FIRST BM PART II: SECOND YEAR SYLLABUS FOR MEDICAL STUDENTS 2025-26

Content and role of the syllabus
The second year of the medical course should be an intellectual step up from first year. Like any syllabus, this syllabus 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 a list of topics to be learned. As in the Year 1 syllabus, the left-hand side defines the 'core' that will be covered in university teaching (lectures, seminars and practical classes) and on which you will be required to answer questions in the MCQ component (Section 1) of the examination paper for subjects 1-3. The topics listed on the right 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 essay component (Section 2) of the examination paper for subjects 1-3 will be based on both parts of the syllabus; and you will have a choice of essay questions to answer. Essays in the second year should reflect the intellectual step up and greater reading of review and primary literature. Psychology for Medicine will be taught in 14 lectures in Hilary Term: your College is expected to provide TWO tutorials for this paper. There will be a take-home assignment to examine this subject. A synoptic paper inviting discussion from material taught in both years of the BM course and covered in different subjects will be set.

Definition of the scope of the courses
The syllabus has been set out in four main sections corresponding to the four courses and examinations. There is an additional section on medical statistics. Do remember, however, that in some areas such a division must be artificial and notice especially the cross-referencing between sections. This is perhaps especially the case in the Applied Physiology and Pharmacology course, in which you are encouraged to integrate very broadly across disciplines and also for Psychology for Medicine, which has clear synergy with the Neuroscience course. Remember also that, though the examinations will specifically address just this second-year syllabus, all subjects taught in the second year assume and necessarily build upon relevant core knowledge of related topics taught in the first year.

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.

Experimental evidence and clinical significance
Credit will be given in the Part B essay papers and in the Psychology for Medicine paper, for appropriate reference to experimental evidence and points of clinical significance.

Clinical conditions
Where appropriate, reference is made to clinical conditions that illustrate the science (often indicated by italics.) You are not expected at this stage to learn clinical details, but should try to understand the basis for the conditions and their treatment in the context of the underlying science you study. You can very easily read more about any clinical condition that interests you by consulting, for instance, the Oxford Textbook of Medicine:
http://oxfordmedicine.com/view/10.1093/med/9780199204854.001.1/med-9780199204854.
Try 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. One of the aims of Learning from Patients course is to help relate basic science to clinical practice.

Objectives of the Second Year of the BM Course

Aims

- To equip students with a comprehensive knowledge and a critical appreciation of the material contained in the core syllabus
- To provide students with a broader understanding of the context of the material covered.
- To instil in students the ability to appraise the robustness of scientific and clinical evidence and to recognise the strengths and weaknesses of alternative theories and scientific approaches.
- To give students opportunities to learn, understand and practise the professional behaviours expected of them.

Outcomes
By the end of your Second Year, you should have a sound appreciation of the material summarised by the core syllabus, and be able to

- Apply knowledge gained in the First BM Part I course.
- Organise the material to produce written summaries with relevant content.
- Solve problems using experimental evidence and clinical context.
- Display professional behaviours in all aspects of their studies.

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 EC: 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 'normal' values in a healthy young adult of certain physiologically important parameters for different areas of the syllabus. You will be expected to know these 'normal; values for examinations as being familiar with these is essential for your understanding of the core material. The 'normal range' is also shown in ( ) but you **will not** be expected to know these ranges for examinations.

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
P_aO_2	90 mm Hg [12 kPa] (range 80-100 mmHg [11 - 13 kPa])	Resting cardiac output	5 L/min
P_aCO_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
Urine osmolarity	30 - 1200 mOsM	Normal heart rate (at rest)	60-100 bpm

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	$\sim 7 \times 10^{9}$	100%
neutrophils		40-70%
lymphocytes		20-40%
monocytes		~6%
eosinophils		~3%
basophils		<1%
Platelets	$150\text{-}400 \times 10^{9}$	

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

It is important that students are familiar with the classes of drugs (e.g. vasodilators, cannabinoids) 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 class**. 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. It should be noted that some drugs included here are used experimentally rather than therapeutically.

Drug	Chapter
acetazolamide	53.3
aciclovir	35.6.4.1
adrenaline	39.1.1 & 54.1
aminophylline	54.1
amitriptyline	25.1.2
amlodipine	52.4
amoxicillin	33.2.2
aspirin	20.2.2, 31.5.4, 41.5 & 53.4
atenolol	52.4
atracurium	54.2
atropine	54.2
beclomethasone	54.1
bendroflumethiazide *	52.4
benzylpenicillin	33.2.2
bupivacaine	54.2
buspirone	25.1.3
carbamazepine	19.6.1
chloroquine	36
chloramphenicol	33.2.2
chlorpheniramine	31.5.3
chlorpromazine	25.2.2
ciprofloxacin	33.2.2
cisplatin	43.4.1
clozapine	25.2.2
codeine	20.2.2
cromoglicate	39.1.1
cyclopentolate	16.5.2.4
cyclophosphamide	43.4.1

Drug	Chapter
dexamethasone	31.5.2 & 53.3
diazepam	24.2
digoxin	52.4
doxazosin	52.4
doxorubicin	43.4.1
erythromycin	33.2.2 & 33.2.4
flucloxacillin	33.2.2
fluoxetine	25.1.2
furosemide *	20.4.2 & 52.4
gentamicin	20.4.2 & 33.2.2
glyceryl trinitrate	52.4
glycopyrrolate	54.2
haloperidol	25.2.2
heparin	41.5
ibuprofen	20.2.2 & 54.2
imatinib	43.4.1 & 43.4.2
ipratropium	54.1
isoflurane	24.2 & 54.2
isoniazid	33.2.2
l-dopa	21.4.2
lamotrignine	19.6.1
lidocaine*	54.2
lithium	25.1.2
losartan	52.4
maraviroc	35..6.4
methotrexate	43.4.1
morphine	54.2
NSAIDs	20.2.2 & 31.5.1

Drug	Chapter
naloxone	54.2
neostigmine	54.2
nicotine	25.5.2
nifedipine	52.4 & 53.3
ondansetron	54.2
oseltamivir	35.6.4
paracetamol	31.5.1
penicillin	33.2.2 & 33.2.4
phenelzine	25.1.2
phenylephrine	54.2
phenytoin	19.6.1
prazosin	52.4
propofol	24.2 & 54.2
propranolol	25.1.3 & 52.4
raltegravir	35.6.4
ramipril	52.4
rifampicin	33.2.2
salbutamol	51.2 & 54.1
saquinavir	35.6.4.1
sevoflurane	54.2
simvastatin	41.5
spironolactone	52.4
streptokinase	41.5
streptomycin	33.2.2
sumatriptan	20.2.2
suxamethonium	54.2
tamoxifen	43.4.2
temazepam	24.2 & 54.2

Drug	Chapter
tetrabenazine	21.4.2
tetracycline	33.2.2
tramadol	20.2.2
trastuzumab	43.4.2
trimethoprim	33.2.2
valproate	19.6.1
venlafaxine	25.1.2
vincristine	43.4.1
warfarin	41.5
zanamivir	35.6.6
zidovudine	35.6.4.1

* First Year Syllabus drugs referenced from within the BMII syllabus

SECOND-YEAR BM SYLLABUS: SUMMARY OF CONTENTS

THE NERVOUS SYSTEM

16. HEAD & NECK

For the second year, knowledge of the core features of the skull, as in the first year, will be expected; particular attention should be paid to bony relations of the CNS, including the orbit and ear.

16.2 OSTEOLOGY

16.2.1 SKULL

16.2.1.2 Bones

Identification on a skull or plain radiograph and as surface landmarks (where appropriate) of the following bones: Ethmoid, frontal, occipital, parietal, temporal, zygomatic.

The following structures: External acoustic meatus, squamous and petrous parts of the temporal bone, greater and lesser wings of the sphenoid, cribriform plate, clinoid processes; and the pituitary fossa, and anterior, middle and posterior cranial fossa.

Air sinuses: Frontal, sphenoid, ethmoid, maxillary; mastoid air cells.

16.2.1.3 Cranial nerve foramina

Identification on a skull or plain radiograph or CT scan of the following foramina, and a knowledge of their principal contents:
rotundum (maxillary trigeminal); ovale (mandibular trigeminal, V):
spinosum (middle meningeal artery); jugular foramen (glossopharyngeal, IX, vagus, X, spinal accessory, XI + internal jugular vein); foramen magnum (spinal cord & vertebral arteries); carotid canal and foramen lacerum (internal carotid artery); stylomastoid foramen (facial, VII); hypoglossal canal (hypoglossal, XII); optic foramen (optic, II & ophthalmic artery); superior orbital fissure (oculomotor, III, trochlear, IV, abducens, VI, ophthalmic trigeminal, V); internal acoustic meatus (facial, VII, vestibular-cochlear, VIII & labyrinthine artery).

16.2.1.4 Meninges

Dura mater, arachnoid mater and pia mater.
Relationships of dura to skull and vertebral canal.
Dural folds: Falx, tentorium and falx cerebelli.
Relationship of dura to major blood vessels.
Innervation of dura by cranial nerves (see **22.1.4, 22.1.7**).
Subarachnoid space and CSF cisterns.

16.4 BLOOD SUPPLY

16.4.1 ARTERIAL SUPPLY

16.4.1.2 Arterial supply to central nervous system, related meninges and soft tissues

To be able to identify the following major vessels on angiograms and on wet specimens, to describe their course and to relate this to the functional areas and fibre tracts they supply, and the deficits caused by occlusion of main vessels.

Common carotid, external carotid, middle meningeal, internal carotid; anterior, middle and posterior cerebral; ophthalmic; vertebral (and its subclavian origin), basilar; anterior and posterior perforating; striate; pontine; posterior inferior cerebellar; anterior and posterior spinal; reinforcement of spinal supply (artery of Adamkiewitz).

Circle of Willis

Stroke; effects of blockage of major arteries.

Arterial anastomoses.

Anterior inferior cerebellar artery; choroidal arteries.

Berry aneurysms.

thrombolytic therapy.

Types of stroke; excitotoxic damage.

Important relations of arteries:

Circle of Willis - *subarachnoid haemorrhage.*

Middle meningeal artery to pterion - *extradural haemorrhage.*

Internal carotid artery to middle ear, cavernous sinus.

16.4.1.3 Extracranial vasculature of head and neck

Palpation points & surface markings: Carotid; facial, superficial temporal, identification on a prosection or angiogram, and an understanding of the functional area supplied by the arteries; identification of visible veins in the living and of all major veins on prosections; understanding of the lymphatic drainage and main groups of nodes.

Arteries:

Common carotid artery – carotid pulse; division into internal and external carotid.

External carotid artery - superior thyroid, facial, lingual, maxillary, (branches of maxillary not 'core' except middle meningeal); middle meningeal relation to pterion - extradural haemorrhage.

Subclavian artery - vertebral artery, inferior thyroid artery; branches to neck and chest (internal thoracic); inferior thyroid relation to recurrent laryngeal branches of vagus.

Pulses: Carotid in neck; facial over jaw; superficial temporal over zygomatic process

Veins:

Deep veins: internal jugular, subclavian.
Superficial veins: external & anterior jugular.
Relation of veins to fascial compartment of neck.
Access to subclavian and jugular veins for central lines. Jugular venous pulse.
Lymphatics:
Lymphatics follow internal jugular (deep), anterior & external jugular (superficial) forming cervical trunks; drainage left into end of thoracic duct.
Lymph node groups. Superficial: submental, submandibular, parotid, mastoid, occipital. Deep: upper and lower deep cervical.
Lingual and palatine tonsils; retropharyngeal lymphatic tissue, adenoids.
Lymphatic drainage of tongue.

16.4.2 VENOUS DRAINAGE

16.4.2.5 Venous drainage of the brain

Superior sagittal sinus, great cerebral vein, transverse and cavernous sinuses; sigmoid sinus; internal jugular vein.

Inferior sagittal sinus; inferior petrosal sinus.
Venous haemorrhages; sub-dural space.

16.5 SPECIAL AREAS

16.5.2 ORBIT AND EYE

16.5.2.1 Orbit and associated structures

Attachments and function of external ocular muscles, suspensory ligament of the eyeball.
Skeletal framework of the orbit; structure of the eyelids.
Lacrimation reflex: Afferent - ophthalmic trigeminal (V) efferent - parasympathetic facial (VII), pterygopalatine ganglion

Emotional stimuli.

Lacrimal gland, nasolacrimal duct.
Levator palpebrae: Innervation by oculomotor (III) and by sympathetic fibres.
Ptosis: failure of sympathetic or oculomotor nerve (III).
Lesions of sympathetic supply (Horner's syndrome).

Carcinoma of apex of lung (Pancoast's tumour).

Blink reflex: Afferent - ophthalmic (V); efferent - facial to orbicularis oculi.

16.5.2.2 Development of the Eye

Development of the retina as an outgrowth of the forebrain.

