelets:
Granule constituents (ADP and 5-HT).
Aggregation and degranulation functions in haemostasis: Vasoconstriction, platelet plug, activation of fibrin deposition (stabilises plug), initiation of vascular and other repair processes (PDGF).
Blood coagulation: Clotting cascade and its control.
Extrinsic and intrinsic pathways, major coagulation factors (tissue factor, factor VIII, prothrombin, fibrinogen). Vitamin K-dependent clotting factors (see **44.2.1.4**).
Fibrinolysis and role of plasmin. *Haemophilia*

44.2.4 ANTIBODIES AND COMPLEMENT

44.2.4.1 Antibodies: Immunoglobulins

Produced by plasma cells (which differentiate from B lymphocytes (see **44.1.2.3**).
Plasma cells derive clonally from a lymphocyte and produce an antibody recognising a specific antigen characteristic for that lymphocyte. Plasma cells as sites of immunoglobulin synthesis in gut, mammary gland, lymphoid organs & bone marrow.
Role of antibodies:
- Bind to microorganisms and prevent their entry into body/cells.
- Bind to organisms and bind also to phagocytes.
- Assists phagocytosis ('opsonisation') and activates phagocytes neutralise bacterial toxins.
- On binding to antigen activates complement and induces inflammation.
- Membrane-bound form as receptor for antigen on B lymphocytes.

Antibody (i.e. immunoglobulin) structure: Glycoproteins; molecular size in relation to distribution in body fluids; heavy and light chains.
Variable and constant regions: Fab region; the Fc region.
Classes of immunoglobulins, the number of binding sites they have for antigen.
Secreted and cell surface forms of antibody.
Antibody function:
Antigen binding region (Fab) for specificity.
Fc region:
- Complement activation.
- Binding to receptors on various cell types, e.g: to macrophages and neutrophils, triggers phagocytosis (opsonisation) and activation.
- Mast cells (IgE), triggers degranulation.
- Epithelial cells for trans epithelial secretion: IgA into tears, saliva, colostrum, the gut, etc. IgG across the placenta.

Turnover time of immunoglobulins as plasma proteins. Relationship to neonatal protection by maternal antibody.

44.2.4.2 Complement

System of neutral proteinases secreted into plasma by the liver (also by macrophages).
Cascade activated by immunoglobulin (IgG or IgM) associated with its antigen (classical pathway).
Cascade activated by C3 ‘tick over (alternative pathway).
Cascade activated by (Mannose binding lectin MBL pathway).
Feed-forward amplification, control by inhibitors.

Physiological outcomes of complement activation:
i) Opsonisation of particles for phagocytosis.
ii) C5a as a chemoattractant.
iii) Membrane attack Complex (MAC).

46. POPULATION HEALTH 1: INTRODUCTION TO MEDICAL SOCIOLOGY [MS]

Further information on this course of eight lectures is posted on Canvas giving details of the key topics covered in the lectures and suggestions for a limited amount of related reading. The most useful single text is a concise paperback: "Sociology as Applied to Health and Medicine" Ed. Graham Scambler; 7th edition, Palgrave, Macmillan Publishers Limited, London, 2018 ISBN 978-1-137-57738 (hardback) and 978-1-137-55737-5 (paperback). The course will be introduced with four lectures in Hilary Term, and you are advised to do some work on the references over the Easter vacation. The course, which concludes in Trinity Term, is designed to be done without tutorials.

46.1 DEFINITIONS OF HEALTH AND ILLNESS

Models of health and illness; Medical; Patient-centred; Social.
The clinical iceberg
Iatrogenesis.
Feminist criticism of the (bio)medical model.
Social constructivism, health and medicine.

46.2 SOCIAL CLASS, GENDER AND HEALTH

Definitions of social class (Registrar General occupational classification, Office National Statistics-Socio-Economic Classification)
Distribution of wealth across social class explanations and effects. Status syndrome (Marmot)
Self-reported health and social class
Life events, social support, social class and health
Gender differences in life expectancy; exercise and diet; smoking; self-reported health
Inequalities in health care provision and use of services between men and women
Black Report; Whitehall studies.
Marx and Weber on social class.
Homelessness and health.
Artefact/Social selection/Cultural-Behavioural/Materialist.
Effects of unemployment on health.