16.5.2.3 Gross Morphology of the Eyeball

Cornea, sclera, conjunctiva; iris, pupil, retina, optic disc, fovea, central artery of the retina; lens, ciliary body, suspensory ligaments, ciliary muscles, anterior and posterior chambers, ciliary processes, canal of Schlemm, optic nerve, lamina cribrosa.	Ciliary nerves and arteries.
Disorders of the lens*: Cataract.*	
Optic nerve and its surrounding extension of subarachnoid space (see **22.1.2**); ocular signs of raised intracranial pressure; *papilloedema, dilated retinal veins.*	
Aqueous humour: Drainage; *raised intraocular pressure, glaucoma.*	'open' and 'closed' glaucoma.
Ophthalmoscopy: Appearance of the normal retina; *papilloedema.*	*Common abnormalities - diabetic retinopathy, abnormal blood vessels.*

16.5.2.4 Internal muscles of the eye

Functions and innervation of ciliary muscles, and of dilator and sphincter pupillae. Pupillary reflexes (see **21.7**).	
Drugs used to dilate pupil eg α-muscarinics; cyclopentolate (especially in paediatrics).	

*16.5.2.5 Oculomotor (III), Trochlear (IV) and Abducens (VI) Nerves; Movements of the Eye (*see **21.6***).*

16.5.4 THE EAR

16.5.4.2 Functional anatomy of the ear

External ear: Pinna, tragus, external auditory meatus, tympanic membrane.	Features of tympanic membrane visible on examination.
Innervation of external auditory meatus by trigeminal (V) and vagus (X), with facial (VII) contributing at the tympanic membrane.	Wax production and removal. *Perforated eardrum*.
	Sound conditioning: role in monaural sound localization.
	Referred pain in ear from e.g. sore throat.
	Vomiting and cardiac depression with syringing of external meatus (vagus X nerve stimulation).
	Ramsay-Hunt syndrome (herpes zoster of geniculate ganglion).
Middle ear:	Innervation: Middle ear and pharyngotympanic tube: Glossopharyngeal (IX) (tympanic branch); tympanic plexus.
Ossicles - malleus, incus, stapes.	
Function of auditory ossicles: impedance matching.	
Muscles:	
Stapedius muscle; innervation by facial nerve (VII); tensor tympani muscle; innervation by trigeminal nerve (V).	
Pharyngotympanic tube.	
Round and oval windows.	
Hyperacusis from facial (VII) nerve damage; Otitis media.	
Inner ear:	*Tinnitus, vertigo.*

Within petrous temporal bone, internal acoustic meatus; cochlea, cochlear nerve, spiral ganglion (see **20.4.2; 20.4.4**).
Vestibular apparatus: Semi-circular canals, utricle and saccule (see **20.5**).

Connections between perilymph and CSF.

16.6 NECK ANATOMY

Surface landmarks: hyoid (body, greater horn), thyroid, cricoid; external occipital protuberance; spine C7 (vertebra prominens).
Anterior and posterior triangles: boundaries, main contents.
Fascial compartments: investing, prevertebral fascia, carotid sheath, pretracheal fascia.
Main muscle groups: sternomastoid, trapezius; scalenes; strap muscles (not individually).
Principal vessels: carotid arteries; jugular veins; jugular venous pulse
Principal nerves:
Vagus (X) in carotid sheath: pharyngeal, laryngeal branches.
Accessory (XI) under the roof of posterior triangle: sternomastoid, trapezius.
Phrenic (C3,4,5) running down over scalenus anterior and into chest: diaphragm, covering pleura and peritoneum.
Cervical plexus - C1-C4 to vertebral & strap muscles; C2-C4 to neck skin (not individual nerves).
Sympathetic chain on prevertebral fascia; inferior, middle, superior cervical ganglia.

17. EMBRYONIC DEVELOPMENT

17.1 DEVELOPMENT OF THE CNS

Neuroectodermal origins of neural and glial cells, basal (motor) and alar (sensory) plates; neural crest and its derivatives; no mitosis of mature neurons; sites of adult neurogenesis (sub-ventricular zone, dentate gyrus).

Regions of the developing CNS and formation of adult brain structures (forebrain = telencephalon & diencephalon, midbrain, hindbrain, spinal cord).

General understanding of CNS patterning, cortex, hindbrain, spinal cord.

Neural tube formation, expansion of the telencephalon.

Abnormalities: *spina bifida.*

General understanding of cell migration and the process of axon outgrowth and formation of neural connections (see **24.6)**.

Role of neural cell death and growth factors (see **19.4**).

Neural cell determination.
Cell migration defects; heterotopias, dysplasias.

Flexures of the developing brain.
Anencephaly.

Neurodevelopmental cognitive disorders: schizophrenia (see **25.2.1**)*, autism, ADHD, dyslexia, childhood epilepsy.*

18. CNS MORPHOLOGY

18.1 CNS COMPARTMENTS

18.1.1 BLOOD-BRAIN BARRIER (BBB)

Homeostasis of the internal environment of the brain – role of endothelial cells; astrocyte induction.
Selective transport through barrier; significance for drugs, infection, immune system.
Ventricular system and ependymal glia lining ventricles.
Choroid plexus.

Chemical and physical interruption of receptor-mediated transport across blood-brain barrier.
Areas lacking blood-brain barrier in CNS (see **23.3.1**).

Brain barrier functions in the embryo, fetus and new-born. e.g. Changes in permeability with regard to CSF composition, infection, immunity.

18.1.2 CEREBRO-SPINAL FLUID

Production (choroid plexus), composition relative to plasma, and absorption via arachnoid granulations.
Circulation: cerebral ventricles: lateral ventricles, third ventricle, aqueduct and fourth ventricle, spinal canal; subarachnoid space, CSF cisterns.
Relationships to structures in **18.2.1** and **18.2.2**.
Hydrocephalus.
Lumbar puncture and spinal anaesthesia (see **52.5**).

Named CSF cisterns: magna, interpeduncular, ambiens, pontine, lateral fissure, and superior.
CSF-vascular shunts.

18.2 NEUROANATOMY

Note: You should be able to identify major structures (set out below) on wet specimens and MRI scans, and major tracts on histological sections. You should know their major afferent and efferent connections, their function and the likely effects of a lesion.

18.2.1 FOREBRAIN

18.2.1.1 Cerebral Hemispheres

Lobes - frontal, parietal, occipital, temporal, insula.
Gyri - pre-central (M1), post-central (S1), insula, uncus, parahippocampal, hippocampal, dentate, cingulate, superior temporal (A1), orbitofrontal,
Wernicke's and Broca's areas, V1 on banks of post-calcarine sulcus.
Sulci: longitudinal (sagittal), lateral, central, parieto-occipital, calcarine and cingulate.
Tracts – internal capsule, optic radiation, cerebral peduncles.
Commissures: corpus callosum; anterior commissure.

Opercula.
Septum.

Developmental abnormalities: lissencephaly; polymicrogyria.

18.2.1.2 Basal Ganglia and Diencephalon

Component nuclei of the basal ganglia (see **21.4**)
Striatum: Caudate and putamen, globus pallidus internal and external, nucleus accumbens (see **25**), thalamus, hypothalamus, mammillary bodies, pineal, pituitary, (see **23**), amygdala (see **24**).

External capsule, claustrum.

18.2.2 *BRAINSTEM AND CEREBELLUM*

Medulla, pyramids, olive, pons, cerebellum, cerebellar peduncles, midbrain, cerebral peduncles, tectum (superior & inferior colliculi).

Tegmentum.

Brainstem nuclei:
Dorsal column nuclei, pontine nuclei, inferior olivary nuclei (olives).
Periaqueductal grey (pain control), locus coeruleus (Noradrenergic), Nucleus Raphe (5HT).

Brainstem cranial nerve nuclei: Location and function (see **22**).
Oculomotor (III), Edinger-Westphal (III parasympathetic); Trochlear (IV); Abducens (VI); Trigeminal (V; mesencephalic nucleus, principle sensory nucleus and spinal nucleus, motor nucleus); Facial (VII), Cochlear & Vestibular (VIII); Nucleus ambiguous; Nucleus solitarius; Vagal (X); Hypoglossal (XII).

Subdivisions of vestibular nuclei.

Tracts: corticospinal, corticobulbar, corticopontine, dorsal columns, internal arcuate/medial lemniscus, lateral lemniscus, anterolateral column (spinoreticular, spinomesencephalic, spinothalamic), medial longitudinal fasciculus, spino-cerebellar, ponto-cerebellar, superior cerebellar peduncle, spinal tract of the trigeminal; posterior commissure

Cerebellar hemispheres, vermis, flocculo-nodular lobe, superior, middle, inferior cerebellar peduncles; spinal/vestibular/cortical divisions; deep cerebellar nuclei (dentate, fastigial) (see **21.5**)

Tonsil, uvula, pyramids, nodule.
'Coning' with raised intracranial pressure; Chiari malformation.

18.2.3 SPINAL CORD

18.2.3.1 Gross Structure

Dura, arachnoid, sub-arachnoid space, pia.

Subarachnoid septum.

Dorsal and ventral roots, dorsal root ganglia, cauda equina, filum terminale. Lumbar and cervical enlargements; connections to sympathetic chain. Level of cord termination in adult and newborn.

Denticulate ligaments.
Radicular arteries and veins.

Subarachnoid space ends at S2.
Vessels: Anterior and postero-lateral spinal arteries; reinforcements (artery of Adamkiewitz).

18.2.3.2 Internal Organization

Dorsal horn: Posteromarginal zone (layer 1), substantia gelatinosa, main sensory nucleus.
Ventral horn: Motor pools (medial and lateral).
Lateral horn: Autonomic, thoracic nucleus (Clarke's column).
Fibre tracts and the consequences of lesions: Corticospinal; dorsal columns; anterolateral columns; spino-cerebellar; Lissauer's; vestibulo-spinal; reticulo-spinal.
Rubrospinal and tectospinal tracts.
Brown-Sequard syndrome; Syringomyelia; Tabes dorsalis.

Laminar organisation of dorsal horn.

Ventral lateral and dorsal spinal cord syndromes.

18.2.4 SPINAL NERVE EXIT FORAMINA AND INTERVERTEBRAL DISCS

Anatomy and MRI appearance of intervertebral exit space.
Consequences of compression of the spinal nerves and of cauda equina.
Spinal (subarachnoid) and epidural anaesthesia.

19. PRINCIPLES OF NEURONAL FUNCTION

19.1 METHODS OF STUDY OF THE NERVOUS SYSTEM

Basic histological techniques (Nissl for cell nuclei; Golgi for cell morphology; Weigert for axon tracts). Immunohistochemistry; in situ hybridisation.

Images obtained using different types of microscopy (eg light, fluorescence, electron microscopy).

CT, MRI, Functional MRI, PET, EEG. MEG and the information each can provide.

Recording methods in Electrophysiology; field; extracellular; intracellular; patch.

Reporter gene-expressing transgenic mice (eGFP, LacZ); tract-tracing techniques. Optogenetics. Designer drugs.

19.2 STRUCTURE AND FUNCTION OF NEURONS AND GLIA

Characteristic appearance and functions of projection neurons and interneurons and their neurotransmitters (see **19.5**).

Excitatory and inhibitory neurons:

Different sub-types including molecular identities, axonal projections and pharmacology.

Neuroglia: Appearance and function of:

Astrocytes, (ion homeostasis, neurotransmitter uptake, local control of blood flow, blood brain barrier, inhibitory role in CNS repair).

Oligodendrocytes (CNS myelination).

Microglia (macrophages of CNS).

Astrocyte involvement in CNS immune response and scar tissue formation

19.3 NEURONAL DISORDERS

Wallerian degeneration, demyelination.

CNS degenerative disorders e.g. *Alzheimer's, Parkinson's* (see **25.3.2; 21.4.3**).

Multiple sclerosis. Motor neuron disease.

Vincristine peripheral neuropathy as an example of a failure of the neuronal cytoskeleton.

19.4 NEURONAL REPAIR AND REGENERATION

Comparison of PNS and CNS regeneration; plasticity (see **24.6**).

Role of growth factors in neuronal survival and plasticity.

Cell therapy: possible application in Parkinson’s disease. Neural transplantation.

Factors affecting CNS regeneration: intrinsic (cell survival, axon regrowth and re-navigation) and extrinsic (glial inhibition, growth factors, microglia).

19.5 SYNAPTIC TRANSMISSION

Variety of neurotransmitters (including ACh, catecholamines, glutamate, GABA and glycine) and receptors.
Excitatory and inhibitory synapses.
EPSPs and IPSPs.
Concept of synaptic integration.
Pre-synaptic inhibition.
Concept of spatial and temporal summation.

Idealised model of a nerve cell (input and output regions; summing point).
Synaptic plasticity; facilitation and depression.
Electrical synapses, gap junctions.

19.5.1 CHEMICAL TRANSMISSION IN THE CNS

Chemical messengers; criteria to establish transmitters; fast & slow transmission.
Pre- and post-synaptic effects.

Concepts of neuromodulation and volume transmission.
Co-transmission. Endocannabinoids. Gases – nitric oxide.
Peptide neurotransmitters.

19.5.2 EXCITATORY TRANSMISSION IN THE CNS

Glutamate: sites of action and putative functions; glutamate receptors.
Differences between AMPA, NMDA, and metabotropic receptors (mGluR).

Molecular biology of receptors and channels.
Excitotoxicity in *stroke* and *ischaemia.*

19.5.3 INHIBITORY TRANSMISSION IN THE CNS

GABA: Synthesis and degradation. Drugs that inhibit GABA breakdown and drugs that mimic GABA actions.
Glycine and glycine receptors.
Mechanisms of action: GABA receptor A & B sub-types, ionotropic and metabotropic, chloride channels, hyperpolarization.
Action of benzodiazepines at $GABA_A$-receptor complex.

Effects of strychnine.

19.5.4 MONOAMINE TRANSMISSION

Noradrenaline (NA), dopamine (DA), serotonin (5HT).
Major sites of production locus coeruleus (NA) substantia nigra pars compacta/ventral tegmental area (DA), reticular formation, nucleus raphe (5HT).
Sites of drug action, receptor diversity and adaptation.

Monoamine receptor subtypes.

19.5.5 CHOLINERGIC TRANSMISSION

Choline acetyl transferase (ChAT) and acetyl choline metabolism.
Nicotinic and muscarinic receptors.
Acetylcholinesterase.

Subtypes of cholinergic receptors.
AChE inhibitors in *Alzheimer's disease.*

19.5.6 REGULATION OF RECEPTOR ACTION

Up- and down-regulation of receptor numbers, and receptor desensitisation, after chronic stimulation or blockade. Long-term potentiation/LTP, long-term depression/LTD (see **24.5**) *Tardive dyskinesia.*

Tachyphylaxis. Possible mechanisms: changes in receptor structure or affinity; second messengers.

19.6 EPILEPTIC DISCHARGES

Concept of epilepsy as uncontrolled excessive synchronisation of CNS activity.

Different forms of epileptic seizure. Causes of epilepsy.

19.6.1 ANTI-EPILEPTIC DRUGS

Pharmacological mechanisms for suppression of epileptic activity: Enhancement of GABA function, modulation of voltage-gated ion channels.

Status epilepticus (acute): Benzodiazepine, phenytoin.

Management of chronic epilepsy valproate, carbamazepine lamotrigine.

Newer anti-epileptics: gabapentin.

Use of carbamazepine in treatment of trigeminal neuralgia.

20. SENSORY SYSTEMS

20.1 SOMATOSENSORY PATHWAYS

20.1.1 RECEPTORS

Classification and morphology of receptors (mechano-, thermo-, noci-).
Types of sensory nerve endings in skin: Meissner, Ruffini, Merkel, Pacinian, free nerve endings, Muscle spindles and Golgi Tendon Organs (see **21.2**).
Mechanisms of sensory transduction and adaptation.
Classification and characteristics of nerve fibres (myelinated vs. unmyelinated).
Classification of conduction properties of nerve fibres A – C.
Sites of termination of peripheral dorsal root ganglion cell and cranial nerve sensory fibres in CNS and their transmitters (e.g. glutamate, substance P).
Dorsal horn laminae: Marginal zone, substantia gelatinosa, nucleus proprius.
Termination of primary sensory neurons.
Substantia gelatinosa, descending monaminergic control.

2-point discrimination.

Impulse generation and coding.

20.1.2 SPINAL PATHWAYS

20.1.2.1 Dorsal Column System

Modality and somatotopy (dorsal columns, dorsal column nuclei and ventro posterior lateral thalamus).
Sensory coding: Receptive fields and lateral inhibition in dorsal column nuclei.

Corticofugal control.

20.1.2.2 Anterolateral System

Dorsal horn laminae: termination of nociceptive sensory neurons; Lissauer's tract, marginal zone.
Concept of modulatory control in dorsal horn substantia gelatinosa e.g. Enkephalin and gate theory (see **20.2).**
Origin of anterolateral projection from main sensory nucleus of dorsal horn
Local crossing of fibres in anterior white commissure to form anterolateral system.
Spinoreticular, spinomesencephalic and spinothalamic projections.
Termination of nociceptive inputs in intralaminar nuclei of thalamus.
Inputs to insula cortex.

Ipsilateral component of nociceptive pathways.

20.1.2.3 Consequences of spinal cord lesions

Spinal nerve levels of dermatomes and basic reflexes (biceps C5; triceps C7; knee L3/4; ankle S1).
To be able to work out the level of a spinal cord lesion from the resultant symptoms and signs.
Systems affected by: *complete transection; Brown-Sequard; partial lesions at different levels; syringomyelia (see* **18.2.3.2***).*

20.1.2.4 Brainstem somatosensory pathways

Projection of dorsal columns to dorsal column nuclei.
Projection of dorsal column nuclei via medial lemniscus (crossed) to ventro-posterior (lateral) thalamus.
Trigeminal central pathways to ventro-posterior (medial) thalamus
Antero-lateral tracts to reticular formation, peri-aqueductal grey and thalamus.
Spino-cerebellar tracts.
Descending control systems to spinal cord.

20.1.3 SOMATOSENSORY CORTEX

Post-central gyrus S1 maps; somatotopic organization. Columnar organisation. Canonical cortical circuits (see **20.3.6**) *S1 lesions in humans*

Cortical processing. Stereognosis. S2. anisotropic maps of body representation.

Development and adult plasticity of S1. Phantom limb.

20.2 PAIN

20.2.1 ROLE AND NEUROPHYSIOLOGY

Protective function

Features of absence of pain perception.

Channels, receptors and transduction mechanisms of peripheral nociception.

Types of pain, possible correlation with fibre type.

Peripheral pathways.

Central pathways:
Dorsal horn circuits, enkephalin interneurons, descending control, periaqueductal grey (see **20.1.2.2**).

Central representation of pain; anterior cingulate gyrus.

Variability of pain perception: Hyperalgesia, psychological modulation of pain. Neuropathic pain.

Anatomical basis of ‘referred’ pain, location of referred pain from heart, fore, mid- and hind-gut.

Referred pain from other organs.

Trigeminal neuralgia and migraine as cranial nerve associated pain.

20.2.2 PAIN RELIEF

Analgesic drugs and techniques:
Peripherally-acting analgesics: aspirin and other NSAIDS (see **31.5.1**), local anaesthetics (mechanisms of action: first year); ibuprofen.
Centrally-acting analgesics: Opioids and their receptors (codeine; tramadol).
Anxiolytics in the management of pain.
For migraine, sumatriptan.

Transmitters in the pain pathway.
NK1 antagonists. Sub-classes of opiate receptor.
Acupuncture. Placebo effect.
Cannabinoids; Gabapentin.

20.3 VISION

20.3.1 STRUCTURE OF THE EYE
(see **16.5.2.3**)

20.3.2 HISTOLOGY AND PHYSIOLOGY OF THE RETINA

Functional histology of retina: Distribution of rods and cones.
Organisation and connectivity of the different classes of interneurons:
Bipolar, horizontal, and amacrine cells.
Ganglion cells as retinal output neurons.
Magnocellular and Parvocellular retinal ganglion cells.
Vascular supply to the retina.
Macular degeneration; diabetic retinopathy.

Müller glial cells.

20.3.3 VISUAL TRANSDUCTION

Visual pigments: Rhodopsin and opsins; *defects of colour vision.*
Visual transduction: Dark current, transducin cascade, light adaptation; release of glutamate.

20.3.4 RETINAL PROCESSING

Rods and cone connectivity to bipolar and horizontal cells.
Generation of centre/surround receptive fields by horizontal cells.
On and off bipolar cells and their glutamate receptors.

Computer assisted vision

20.3.5 VISUAL PATHWAYS

Optic nerve, partial decussation at optic chiasm, optic tracts; lateral geniculate nucleus; optic radiation.
Laminar organisation of the LGN
Functional parallel processing magnocellular and parvocellular pathways.
Other sub-cortical visual centres - superior colliculus (see **20.7.1**), suprachiasmatic nucleus (see **23.2.1**), pre-tectal nucleus (see **21.7**).
The consensual pupillary light reflex.
Relationship of chiasm to pituitary.
Effect of pituitary tumours – bi-temporal hemianopia.

Meyer's loop.

Lesions of LGN

20.3.6 VISUAL CORTEX

Striate cortex. V1. Columnar organization. Pinwheel structure of orientation columns, ocular dominance columns, colour blobs.
Two visual outflows: V4 to inferotemporal cortex for colour and pattern, visual agnosia; V5 to posterior parietal cortex for location and motion, space sense.
Effects of lesions (see **20.3.7**).
Development and plasticity of the visual system.
*Effects of amblyopia, strabismus on cortical development (see **24.6**).*

Effects of rearing in the dark.
Extra-geniculo-striate pathways. *'Blindsight'*. The "binding problem".

20.3.7 VISUAL FIELDS

Visual field representation from eye to cortex; consequences of lesions of optic nerve, optic chiasm, optic tract and visual cortex.
Visual field examination. Perimetry.
Binocular vision: Distance perception, disparity and stereopsis.
Macular sparing.

Field defects due to optic neuritis, retinal arterial emboli.

20.3.8 VISUAL FUNCTION: OPTICAL AND NEURAL DETERMINANTS

Bipolar and ganglion cell receptive fields; Centre-surround, colour opponency.
Acuity, intensity, wavelength discrimination.
Optics; refractive errors; myopia & hypermetropia, astigmatism, and their effects on visual performance; visual testing.
Effects on visual performance of glaucoma, cataract, macular degeneration.

Cortical determinants of acuity.

Diffraction. Emmetropization during development.
Optical and neural determinants of contrast sensitivity.

20.3.9 CONTROL OF EYE MOVEMENTS

Role of frontal eye fields, posterior parietal cortex, superior colliculus, vestibular nuclei (see **21.7**).

20.4 AUDITION

20.4.1 PERIPHERAL STRUCTURES (see **16.5.4.2**)

20.4.2 INNER EAR

Cochlea: Gross structure and histology. Scala media, scala vestibulae and scala tympani; Basilar membrane; tectorial membrane; stria vascularis.
Formation and composition of endolymph and perilymph.
Inner hair cells and transduction; tip-links. Outer hair cells as motors.
Drug-induced ototoxicity: e.g. gentamicin, furosemide, aspirin, quinine.

Olivocochlear bundle and centrifugal control.

20.4.3 AUDITORY FUNCTION

Audiometry. Frequency resolution, sound localisation (by binaural timing and intensity differences).
Conduction vs. neural deafness: tuning fork tests (Weber & Rinne)

Sound pressure level thresholds.
Monaural cues to sound localisation.
Deafness in ageing. Tinnitus.

20.4.4 AUDITORY PATHWAYS

Spiral ganglion, auditory nerve, dorsal and ventral cochlear nuclei, trapezoid body, superior olive medial and lateral, inferior colliculus, medial geniculate nucleus; superior temporal gyrus A1.
Tonotopicity, phase locking, cochlear (VIII) nerve tuning curves.
Binaural interaction in superior olivary nuclei for sound source localization.
Acoustic neuroma.

20.4.5 SPEECH AND LANGUAGE

Mechanisms of speech production (see first year syllabus **8.2.1)**
Speech perception.
Aphasias: Wernicke's area and sensory aphasia; Broca's area and motor aphasia. Hemispheric specialization.

Arcuate bundle.
Aphasia c.f. dysarthria.
Wernicke-Lichtheim model
Arcuate fasciculus and conduction aphasia

20.5 VESTIBULAR SYSTEM (see **16.5.4.2)**

Otoliths (linear acceleration, head position).
Semi-circular canals (angular acceleration).
Vestibular ganglion and nerve (VIII).
Vestibular pathways: Vestibular nuclei, vestibulo-spinal tracts.
Vestibulo-spinal reflexes.
Vestibulo-ocular reflex stabilises gaze.
Vestibular connections with cerebellum; flocculonodular lobe.

Mechanisms of vestibular transduction.

Cerebellar calibration.
Placing and neck reflexes.

20.5.1 DISORDERS OF EQUILIBRIUM

Vertigo, motion sickness, nystagmus.

Drugs for motion sickness: hyoscine, antihistamines.

20.6 SMELL AND TASTE

Olfactory system: Chemoreceptors in nasal mucosa, afferents olfactory (I) via cribriform plate; olfactory bulb, olfactory tract, primary olfactory cortex of temporal lobe, hypothalamus, secondary olfactory cortex (orbitofrontal) (see **22.1.1**)

Importance of smell to limbic system.
Genetics of olfactory and taste receptors.
Turnover of receptors and neurogenesis.

Taste system: Taste receptors, projections via facial (VII) and glossopharyngeal nerves (IX) to nucleus of the solitary tract, to the hypothalamus and orbitofrontal cortex.