46.3 CHANGING PATTERNS OF DISEASE AND THE ROLE OF MEDICINE

Life expectancy since the mid-19th century
Variations in disease prevalence in the UK since the industrial revolution
Causes of disease and reasons for changes in the patterns of health and disease in the UK
Impact of COVID-19 on patterns of disease
Variations in health cross-culturally.
McKeown and the impact of medicine on health.
Criticisms of McKeown.

46.4 PATIENT REPORTED OUTCOMES AND EXPERIENCES

Patient reported outcome measures (PROMs) and carer outcome measures
Patient reported experience of health care
Quality of life as a multidimensional concept; Quality adjusted life yearsUnidimensional and multi-dimensional measures of outcome
Generic and disease specific measures; validity; reliability; sensitivity to change
Translation and cross-cultural adaptation of measures.
SF-36, EuroQol and disease specific measures (e.g. PDQ-39, AIMS).
Value of patient-reported outcomes and experiences

46.5 ETHNICITY AND HEALTH

Race and ethnicity; variations in: Morbidity and mortality; patterns of illness and disease.
Explanations for variations in health/illness across ethnic groups: Genetic; Biological; Behavioural Cultural; Material and Structural factors;
Self-reported health across ethnic groups.
COVID-19 in different ethnic groups

46.6 AGEING AND HEALTH

Life expectancy in the UK
Population changes due to ageing; disability across age groups; mental health; use of services; polypharmacy.
Theories of aging and health: Role; Disengagement; Structured dependency; Third Age
Cultures of ageing.
Moody's four scenarios.
Role of informal carers
Multi-morbidity.

46.7 ILLNESS BEHAVIOUR AND THE EFFECTS OF ILLNESS ON PATIENTS

Bury's distinction between health as an attribute and as a relation
Distinction between; health, illness and disease
Quah's distinction between: Preventive, Illness, and Sick role behaviour
Symptoms and illness behaviour; Stigma and disease; Lay referral and "triggers"
Doctor-patient communication; types of medical consultation

46.8 HEALTH POLICY: HEALTH CARE PROVISION AND THE NHS

Foundations; structure and recent changes in the NHS.
Provision of social care: integration of health and social care
Patient and public involvement: Patient choice.
Health care provision in the UK prior to the NHS.
Variations in structure, evaluation and financing of health-care systems.
Sustainability of health care

47. MEDICAL STATISTICS

Medical statistics is taught in years one and two as a series of workshops. These constitute part of the practical requirements for BM: all medical students are required to attend these workshops. The aim of these workshops is for students to become familiar with statistical concepts relating to the analysis of Normally Distributed data. Techniques relevant to the analysis of other types of data will be introduced during the second year. The statistical concepts to be covered are basic and count as core material that may be needed in the compulsory questions in Part A examinations. Likewise, essay questions may be set that require a knowledge of the syllabus below.

47.1 DESCRIPTIVE STATISTICS

Types of data: Binary, categorical, continuous.
Types of variable: Continuous, discrete, dependent, independent.
Summary statistics: Means, medians, proportions and standard deviations.
Sampling theory: Population vs. sample, frequency distributions.
Principles of graph and table construction.

47.2 THE NORMAL DISTRIBUTION

The Normal curve from continuous data.
Estimation including mean, standard deviation and normal range, standard error and confidence intervals.
Inability of the normal distribution to describe all continuous data.

47.3 STATISTICAL INFERENCE

This section refers exclusively to work with 'large' samples. For instance: for statistical significance, the z-test, *not the t-test*, is included.
Sample statistics and population parameters.
Distribution of the means of repeated random samples from the same population (i.e. sampling distribution of a mean).
Sampling distribution of the difference between two means: standard errors of means.

47.3.1 ESTIMATION

Confidence intervals for a single mean and the difference between two means.

47.3.2 HYPOTHESIS TESTS

The null hypothesis. The test statistic. The p-value.
Test of statistical significance for comparing two means ('z-test' for large samples: **Not** the t-test for smaller samples).
Assumptions of methods.

47.4 TWO-SAMPLE ANALYSES

Hypothesis testing and confidence intervals for unpaired and paired normal data.
Chi-squared for proportions.
Link between estimation and hypothesis testing.

47.5 DICHOTOMOUS DATA

Binomial distribution.
Sampling distribution of proportions including large sample approximations.
Confidence intervals and hypothesis testing.

47.6 RELATING TWO VARIABLES

Parametric and non-parametric measures of correlation.