Pleasant and unpleasant taste/odour zones in orbitofrontal cortex.

20.7 SENSORY INTEGRATION

20.7.1 AUDITORY-VISUAL INTEGRATION

Superior colliculus (auditory & visual interaction).

Organization: inputs, topography, multimodality. Development of maps.
Function: orientating eye (saccadic), head and body movements.

20.7.2 ASSOCIATION

20.7.2.1 Posterior parietal cortex

Inputs: visual, somaesthetic, auditory, motor, limbic; the “where” stream
Outputs: frontal cortex, basal ganglia, cerebellum.
Multimodal sensorimotor association area for direction of attention, movement, speech and reading.
Lesions give neglect syndromes and acquired dyslexias.

Superior parietal lobule; integration of sensory motor and motivational signals for representation of body image and "active touch".
Inferior parietal lobule; visual “where” and eye movement signals integrated for “active sight” and representation of visual space.
Hemispheric localisation and lesions:
Right hemisphere - visuo-spatial (lesion gives left neglect).
Left hemisphere - language and reading (lesion gives acquired dyslexia or apraxia).
Concerned with egocentric space (as opposed to the hippocampus which is concerned with allocentric space).

20.7.2.2 Prefrontal cortex

Reciprocal connections with limbic, visual systems and basal ganglia.
Functions: working memory, intention, decision.

Medial (orbitofrontal): receives limbic and visual "what" signals, assessment of significance.
Lateral: receives visual "where" signals, also input from basal ganglia, choice of behaviour.
Lesions: perseveration, indecisiveness, impulsiveness c.f. schizophrenia.

21. MOTOR SYSTEMS

21.1 LOWER MOTOR NEURON POOLS

Spinal motor neurons in ventral horn; neurotransmitter (ACh); peripheral myelinated axon.
Motor units: size principle, temporal and spatial facilitation, central pattern generator, reciprocal inhibition.
Lesions: flaccid paralysis and wasting as consequence of a *lower motor neuron lesion; fasciculation.*

Motor neuron disease; Spinal Muscular atrophy; Amyotrophic lateral sclerosis.

21.2 MUSCLE STRETCH REFLEX

Muscle spindles structure and function, primary and secondary spindle afferents; γ-efferent control (see **20.1.1**).
Golgi tendon organs structure and function (see **20.1.1**).
Contribution of spindle and joint receptors to position sense.
Reflexes: tendon jerk; monosynaptic component; tonic stretch reflex for posture; crossed extensor reflex.
Spinal interneurons (Ia & Ib inhibitory and Renshaw).
Spinal levels of major reflexes (see **20.1.2.3**).

Role of type II afferents.

21.3 UPPER MOTOR NEURONS

21.3.1 DESCENDING PATHWAYS TO SPINAL CORD

Functional anatomy of pathways to spinal cord: Origins, course and terminations.
Corticospinal, (motor and sensory components), vestibulospinal, reticulospinal, rubrospinal and tectospinal tracts.
Lateral and medial descending systems.
Effects of damage to descending tracts at different levels on voluntary movement, muscle tone, spinal reflexes; *'upper' and lower motor neuron lesions.*

Decerebrate preparation. Hemiplegia. Hemiparesis, paraplegia, spasticity, rigidity. Babinski response.

Effects of haemorrhage from thalamostriate and lenticulostriate arteries into internal capsule.
Spinal cord arterial syndromes.

21.3.2 CORTICAL CONTROL OF MOTOR ACTIVITY

Motor cortex (Area 4) – functional anatomy.
Principal inputs: Supplementary motor area, premotor and somatosensory cortex, ventral anterior and ventral lateral thalamus (from cerebellum and basal ganglia).

Principal outputs: Corticospinal tract, corticostriate (caudate and putamen), corticobulbar (pons, cranial nerve nuclei, colliculus, reticular formation, red nucleus).

Premotor cortical areas:

Premotor cortex (lateral area 6) for sensory guidance of movements and postural adjustments.

Supplementary motor cortex (area 6) for planning spontaneous and bimanual movements**.**

'Mirror neurons'.

21.4 BASAL GANGLIA

21.4.1 COMPONENTS, CONNECTIONS AND FUNCTIONS

Nuclei: Caudate & putamen (striatum); globus pallidus (internal & external); subthalamic nucleus; substantia nigra pars compacta, (dopaminergic cells) and pars reticulata (similarity to GPi) (see **18.2.1.2**).

Limbic components: ventral striatum and pallidum.

Subcortical loops via thalamus back to cortex and to brainstem via basal ganglia; Nigro-striatal pathway. *Degeneration in Parkinson's Disease*

Hyperdirect pathway. Critique of rate model**.**

Direct and indirect pathways. Effect on ventral anterior and ventral lateral thalamic nuclei. Disinhibition.

Functions: selection and control of expression and execution of internally generated motor programmes.

Function with limbic system: selection and control of expression of emotions.

21.4.2 NEUROTRANSMITTERS AND PHARMACOLOGY

Principle neurotransmitters:

Excitatory (glutamate) inputs from cerebral cortex to striatum, and from subthalamic nucleus to GPi.

Inhibitory (GABA) from striatum, GPe and GPi. *Degeneration of GABA neurons (striatopallidal) in Huntington's disease.*

Huntington's genetics

Dopaminergic from substantia nigra pars compacta to striatum activates direct and inhibits indirect pathways (D1 vs D2 receptors respectively). *Degeneration of nigrostriatal dopamine neurons in Parkinson's disease. MPTP.*

Cholinergic interneurons

Causes of Parkinson's disease: familial, genetic and sporadic.

Animal models of Parkinson's disease: 6-OHDA and other toxins, transgenic, viral and protofibril injections.

Pharmacology of Parkinson's disease: Disease treatment: Dopamine replacement therapy (L-DOPA plus DOPA decarboxylase inhibitor). Problems with L-DOPA e.g. on/off *dyskinesias*.

Other therapies: Deep Brain Stimulation, MAO/COMT inhibitors, other neurotransmitters, cell transplantation, symptomatic versus neuroprotective strategies.

Pharmacology of Huntington's disease (anti-dopaminergics e.g. tetrabenazine, neuroleptics, benzodiazapines).

Non-motor symptoms in PD.

Pathology: Lewy bodies; alpha-synuclein aggregation.

21.4.3 CONSEQUENCES OF DISORDERS

Hypo- or hyper-kinetic movement disorders.
Involuntary movements (e.g. tics, tremor, dystonia) or inability to make voluntary movements (e.g. akinesia, bradykinesia).
Parkinson's disease.
Huntington's disease: Chorea, impaired movements
Subthalamic lesions: Ballism.

*Dystonias; Tourette's; Obsessive-compulsive disorders; eating disorders (see **26.11**); addiction disorders (see **25.5**)*

21.5 CEREBELLUM

Functional subdivisions reflected in connectivity: Vestibulocerebellum (flocculonodular); spinocerebellum (vermis); pontocerebellum (hemispheres) (see **18.2.2**)
Cytoarchitecture: Three layers: molecular layer (parallel fibres), Purkinje cell layer, and granule cell layer.
Cell types: Purkinje, Golgi, granule, stellate and basket; Purkinje as sole output from cerebellar cortex to deep nuclei (GABA).
Inputs: Mossy fibres to granule cells and deep nuclei: pontocerebellar, spinocerebellar, vestibulocerebellar (simple spikes).
Climbing fibres from inferior olive to Purkinje cells and deep nuclei: (complex spikes).
Deep nuclei and outputs: Medial (fastigial nucleus) to vestibular and descending spinal systems; interposed (globose and emboliform nuclei) to red nucleus and descending spinal systems; lateral (dentate nucleus) to ventral anterior and ventral lateral thalamus, thence to motor and premotor cortex.
Function: Motor coordination: calibrating, learning and automating motor skills
Long-term depression of Purkinje cell synapses by climbing fibres.

Challenges to long-term depression for motor learning

Effects of lesions: *Incoordination, postural ataxia, intention tremor, nystagmus*

Causes of cerebellar lesions: Spinal cerebellar ataxia; Friedreich's ataxia; multiple sclerosis; tumours, ethanol; Fragile-X associated tremor/ataxia

21.6 LOCOMOTION

Walking: Brainstem and spinal pattern generators, proprioceptive feedback

Swing and stance phases.

Abnormal gaits: *Freezing and festination (i.e. small steps) in Parkinson's disease; limping in hemiplegia; abnormal gaits due to absent proprioception in syphilis (tabes dorsalis) and peripheral neuropathy.*

21.7 EYE MOVEMENT CONTROL AND PUPILLARY REFLEXES

Cranial nerves: Oculomotor (III), trochlear (IV), abducens (VI): Origins and course; consequences of lesions (see **18.2.2** and **22.1.3**).

Eye movements: Smooth pursuit, saccadic, vergence, vestibulo-ocular.

Central control: Nuclei of oculomotor (III), trochlear (IV), abducens (VI); medial longitudinal fasciculus linking superior colliculus, oculomotor nuclei and vestibular nuclei with gaze control centres.
Controlled by posterior parietal cortex, frontal eye fields, superior colliculus, vestibular nuclei.

Clinical disorders of oculomotor control.
Effects of myasthenia: *ptosis, diplopia.*

Pupillary reflexes: Consensual light response involving optic nerve, bilateral innervation of pre-tectal nuclei, Edinger-Westphal nucleus of oculomotor nerve (III), ciliary ganglion, short ciliary nerves.

Argyll-Robertson pupil.

Accommodation reflex: Involvement of visual cortex; parasympathetic and sympathetic control of pupil.

Lesions of the sympathetic supply: *partial ptosis and Horner's syndrome.*

22. CRANIAL NERVES

Note: The following should be known for each cranial nerve: function(s); origin; emergence from CNS; intra- and extra-cranial course; peripheral distribution; testing of function; consequences of lesions at different levels; control and interrelations of cranial nerve nuclei. Classification of fibres: *sensory fibres* supplying somatic tissues, viscera; *motor fibres* to striated muscle; *autonomic fibres* to glands and smooth muscle. Particular points for each nerve are listed below.
You should also know the related sympathetic cervical ganglia; parasympathetic ganglia (ciliary, pterygopalatine, submandibular, otic), the control of sweating, lacrimation, salivation, and eyelid and pupillary reflexes (see **21.7**).

Sections follow on specific cranial nerves.

22.1 SPECIFIC CRANIAL NERVES

22.1.1 OLFACTORY (I)

(see **20.6**)
Test: Examine sense of smell.

Anosmia after skull fracture. *Kallman's syndrome.*
Medial and lateral olfactory striae; septal olfactory area; inputs to limbic system.

22.1.2 OPTIC (II)

(see **20.3**)

22.1.3 OCULOMOTOR, TROCHLEAR, ABDUCENS (III, IV, VI)

See control of eye movement (see **21.7**).
Tests: Examine pupillary reflexes and eye movements.
Damage to III: Loss of upward, downward and medial movement of eye; ptosis; (pupillary dilatation), Diplopia.
Damage to IV: Diplopia on looking downward and medially.
Damage to VI: Loss of lateral movement of eye, diplopia on looking to the affected side.

Position of nerves in cavernous sinus.
Relation of nerves to internal carotid artery and other main cerebral arteries.

22.1.4 TRIGEMINAL NERVE (V)

Motor to muscles of mastication.
Sensory to anterior scalp, face, floor of mouth, teeth, tongue, and dura mater.
Ophthalmic and maxillary afferents in coughing and sneezing.
Trigeminal ganglion; principal sensory and spinal sensory nuclei; motor nucleus.
Lateral medullary syndrome: Losses of pain and temperature sensation from ipsilateral face & contralateral body.
Tests: examine sense of touch in cornea and face; check that jaw closes symmetrically.
Tooth ache; headache, *migraine and trigeminal neuralgia.*

Motor to tensor tympani, tensor palatini.

Mesencephalic nucleus of V.

Jaw jerk (mental) reflex.

On opening, jaw deviates towards side of any paralysis.

22.1.5 FACIAL NERVE (VII)

Motor supply to muscles of facial expression, stapedius; motor nucleus.

Facial colliculus (fibres of VII around Vi nucleus). *Differentiation of central and peripheral facial palsy.*

Sensory supply via chorda tympani (taste to anterior 2/3 of tongue); geniculate ganglion, nucleus solitarius.

Parasympathetic supply to lacrimal glands & nose via pterygopalatine ganglia; and to submandibular & sub-lingual salivary glands via chorda tympani & submandibular ganglion.

Damage in cerebello-pontine angle.

Tests: examine control of facial muscles; check symmetry of expression *Bell's (facial) palsy. Hyperacusis.*

Unilateral and bilateral cortical control.

22.1.6 VESTIBULO-COCHLEAR NERVE (VIII)

(see **20.4.4**)

Tinnitus (unilateral).

Tests: audiometry, use of tuning fork to distinguish sensorineural and conductive hearing loss. *Acoustic neuroma.*

Damage in cerebello-pontine angle.

Examine vestibular function with caloric or rotational tests; *nystagmus.*

22.1.7 GLOSSOPHARYNGEAL, VAGUS, ACCESSORY NERVES (IX, X, XI)

Sensory supply to oropharynx, dura mater, carotid sinus, carotid body (IX); and to foregut and midgut derivatives (X, cranial XI), projection to nucleus solitarius.

Motor fibre supply from nucleus ambiguus (IX, X, XI) to muscles of palate, larynx, pharynx.

Role of the afferents and efferents in coordinating swallowing (also XII).

Disorders of swallowing, speech with fractures through the jugular foramen.

Actions of sternomastoid and trapezius muscles (spinal XI).

Autonomic: Preganglionic parasympathetic fibres from IX (inferior salivatory nucleus) to parotid gland, and dorsal motor nucleus of X to pharynx, larynx and all of the gastrointestinal tract derived from fore- and mid-gut.

Tests: Gag reflex (IX and X). Voice and swallowing.
Palatal movements (X).
Actions of sternomastoid and trapezius muscles (spinal XI).

22.1.8 HYPOGLOSSAL NERVE (XII)

Motor supply to muscles of the tongue; hypoglossal nucleus.

Tests: observe tongue for paralysis and wasting - tongue deviates on protrusion towards paralysed side.

Damage to hypoglossal nuclei in medial medullary syndrome (anterior spinal artery lesion).

23. CORTEX, THALAMUS [NEURO] AND HYPOTHALAMUS [NEURO; APP. P&P]

23.1 CORTEX

Cytoarchitecture areal variations; myeloarchitecture.

Cerebral cortex microstructure.
Neocortex – 6 layers. Hippocampus – 3 layers.
Columnar organisation.
Cells and connections of layers: Thalamic afferents end on layer 4/granular cells; output pyramidal cells in layers 3, 5 and 6.
Origin, course & major terminations of fibres in: Corpus callosum, internal capsule, fornix.
Classification of commissural, association, projection fibres.
Functional anatomy of the cortex: Somatosensory (see **20.1.3**): Motor & Pre-Motor (see **21.3**): Visual (see **20.3.3.6**): Auditory (see **20.4.4**): Posterior Parietal (see **20.7.2.1**): Orbitofrontal (see **20.7.2.2**) Olfactory (see **20.6**): Limbic (see **24.4**).
Major cortico-thalamic and thalamo-cortical connections.
Cortical blood supply (see **16.4**).
Effects of lesions in visual, motor, somatosensory, posterior parietal cortex.
Physical lesions eg gunshot; Stroke.

23.2 THALAMUS

Functions. Concept of primary (relay) and higher order nuclei.
Afferent and efferent connections of the following thalamic nuclei: Anterior (limbic); ventral anterior and ventral lateral (motor: basal ganglia, cerebellum), ventral posterior medial and lateral (somatosensory), lateral geniculate (visual), medial geniculate (auditory), Pulvinar (visual).
Afferent relay to cortex, topographical organization, reciprocal connections with cortex.

Thalamic reticular and perireticular nucleus role in attention.
Dorsomedial nuclei (limbic).
Pulvinar-cortico-cortical circuits and communication.
Intralaminar nuclei – relation to nociceptive inputs to limbic cortex.
Dorsomedial nucleus – relation to septum, hypothalamus.

23.3 HYPOTHALAMUS

Structure and connections of the hypothalamus in relation to the physiological control of internal systems via the autonomic and endocrine systems; the biological clock; reproductive functions (see **51** and **52.1**).

23.3.1 COMPONENTS AND CONNECTIONS OF THE HYPOTHALAMUS

Principal nuclei and functions of:
Suprachiasmatic nucleus (biological clock, input from light-sensitive retinal ganglion cells).
Anterior hypothalamus (thermoregulation). *Fever*
Posterior hypothalamic area (sympathetic) - fear and aggression.
Supraoptic/paraventricular nucleus (posterior pituitary secretion oxytocin & Anti-diuretic hormone).
Median eminence/arcuate nucleus/paraventricular nucleus (control of appetite, metabolic rate, anterior pituitary).
Ventromedial nucleus (satiety 'centre').
Lateral hypothalamus (hunger 'centre'); Orexin-hypocretin.
Mammillary body (memory); *Korsakov syndrome.*
Periventricular organs (deficient blood-brain barrier): Organum vasculosum of lamina terminalis (OVLT).
Subfornical organ (SFO) - thirst, osmoreception.
Neural connections: Large fibre bundles - fornix, stria terminalis, mammillothalamic tract, and medial forebrain bundle. Largely reciprocal.
Afferents: From sensory receptors, visceral (via reticular formation and solitary tract); from brainstem (locus coeruleus, raphe, periaqueductal grey); higher centres (hippocampal formation, amygdala, orbitofrontal cortex via mediodorsal thalamus).
Efferents: Endocrine control via posterior pituitary, and anterior pituitary via portal system; descending control of autonomic centres in brainstem and spinal cord; mammillothalamic tract.
Vasculature of hypothalamus and pituitary from internal carotid, capillary plexus in median eminence; portal vessels to anterior pituitary; direct supply to posterior pituitary.

Dorsomedial nucleus, lateral tuberal nucleus (very wide GABA projections, cf. raphe, locus coeruleus), medial mammillary nucleus, lateral mammillary nucleus.
Animal models using optogenetics and designer drugs to target specific hypothalamic neurons and functions.
Fröhlich's syndrome (GnRH).

Superior and inferior hypophyseal arteries.
Long and short portal vessels.

23.4 EPITHALAMUS

Pineal: control by postganglionic sympathetic fibres; melatonin production.

Control of day-night rhythm. Habenular nuclei.

24. HIGHER CEREBRAL FUNCTIONS

24.1 CONSCIOUSNESS

24.1.1 COMA

Coma. Persistent vegetative state. Minimally conscious state.

24.2 SLEEP

Circadian rhythms, entrainment to the light-dark cycle, and melatonin as a marker of the endogenous biological clock.

Basic neuroanatomy and neurochemistry of sleep control: subcortical circuits (hypothalamus, brainstem, basal forebrain) and neurotransmitters (GABA, acetylcholine, orexin).

EEG stages of sleep, slow wave sleep (I-III) and rapid eye movement (REM) sleep.

Appreciation that the EEG pattern of sleep varies with age and some diseases; e.g. Schizophrenia (see 25.2) and neurodegenerative diseases.

Sleep need and consequences of sleep deprivation (vigilance, attention, cognitive functions).

Cellular and network mechanisms of sleep oscillations (slow waves, spindles).

Sleep disorders, including insomnia, obstructive sleep apnoea and parasomnias (somnambulism, REM behaviour disorder).

24.3 COMPONENTS AND CONNECTIONS OF THE LIMBIC SYSTEM

Circuit of Papez: cingulate gyrus, parahippocampal gyrus (reciprocal connections with most association cortex), dentate gyrus and hippocampus, fornix/fibria, mammillary bodies, mammillothalamic tract, anterior thalamus.

Amygdala: links with olfactory system, association cortex, hypothalamus and brainstem; amygdalofugal tract and stria terminalis.

Orbitofrontal cortex; ‘error’ neurons, perseveration in lesions.

Klüver-Bucy syndrome. Mesial temporal/ limbic system disorders. e.g.. *Medial temporal sclerosis* (hippocampal epilepsy) and *Alzheimer’s disease.*

24.4 FUNCTIONS OF THE LIMBIC SYSTEM

Functions of frontal lobe: Orbitofrontal cortex and behaviour, discrimination, decision making.

Amygdala and fear.

Effect of lesions of hippocampus (memory) and amygdala (fear) in man

Self-stimulation.

'Face', 'food', 'error detection' neurons.

Learning: one-trial, multi-trial.

24.5 MEMORY

Hippocampal LTP role in spatial or episodic memory.
‘Hebbian synapse’.
Korsakov syndrome (see **23.3**).

c.f. cerebellar LTD for automating skills (see **22.5**).

Human amnesias. Insights from ‘HM’ and others with bilateral hippocampal damage/removal. Links with Alzheimer’s disease, epilepsy, hypoxic-ischaemic encephalopathy.

24.6 NEURONAL PLASTICITY

Concept of neuronal plasticity in synaptic reinforcement and rearrangement.
Role in development and learning.
Critical period in development (see **20.3.6**).
Basis of NMDA mediated LTP.

Neuronal plasticity in recovery from stroke or other damage.

25. PSYCHIATRIC DISORDERS AND PSYCHOPHARMACOLOGY (NEURO, PSY)

Note: Psychological and behavioural aspects of the major psychiatric disorders are examined chiefly in the Subject: *Psychology for Medicine*; Neuroanatomical and physiological aspects of the disorders in the Subject *Neuroscience*
See also pharmacology of *Parkinson's* **21.4.2**; anti-epileptic drugs **19.6.1**; pharmacology of pain **20.2.2**
See also *variant Creutzfeldt-Jacob disease* (vCJD) and prions **42.5**

25.1 MOOD DISORDERS (SEE 26.9)

25.1.1 DEPRESSION AND ANXIETY

Classification of disorders (unipolar and bipolar mood disorder; anxiety-related disorders), principal clinical features and risk factors.
How specific features might link to abnormalities in neuroanatomical, neurochemical and neuropsychological systems.
Simple rationale for how psychological and social treatments might work.

25.1.2 ANTI-DEPRESSANT DRUGS

Main classes of anti-depressants: tricyclics, selective 5-HT (serotonin) re-uptake inhibitors ('SSRIs') (fluoxetine), MAO inhibitors (phenelzine), selective serotonin and noradrenaline reuptake inhibitors ('SNRIs' venlafaxine).
Use of lithium as a mood stabiliser; Tricyclic antidepressants (TCAs): amitriptyline.
Molecular mechanism of action of antidepressants: origins of the monoamine hypothesis of depression.
Adverse effects including psychological and physical dependence.

Other antidepressants; mianserin, mirtazapine, agomelatine.
Monoamine hypothesis of depression: validity of evidence.
Neuroanatomical substrates of antidepressant drug action.
Indications from drug therapy for ideas of cause of depression; validity of evidence.

25.1.3 ANXIOLYTIC DRUGS

Molecular mechanism of action of anxiolytic drugs.
GABA potentiation (barbiturates, benzodiazepines (see **19.5.3**).
$5HT_1$ agonists (buspirone).
β-blockers (propranolol).
Hypnotic effect of anxiolytics.
Adverse effects and benzodiazepine dependence.

Antidepressants as anxiolytics.
Neuroanatomical substrates of anxiolytic drug action.

25.1.4 OTHER TREATMENTS FOR DEPRESSION

Psychological and social approaches.
Linking pharmacological and psychological mechanisms.
Electroconvulsive therapy as a treatment for depression.
Anticonvulsants as mood stabilizers.

25.2 SCHIZOPHRENIA

25.2.1 SCHIZOPHRENIA

Principal clinical features and risk factors.
Neurobiology of psychoses: genetics, neurodevelopmental model, dopamine hypothesis; brain imaging.
How specific features might link to abnormalities in neuroanatomical, neurochemical and neuropsychological systems; newly identified transmitters in schizophrenia. Sleep disturbance (see **24.2**).

Commonalities and differences from autism, bipolar disorder.

25.2.2 PHARMACOLOGY OF ANTI-PSYCHOTIC DRUGS

Typical (haloperidol) and atypical (clozapine) antipsychotics: mechanisms of action, adverse effects.
Dopamine antagonists (e.g. chlorpromazine); adverse effects including those on motor control (tardive dyskinesia).

Unique properties of clozapine.
Novel and potential schizophrenia drugs: treating cognitive and negative symptoms.

25.3 COGNITIVE DISORDERS OF OLD AGE

25.3.1 GLOBAL IMPAIRMENT OF COGNITIVE FUNCTION

Classification of disorders.
Principal clinical features of dementia and delirium.
Risk factors for dementia and delirium.
Types of dementia eg Alzheimer's disease, fronto-temporal dementias, vascular dementia; Lewy body disease; Prion disease, Creutzfeldt-Jacob disease.
Psychological and social aspects of treatment.

How specific features might link to abnormalities in neuroanatomical, neurochemical and neuropsychological systems Neurobiology of cognitive impairment: ideas and clues from neuropharmacology, neuropsychology, brain imaging and genetics.

25.3.2 ALZHEIMER'S DISEASE

Comparison of *Alzheimer's disease* and normal ageing.
Alzheimer's disease: role of amyloid, plaques and tangles; basal forebrain cholinergic systems. Memory loss.

Familial and sporadic Alzheimer's disease. Varieties of dementia.

25.3.2 TREATMENT OF DEMENTIA

Simple rationale for how pharmacological treatments might work.
Anti-cholinesterase treatment.

Treatment of behavioural symptoms of dementia.
Other therapies for Alzheimer's disease.

25.4 EATING DISORDERS

25.4.1 THE EATING DISORDERS

Classification of disorders.
Principal clinical features of anorexia nervosa, bulimia nervosa and binge eating disorder.
Risk factors for anorexia nervosa & bulimia nervosa.

Obesity as an eating disorder.
How specific features might link to abnormalities in neuroanatomical, neurochemical and neuropsychological systems.

25.4.2 TREATMENT OF EATING DISORDERS

Simple rationale for how psychological treatments might work.
Effective psychological treatments.

Physical and social aspects of treatment.

25.5 DRUG ADDICTION AND RECREATIONAL DRUGS

25.5.1 NEUROBIOLOGY OF ADDICTION

Role of ventral tegmental area, nucleus accumbens and dopamine.
Dopamine neuron activity and reward prediction errors, not rewards *per se.*
Site of drug action.

Aberrant reinforcement learning.

Involvement of wider circuits; dorsal striatal dopamine systems (caudate-putamen). PFC.
. LTP/LTD; Plasticity in wide range of circuits.
Other addiction disorders e.g. gambling, food

25.5.2 RECREATIONAL DRUGS

Dependence liability.
Opiates, nicotine, cannabinoids, psychostimulants, ethanol, benzodiazepines, psychotomimetics (LSD, mescaline); amphetamines; cocaine.

Molecular mechanisms of tolerance, dependence, and withdrawal.
Treatments of addiction: pharmacological, behavioural, DBS

PSYCHOLOGY FOR MEDICINE

Note: This subject will be taught in 12 lectures (in Hilary Term). The level of treatment of the syllabus will be established by the lecture course.

26. PSYCHOLOGY FOR MEDICINE

26.1 PSYCHOLOGICAL ASPECTS OF MEDICAL PRACTICE

The importance of understanding mental processes for medicine.

The difference between illness and disease.
Limitations of disease in explaining illness.
Incidence & prevalence of symptoms without disease.
Aetiology of symptoms.

Example 1 Illness with no disease: medically unexplained symptoms
Example 2. Illness disproportionate to disease: cancer and comorbid depression.
Social determinants of health
How a biopsychosocial perspective can improve patient care.
The importance of cultural awareness and sensitivity in patient care

Making and applying a biopsychosocial formulation.

Psychosocial factors in medical conditions

Role of psychosocial factors in cardiovascular, respiratory gastrointestinal and neurological disease.

Psychological responses to illness
Death, dying and bereavement: psychological factors in palliative care. Responses to death, stages of grief.

Adjustment to chronic illness

Non-adherence with medical advice

Principles of behaviour change

Cognitive reframing, motivational interviewing

Clinical reasoning and decision marking

Sources of bias in clinical decision making

Wellbeing & burnout

Reflective practice in ongoing professional development
Understand the factors that contribute to burnout in medical professionals.

Psychological debriefing

Understanding responses to stress in the workplace

26.2 ATTENTION AND MEMORY (SEE 24.5)

The role of attention in cognition
The functional anatomy of attention
Selective and sustained attention
Disorders of attention: unilateral neglect, extinction
Long and short-term memory
Primacy and recency effects
Working memory
Reconstructive memory.
Anterograde amnesia; retrograde amnesia; “Ribot’s Law”

False memories

Temporal gradients in memory
The hippocampus and medial temporal lobes (see **24.3**)
Confabulation

26.3 EMOTION

Nature, causation, and differentiation of emotions
Biological and psychological function of emotions
Recognition of emotions in others, and our selves
Dysfunctional emotional responses
Depression and emotional blunting
Prefrontal cortex and amygdala lesions and emotional responses
Emotional labour
Psychopathy

26.4 COMMUNICATION: PRODUCING AND UNDERSTANDING LANGUAGE

Language development
Language and genetics.
Localisation of language in the brain (see **20.4.5).**
Comprehension and production similarities and differences.
The role of memory in speech processing.
Speaking and reading.
Language disorders (acquired and developmental): Aphasia, dysarthria, dysphasia, dyslexia, Specific language impairments.
Phonology, syntax and semantics in language comprehension and production
Localisation of language in the brain (see 20.4.5 for acquired aphasis)
Syntax – comprehension in Broca's aphasia of complex syntax
Primary progressive aphasias – nonfluent, semantic dementia, logopenic
Implications of language complexity for patient communication.
The nature of language breakdown in acquired and developmental cases.
The relevance of culture and identity to patient communication

Implications of language complexity for patient communication
Role of arcuate fasciculus in syntax comprehension (nonfluent PPA) and phonological processing (logopenic PPA)

26.5 LEARNING AND CONDITIONING (SEE 25.5)

Paradigms of Operant and Classical Conditioning – different reinforcement paradigms.
Social learning and modelling of health-related behaviours
Constraints on learning, temporal contingency versus predictability e.g. learned taste aversion.
Maladaptive learned behaviour - learning paradigms to explain the progression to mental illness of learned helplessness (Seligman), agoraphobia, anticipatory nausea and vomiting (ANV).
Psychological principles of learning to explain phobias, Obsessive-compulsive behaviour, drug addiction, schizophrenia: Kamin's blocking, conditioned morphine tolerance.
Biological, psychological (personality individual differences), cultural and sociological factors related to these mental illnesses.

26.6 TYPICAL AND ATYPICAL DEVELOPMENT / PSYCHOLOGY ACROSS THE LIFESPAN

26.6.1 BASIC PRINCIPLES

Defining atypical development at multiple levels: genetic. Behaviour, cognition, neuroscience, genetics.
The importance of timing for understanding typical development and developmental disorders (pre- and perinatal events insults vs later in childhood). Down's, Williams and Fragile X syndrome.

26.6.2 CHILDHOOD

Define normal and abnormal attachment Ainsworth – Strange situation, Bowlby,
The impact of adverse childhood experiences on long term physical and mental health outcomes including brain development and capacity to parent in the future
Age-dependent understandings of illness

26.6.2 ACQUIRED DEVELOPMENTAL DISORDERS

Contrast the effects of perinatal / early childhood vs adult brain lesions: language, visuo-spatial cognition, executive functions. Plasticity / compensation following lesions of language areas.
Comparison with effects of early lesions on visuo-spatial cognition and executive functions.
Impact of adversity on executive function

26.6.3 FUNCTIONALLY DEFINED DEVELOPMENTAL DISORDERS

Neurocognitive theories of attention deficit / hyperactivity (ADHD): executive dysfunction, working memory, sustained attention difficulties. Neural correlates of ADHD – shift in emphasis from frontostriatal circuitry to broader network abnormalities.
Neurocognitive theories of autistic spectrum disorders (ASD): mentalizing, executive dysfunctions, weak central coherence, multiple-hit hypotheses. Differences by culture and ethnicity in likelihood of and barriers to diagnosis.

26.7 ADOLESCENT PSYCHOPATHOLOGY

26.7.1 BASIC PRINCIPLES

Defining adolescence. Convergence of social, behavioural, cognitive and biological factors.
Adolescence as a period of social upheaval. Second sensitive period of development
Protracted brain development in adolescence. Cognitive development, individuation, emergent social conscience
Limbic vs prefrontal time-frame for maturation, their interplay. Influence of peers

26.7.2 RISK FOR PSYCHOPATHOLOGY

Adolescence as a critical period for the onset of many psychiatric problems.
Vulnerability to psychopathology. Belonging / homophily, potential for improved intergroup interactions
Amenability to interventions.

26.8 ANXIETY DISORDERS AND PSYCHOLOGICAL THERAPIES (see 25.1)

Classification of anxiety disorders: generalised anxiety, panic disorder, social anxiety, phobic anxiety, PTSD.
Clinical features of the different anxiety disorders.
Incidence and prevalence of anxiety disorders.
Aetiology of / risk factors for anxiety disorders.
Core mechanisms in Cognitive Behavioural Therapy for anxiety disorders.

Examples of use of CBT in specific anxiety disorders.
Development and evaluation of effective psychological treatments.
Improving access to effective psychological treatments (IAPT) (including cultural differences in accessing treatment).

26.9 MOOD DISORDERS AND SCHIZOPHRENIA (SEE 25.1 AND 25.2)

Classification of mood disorders.
Incidence & prevalence of mood disorders.
Clinical features of mood disorders.
Aetiology of / risk factors for mood disorders.
Effective psychological and social treatments and their evidence base.
Core mechanisms in Cognitive Behavioural Therapy for mood disorders.

How specific features might link to abnormalities in neuropsychology.
Possible psychological mechanisms underlying pharmacological treatment of depression.
Challenges of delivering effective cognitive-behavioural treatments.
How mood orders present in other cultural contexts.

Schizophrenia: principal clinical features and risk factors.
Neurobiology of psychoses: genetics, neurodevelopmental model, dopamine hypothesis; brain imaging.
How specific features might link to abnormalities in neuroanatomical, neurochemical and neuropsychological systems; newly identified transmitters in schizophrenia. Sleep disturbance (see **24.2**).

Commonalities and differences from autism, bipolar disorder.

26.10 COGNITIVE DISORDERS OF OLD AGE (SEE 25.3)

26.10.1 GLOBAL IMPAIRMENT OF COGNITIVE FUNCTION

Definition of normal cognitive ageing.
Classification of cognitive disorders of old age.
Sub-types of dementia.
Incidence & prevalence of dementia (and its subtypes) and delirium.
Aetiology of / risk factors for dementia and delirium.
Clinical features of dementia and delirium.
Psychological and social aspects of treatment.

How specific features might link to abnormalities in neuropsychological systems.
Profiles of cognitive impairment across types of dementia: ideas and clues from neuropsychology and brain imaging.
Treatment of behavioural symptoms of dementia.

26.10.2 ALZHEIMER'S DISEASE

Comparison of *Alzheimer's disease* and normal ageing.
Alzheimer's disease: Memory loss and other cognitive characteristics.

Other therapies for Alzheimer's disease.

26.11 EATING DISORDERS (SEE 25.4)

26.11.1 THE EATING DISORDERS

Classification of eating disorders.
Incidence & prevalence of eating disorders.
Clinical features of anorexia nervosa, bulimia nervosa and binge eating disorder.
Aetiology of / risk factors for anorexia nervosa & bulimia nervosa.
Empirical evidence: starvation studies.
Obesity as an eating disorder.
How specific features might link to abnormalities in neuropsychological systems.
Other specified feeding or eating disorder (OSFED).
Social and cultural influences on eating.

26.11.2 TREATMENT OF EATING DISORDERS

Simple rationale for how psychological treatments might work.
Effective psychological treatments and their evidence base.
Physical and social aspects of treatment.

PRINCIPLES OF PATHOLOGY

30. OVERVIEW OF INFECTION AND IMMUNITY

Note: This section summarises key concepts in infection and immunity which are elaborated in following sections.

30.1 RELATIVE IMPORTANCE OF INFECTION AS A CAUSE OF MORBIDITY AND MORTALITY

30.1.1 IMPACT OF INFECTIOUS DISEASES ON HUMAN MORBIDITY AND MORTALITY

Differences between wealthy and resource-poor settings. Comparison with cancer and cardiovascular disease.
Age distribution of infectious disease.
Illustrative examples: tuberculosis, diarrhoea, respiratory infection.

30.2 PATHOGENIC ORGANISMS

30.2.1 PATHOGENS AS A SPECIFIC SUBSET OF MICROBES

Concept that pathogens have evolved specific mechanisms to evade and avoid host defence mechanisms.
Properties of prokaryotic cells compared with eukaryotes.
Commensals and pathogens, virulence factors.
Importance of horizontally acquired DNA.
The germ theory of disease.
Bacteria:
Fundamentals of Gram staining (see **33.3.2**).
Bacteria: major groups of pathogenic bacteria:
- Pyogenic (pus-forming).
- Enteric bacteria.
- Exotoxin producers (e.g. cholera toxin, diphtheria toxin, tetanus toxin). Mechanisms of toxin action with examples.
- Facultative intracellular parasites (e.g. *Shigella*).

Viruses:
- Obligate intracellular parasites which can cause disease by inducing inflammation, causing cell death, and/or increasing the likelihood that a tumour will develop.

Eukaryotic parasites causing e.g. malaria, Leishmaniasis, sleeping sickness.
Fungi causing e.g. thrush, athletes' foot, ringworm.

Quantum leaps in microbial evolution.

The microbiota.
Diversity of the microbiota and microbial world.
The importance of commensal bacteria in immune system development and function and the concept of dysbiosis.

Host susceptibility to infectious agents.

Non-pathogenic micro-organisms (usually-harmless organisms, role in protection from pathogens).
Disease in immunosuppressed individuals: e.g. AIDS, immunosuppression after transplantation, people with inherited defects of the immune system e.g. primary immune deficiencies.

30.3 DEFENCE AGAINST INFECTIOUS DISEASE

30.3.1 INNATE MECHANISMS

Independence from and interactions with the *specific immune response.*
Barriers to infection: skin, mucus, gastric acid, bile salts, normal microbiota.
Cells:
Pathogen sensing:
Pathogen-associated molecular patterns (PAMPS) and pattern recognition receptors (PRRs). Specific PRRs - TLRs, NLRs, nucleic acid sensors.
Type-I interferon induction (Interferon Stimulated Genes (ISGs) and viral interferon evasion strategies.
Inflammasomes and consequences of their activation

Effector functions:
Respiratory burst: neutrophils, monocytes, macrophages. Fc receptors, complement receptors.
Degranulation: mast cells, eosinophils, basophils.
Phagocytosis and phagolysosomal degradation: Neutrophils, macrophages.
Opsonin-assisted functions of macrophages and neutrophils.
Natural killer (NK) cells.
Soluble molecules: Complement, (classical, alternative and MBP pathways), type I interferons (alpha and beta), type II interferon (gamma) and other secreted molecules.
Innate immune evasion strategies:
Avoidance of phagocytosis by capsules (e.g S*treptococcus*).

Innate defence is often inadequate e.g. poliomyelitis, tuberculosis, tetanus, rabies, AIDS.

Evolution of inflammasomes and their role in host defence

Innate lymphoid cells.

30.3.2 SPECIFIC IMMUNE RESPONSE

30.3.2.1 Induction

Dependence on T and B lymphocytes. Antigen-specific recognition. Self vs non-self-recognition.
Clonogenic distribution of antigen receptors.
Generation of antigenic diversity in T and B cells.
T cell recognition of peptide antigens presented by MHC molecules.
B cell recognition of a wide variety of native antigens.
Linked recognition of antigen.

Evolutionary relationship between innate mechanisms (ancient) and adaptive immunity (comparatively recent).

Selection, clonal expansion, and differentiation of lymphocytes that recognise the antigen. T cell education in the thymus. Central vs peripheral tolerance.
Immunological memory for a specific antigen:
The primary response to an antigen.
The secondary response (faster and more effective) to the same antigen.

30.3.2.2 Effector mechanisms

B-cell differentiation to antibody-secreting cells (plasma cells). Distinction between short-lived and long-lived plasma cells.
Antibodies: Concepts of antibody affinity and avidity.
Prevention of entry of pathogens (e.g. viruses and mucosal bacteria), neutralisation of bacterial toxins, opsonisation of bacteria, initiation of acute inflammation via complement cascade (‘classical pathway’).
T-cells - two types: CD4 T helper (Th) cells and CD8 cytotoxic (Tc) cells.
Tc cell killing of virus infected and tumour cells directly.
T cells secretion of cytokines: activation of macrophages and NK cells to improve effectiveness of innate immunity.
T cell-dependent antibody class switching and isotype switching.
T cell activation of B cells in lymph node germinal centres.
Autoimmunity caused by breakdown of immune tolerance.
Possible immune disease as a consequence of excessive release of inflammatory cytokines (Super antigens, cytokine storm, sepsis, anaphylaxis).

31. CELL DEATH AND REPAIR, INFLAMMATION, ANTI-INFLAMMATORIES

31.1 NECROSIS AND APOPTOSIS

Apoptosis: 'programmed' cell death directed by the expression of specific genes; produces no inflammation. Mechanism and regulation of apoptosis.

Role in normal tissue homeostasis, embryonic morphogenesis and deletion of self-reactive lymphocytes.

Role of *Fas,* caspases, and *BCL2.*

Necrosis: damage to the cell raises intracellular calcium and activates hydrolytic enzymes.

Resultant cell death and the release of inflammatory mediators.

Pyroptosis: controlled form of cell necrosis. Activation by caspases and caspase-mediated cleavage of gasdermin-D. Role in death of bacterially infected cells and the bacteria they contain.

Autophagy: Role in cell response to injury.

31.2 ACUTE INFLAMMATION

31.2.1 FUNCTION IN DEFENCE

Time course: minutes to days (see **31.2.6**).

Role in neutrophil (polymorphonuclear leukocyte; PMN) recruitment to combat pyogenic bacterial infection and facilitation of phagocytosis by PMN.

31.2.2 CARDINAL FEATURES

Heat (vasodilation), redness (vasodilation), swelling (oedema), pain (chemical mediators). Leads to loss of function.

31.2.3 HISTOLOGY

Vasodilation, oedema, adhesion of PMN to venule walls.

Cellular infiltration by PMN (major) and monocytes / macrophages (minor).

Formation of pus. Abscesses: structure, formation and fate.

31.2.4 LEUKOCYTES: NEUTROPHILS (PMNS OR 'POLYMORPHS')

The basic biology and normal abundance of neutrophils, and the significance of increased blood counts of neutrophils, (first year syllabus **44.3.1.**) Colony stimulating factors (CSFs).

Adhesion to vascular endothelium. Diapedesis. Rolling (selectins), firm adhesion (integrins).

Migration and chemotaxis along gradients of inflammatory mediators.

Chemokines and their receptors, G-protein coupled receptors
C5a, leukotrienes, bacterial peptides, chemokines.
Cell biology of chemotaxis.

CD31.

Phagocytosis:
Opsonisation by Ab and complement.
Lysosomal fusion.
Killing and digestion of micro-organisms.

Zipper mechanism of phagocytosis.
Other opsonins and receptors for phagocytosis (lectins).

Phagocyte killing mechanisms:
Respiratory burst (NADPH oxidase). Degranulation.
Non-oxygen-dependent killing mechanisms; anti-microbial peptides e.g. LL-37.
Defects: Chronic granulomatous disease, complement deficiencies.
Neutrophil Extracellular Traps (NETs).

Secreted and released enzymes.

31.2.5 MACROPHAGES

31.2.5.1 Life history and distribution

Two distinct origins: embryonic yolk sac derived tissue macrophages (long-lived, self-renewing) and bone marrow-derived infiltrating monocytes.
Two major classes: tissue resident (e.g. Kupffer cells, microglia (see **19.2**), mediating homeostasis, repair and remodelling; infiltrating monocytes becoming inflammatory macrophages that mediate antimicrobial functions. Macrophage differentiation/polarisation e.g M1 and M2 in response to cytokines M-CSF, GM-CSF.
Adhesion of monocytes to vascular endothelium, migration and chemotaxis - as for PMN.
Chemokine receptors (see **35.1** HIV).
Molecules involved in recruitment; adhesion molecules, chemokines.
Recognition molecules (scavenger receptors, lectins).

Other tissue macrophages: e.g. splenic, alveolar, skin (Langerhans cells).

31.2.5.2 Functions

Defence: presence at or recruitment to sites of infection.
O_2-dependent killing of facultative intracellular pathogens
e.g. *Mycobacterium tuberculosis, Leishmania*, requirement for activation by IFN-γ
activation by endotoxin.
clearing of virus from blood.

production of type-I interferons (α/β).
secretion of cytokines e.g. TNFα, IL-10.
Pathogen sensors: PRRs including TLRs, NLRs and nucleic acid sensors.
Cytotoxic mechanisms: oxygen metabolites, nitric oxide (i-NOS).
Other secretory products: Hydrolytic enzymes, complement components.
Tissue homeostasis: remodelling and repair.
Removal of apoptotic and necrotic cells.
Pathogenic role in chronic inflammation (see **31.3**).
Osteoclasts in bone remodelling.

31.2.5.3 Activation

Activation alternatively by endotoxin, IFN-gamma, IL-4, IL-13.
Pro-inflammatory cytokines (TNF-α, IL-1, IL-6).
Other cytokines (IL-10, IL-12).
NFκB and other pro-inflammatory transcription factors.

31.2.6 MEDIATORS OF INFLAMMATION

31.2.6.1 Complement

A knowledge will be assumed of the basic biology of complement as contained in the first-year syllabus (see **44.6.6).**
Classical, alternative and lectin pathways for complement activation.
Individual components, regulation of activation, immunodeficiencies.
Role of C3, C3a, C5a.
Interaction with coagulation, kinin and fibrinolytic cascades.

31.2.6.2 Other mediators

Products of coagulation cascade.
Products of fibrinolytic cascade.
Kinins, prostaglandins and leukotrienes.
Roles of Hageman factor and thrombin.
Activation of plasminogen.
role of plasmin in producing other mediators.

31.2.6.3 Effects of mediators on cells

Effects of cytokines and other mediators on vascular endothelium, PMNs, macrophages, mast cells, fibroblasts.

31.2.6.4 Regulation of acute inflammation

Concept of inactivators for active mediators.
α1-anti-trypsin and emphysema.
C1 esterase inhibitor and angio-neurotic oedema.

31.2.7 SYSTEMIC EFFECTS OF ACUTE INFLAMMATION

Acute phase response; fever.
Induction and function of acute phase proteins (C-reactive protein, complement factors, coagulation cascade components, alpha 1-antitrypsin, serum amyloid A, haptoglobin) – knowledge assumed from first-year syllabus.
Roles of IL-1, TNF-α and NO.
Role of lipoteichoic acid (cell wall component of Gram-positive bacteria with effect like endotoxin).
Septic shock, role of endotoxin (see **52.5**).
Current ideas about pathology of sepsis and septic shock.

31.3 CHRONIC INFLAMMATION

31.3.1 GENERAL

Defined by time it lasts - weeks to years.
Mononuclear cell infiltrate i.e. macrophages (possible involvement of giant cells and epithelioid cells) and lymphocytes.
Absence of PMNs and pus (PMN presence in *repeated and long-standing* acute inflammation).
Vascularisation and collagen deposition (possibly excessive), but little oedema.

31.3.2 PATHOGENESIS

Either: toxic and innate immune-triggered.
Toxic, non-antigenic, particle activation and killing of macrophages.
Stimulation of further recruitment and death of macrophages.
Release of mediators by macrophages to cause persistent repair reaction. Resultant fibrosis and loss of function (e.g. silicosis).
Endogenous pathways involved in resolution of inflammation IL-10, TGFß.
Repeated bouts of acute inflammation: resultant fibrosis and scarring (e.g. cholecystitis). Chronic inflammation as a failure of proper resolution of inflammation.
Long standing acute inflammation (e.g. presence of foreign body – chronic osteomyelitis).
Or: adaptive immune-triggered.
$CD4^+$ T-cell-mediated immune response to persistent antigens.
Structure of a granuloma and its evolution.
Macrophage as a secretory cell causing tissue damage.
Resolvins, Annexin A1, efferocytosis (macrophage phagocytosis of apoptotic neutrophils).

Animal models: reasons for antigen persistence.
Molecules secreted by activated macrophages; H_2O_2, enzymes - collagenase, elastase, other proteases.
Genetic basis for susceptibility (and evidence from twin studies & mice).
Schistosomiasis.

Roles of IFN-γ and TNF-α.
Examples: tuberculosis, rheumatoid arthritis, cirrhosis.
Treatment of rheumatoid arthritis (see **31.5.4**).
Contact sensitivity; Mantoux test. Sarcoidosis, systemic lupus erythematosus (SLE) and other auto-immune diseases.

31.4 REPAIR

Histology of repair of a clean incision.

31.4.1 CELLULAR BASIS OF REPAIR

Granulation tissue (do *not* confuse with 'granuloma').
Roles of blood and lymphatic vessels, blood platelets, endothelium, macrophages and fibroblasts.

31.4.2 REGULATION OF REPAIR

Roles of cytokines (PDGF, TGFβ), proteases, fibrinolysis.

Resolution, organization and fibrosis. Scar formation.
Repair in epithelia; healing of a skin wound.
Factors inhibiting repair — infection, vascular insufficiency (e.g. varicose ulcers, diabetes) malnutrition, glucocorticoids, radiation.

Future approaches to improving wound repair – stem cells and gene therapy (regenerative medicine).

31.5 PHARMACOLOGY OF INFLAMMATION

31.5.1 ASPIRIN AND OTHER NSAIDS (NON-STEROIDAL ANTI-INFLAMMATORY DRUGS)

Mechanism of action:
cyclo-oxygenase (COX) inhibition - suppression of prostanoid synthesis, Aspirin as a non-specific COX-inhibitor.

Systemic effects.
Adverse effects: Gastrointestinal haemorrhage (COX-1 inhibition).
Use in rheumatoid arthritis.
Treatment of rheumatoid arthritis, (see **31.3.2** & **31.5.4**).

Paracetamol's action as an analgesic and not as an anti-inflammatory.
Inhibition of a specific COX to produce analgesic and antipyretic effects only: absence of an effect on the inflammatory processes underlying rheumatic disease.

Search for new classes of anti-inflammatory drugs
Other potential targets for anti-inflammatory action:
complement and complement fragments
kinins, reactive oxygen species, TNFα (see **31.5.4**).

31.5.2 STEROIDS

Mechanism of action (e.g. dexamethasone): modulation of gene expression and reduced activity of phospholipase A_2 - effect to reduce production of prostaglandins, leukotrienes and platelet activating factor. Systemic effects on inflammatory processes.

Use in allergic conditions including asthma: (see **54.1**)

Adverse effects:

Immune depression increasing susceptibility to viral infection.

Hypertension via effects on fluid and electrolyte balance.

Bone resorption (osteoporosis); diabetes; peptic ulcers; effects on the skin.

31.5.3 ANTI-INFLAMMATORY HISTAMINE ANTAGONISTS (H1 BLOCKERS)

Role of histamine in inflammation: uses and limitations of anti-histamines in therapy e.g. chlorpheniramine.

Anaphylaxis: principles of cause and treatment, including use of anti-histamines (see **39.1.1**).

31.5.4 DRUGS FOR TREATING RHEUMATOID ARTHRITIS

Aspirin and other NSAIDs (mechanism, see **31.5.1**).

Corticosteroids (mechanism, see **31.5.2**).

DMARDS - disease modifying anti-rheumatic drugs.

Depression of the immune response over time (full effect takes several months).

Use of immunosuppressants (e.g. methotrexate; depress the production of immune cells).

Therapeutic antibodies e.g. anti-IL-6; anti-TNF.

Rituximab (B cell-depleting mAb); abatacept (Ig-CTLA-4 fusion protein).

32. SPECIFIC IMMUNE RESPONSE

32.1 STRUCTURE AND PHYSIOLOGY OF THE IMMUNE SYSTEM

32.1.1 PRIMARY LYMPHOID ORGANS

Sites of lymphocyte production, not activation.
- Bone marrow, then thymus - T cells.
- Bone marrow - B cells.

Thymus structure – roles of cortical and medullary thymic epithelial cells (TEC). Histology and embryology of thymus and bone marrow.

Lineage commitment of $CD4^+$ and $CD8^+$ T cells.

Positive selection of the T cell repertoire and the role of avidity.

Overproduction of lymphocytes and apoptosis in primary organs.

32.1.2 LYMPHOCYTES

Major surface molecules of T cells.
- T cell Ag receptor, CD3, CD4, CD8, adhesion molecules, cytokine and chemokine receptors (e.g. IL-2R). Surface phenotype of T cell subsets.

Major surface molecules of B-cells.
- surface Ig, MHC class II, adhesion molecules, chemokine and cytokine receptors.

Individual co-stimulatory molecules: CD40L, CD28 and other signalling molecules e.g. PD1, CTLA4, Fas ligand and Fas (CD95).

Schematic structure of these molecules.

Individual adhesion molecules: selectins, integrins, ICAMs.

B cell Ig co-receptors.

32.1.3 SECONDARY LYMPHOID ORGANS

Origin of immune responses - sited to monitor pathogen entry.
- Lymph nodes - monitor solid tissues.
- Spleen - monitors blood.
- Peyer’s patches and equivalents - monitor mucosae.

Basic structure of secondary lymphoid organs.
- T and B cell areas – primary follicles and germinal centres.
- Routes of Ag entry.

Lymphocyte recirculation.

High endothelial venules as site of lymphocyte exit from blood.

Recirculation to allow accumulation of Ag-specific lymphocytes at sites exposed to Ag – amplification of response.

Differential expression of molecules on lymphocyte and endothelium to determine sites of exit - selectins, chemokines, integrins.

Different migratory properties of resting and activated lymphocytes.

32.2 INDUCTION OF IMMUNE RESPONSES

32.2.1 THE NATURE OF ANTIGENS

Concepts of antigenicity and immunogenicity.
Intact proteins and other native biomolecules as B cell antigens; peptides as T cell antigens. Tumour antigens.
Haptens and carriers.
Concept of thymus-dependent (T-dependent) ‘strong’ antigens and T-independent ‘weak’ antigens.
Characteristics of T-independent response, typically IgM.
Response to polysaccharides (e.g. to bacterial capsules) – absence of T cell involvement and consequent weak, short-lived response; relevance to vaccination.

32.2.2 ANTIGEN PRESENTING CELLS (APC)

Professional APC: dendritic cells (DCs), that activate naïve CD4 and CD8 T cells.
Dendritic cell activation and maturation by PRR engagement.
Expression of costimulatory molecules (e.g. CD80, CD86, CD40).
Capture of antigen and migration to lymph nodes to present to T cells.
Macrophages and B cells as other types of APC.
Structure and function of MHC class I and II molecules
Structural basis of peptide binding. The importance of polymorphism within the MHC.
Antigen processing, antigenic peptide fragments:
Endocytosis of exogenous proteins by antigen presenting cells, degradation into peptides, presentation of fragments on MHC class II to CD4 Th cells.
Fate of endogenously synthesized proteins, including host proteins but also viral proteins: fragments displayed on MHC class I to CD8 CTL.
Antigen cross-presentation by dendritic cells.

32.2.3 ANTIBODY STRUCTURE AND FUNCTION

A knowledge will be assumed of the structure and function of immunoglobulins including the structure and functions of immunoglobulin sub types in health and disease (First BM Part I Syllabus **44.6.5**).

32.2.4 ANTIBODY AND TCR GENES

Basic principles of generation of diversity of antigen-binding sites.
Somatic gene rearrangement: V(D)J recombination. Sites of somatic gene rearrangement: Bone marrow and thymus.

Affinity maturation of antibodies by somatic hypermutation. Role of activation induced deaminase (AID) in somatic hypermutation and class switch recombination.

32.2.5 CLONAL SELECTION

Expression of many copies of one Ag receptor (Ig or TCR) by each lymphocyte.
Wide diversity of Ag receptors: greater than 10^9 specificities produced. Only about 1 in 10^5 lymphocytes react to any one Ag. Evidence for clonal selection.
Stimulation of lymphocytes binding Ag strongly to divide and produce clones of effector/memory cells.

32.2.6 PHYSIOLOGY OF THE IMMUNE RESPONSE

Ag transport to secondary lymphoid organs by dendritic cells or free in lymph.
Antigen-specific T cell adherence to dendritic cells and receipt of activation signals.
Exit of activated lymphocytes from secondary lymphoid organs to become effector/memory cells.
CD4+ T cell help for CTL responses. Licensing of dendritic cells to provide a temporal bridge between Th cells and CTL.

32.2.7 ACTIVATION OF T CELLS

Requirement for T cell activation for most adaptive immune responses.
T cell recognition of peptide-MHC complexes.
Basic structure of MHC molecules.
Structural basis of peptide binding.

Nature of T cell Ag receptor: MHC restriction specificity.
CD4+ T cell recognition of MHC class II.
CD8+ T cell recognition of MHC class I.

Formation and structure of the immunological synapse.
Naive T cell requirement for co-stimulatory signals.
Nature of co-stimulation, B7 (CD80, CD86), CD28, CTLA-4, differential signalling pathways, anergy induction in absence of co-stimulation.
Stimulation of activated T cell by other APCs (B cells, macrophages etc.).
Activated CD4+ T cell expression of IL-2R, secretion of IL-2: Role of IL-2 as a growth factor for T-cells.

Evidence from immunodeficient humans and animals.
Transduction of signals via CD3. Ca^{2+} signal.

32.2.8 REGULATION OF IMMUNE RESPONSES

Subsets of CD4+ T cells: Th1, Th2, Tfh, Th17, Treg.
Secretion of cytokines by activated CD4+ T cells ('helper' cells) to promote growth and differentiation of other lymphocytes, activation of macrophages: e.g. IL-2, IL-4, IFN-γ. IL-10, IL-12, functions of cytokines.
Cytokine secretion by CD4+ T cell subsets.
Clinical relevance: e.g. Th2 response ineffective in leprosy.
FoxP3 as a transcription factor determining regulatory T cells (Treg).
Induced verses natural Treg cells.

32.2.9 ACTIVATION OF B LYMPHOCYTES

The germinal centre reaction.
Requirement for CD4+ T cell help for robust antibody responses.
B cell action as APC for primed T cells; subsequent activation of the B cell.
Mechanisms of Ag presentation by B cells, nature of signals involved in B-T collaboration.
Long-lived and short-lived plasma cells (see also **30.3.2.2**).
Mechanisms of affinity maturation.
Possibility of proliferating B-cell switch from producing IgM to the other Ig isotypes (class switch recombination; not to be confused with V(D)J recombination); change to produce antibodies with increased affinity (affinity maturation).
Antibody-secreting cells (plasma cells) location in secondary lymphoid organs, mucosae (IgA) and bone marrow.

32.2.10 IMMUNOLOGICAL MEMORY

T- and B-cell memory longevity of many years (e.g. tetanus immunization 10-year protection).
Mechanisms of B cell memory, follicular dendritic cells, retention of Ag/Ab complexes. Evidence for Ag-dependence of memory.
Subsets of memory T cells: central vs effector memory T cells.

32.2.11 IMMUNOLOGICAL TOLERANCE

Random generation of Ag specificity of newly-formed lymphocytes.
Existence of some lymphocytes with receptors for self-antigens; inactivation in thymus (central tolerance) or periphery (peripheral tolerance).
Negative selection in thymus, mechanisms of central and peripheral tolerance, incomplete nature of tolerance in T and B cells. Evidence for different mechanisms of tolerance: Deletion, anergy, regulation. Role of

AIRE transcription factor in promiscuous gene expression by medullary TEC (mTEC).
Mechanisms of fetal-maternal tolerance.

32.2.11.1 A*utoimmunity*

Concept that immune responses may be initiated by self-Ag.
Implication that self-reactive lymphocytes exist in the periphery.
Genetic predisposition to autoimmunity – role of the MHC.
Hypotheses to explain activation of these lymphocytes in autoimmunity e.g. molecular mimicry.
Concept and mechanisms of privilege.
Examples of autoimmune disease, brief details of pathogenic mechanisms:
cell-mediated - insulin-dependent diabetes, rheumatoid arthritis.
antibody-mediated - myasthenia gravis, Graves' disease. (hyperthyroidism), and rheumatic fever.
Experimental models of autoimmune disease:
non-obese diabetic (NOD) mice.
experimental autoimmune encephalomyelitis (EAE).
IPEX syndrome caused by FoxP3 mutation and APECED resulting from failure of the AIRE gene.

32.2.11.2 Major histocompatibility complex

Allelic polymorphism of MHC genes leads to preferential presentation of certain antigens and may lead to disease association e.g. insulin-dependent diabetes, rheumatoid arthritis.
Epitope spreading in autoimmunity.

32.2.12 MONOCLONAL ANTIBODIES

Principles of production and use of monoclonal antibodies including flow cytometry and ELISA.
Therapeutic use of monoclonal antibodies in treating autoimmunity and cancers.

32.3 EFFECTOR MECHANISMS IN IMMUNITY TO INFECTION

32.3.1 ANTIBODY

32.3.1.1 Defence against Infection

Elimination of infection; opsonization, initiation of acute inflammation.
Resistance to reinfection:
prevention of pathogen binding to and entering host cells - virus

neutralization.
neutralization of bacterial products, including exotoxins.
Fc receptor-mediated antibody functions such as antibody-dependent cell mediated cytotoxicity (ADCC). Fc receptor-expressing cells include monocytes, macrophages, NK cells.

32.3.1.2 Mucosal Immunity

Mucosae as the major site of pathogen entry.
Concept of common mucosal immune system.
Need to protect against infection but not make harmful responses to food. Oral tolerance. Importance of common mucosal system in neonatal immunity.

Secondary lymphoid tissues - Peyer's patches.
Functions of IgA. Mechanisms of IgA synthesis and transport.
Regulation of IgA synthesis.
Functional interaction with microbiota.

32.3.2 CD8+ T-CELLS

Recognition of peptide-MHC class I complex.
Cytotoxicity: induction of apoptosis in target cell; killing of virally infected cells to abort infection; potential killing of tumour cells.
Mechanisms of lysis: perforin/granzyme vs FasL killing.

32.3.3 NATURAL KILLER CELLS

Receptors on NK cells; killer inhibitory receptors (KIRs), recognition of lack of MHC class I (the 'missing self' hypothesis).
Molecules activating NK cells: IL-12, IL-2, IFN-γ.
Role in innate immune system; interplay with the specific immune response.
Lack of TCR or Ig expression; potential to kill virally infected cells.
Secretion of IFN-γ, activation of macrophages early in response.
Human NK cell deficiencies.

32.3.4 MACROPHAGES

Expression of MHC class II on activation; role as APC for CD4+ T cells. Activation of macrophages by CD4+ cells (e.g. response to mycobacterial infection; see **33.5.3**).
Role in the innate immune system (see **31.2.5**); interplay with the specific immune response.

33. BACTERIOLOGY

Note: The following sections to be read in conjunction with the core and extension lists of specified pathogens (see **33.5**).

33.1 BACTERIAL STRUCTURE AND PHYSIOLOGY

33.1.1 BACTERIAL SIZE, SHAPE AND COMPOSITION

Bacteria as prokaryotes: principal differences between bacterial and eukaryotic cells. Relative sizes. Properties and functions of essential cellular structures: nucleoid, ribosomes, cytoplasmic membrane.

The schematic structure of the bacterial cell envelope: peptidoglycan, teichoic acids, mycolic acids, outer membrane including lipopolysaccharide. Chemical description of peptidoglycan and lipopolysaccharide structure

33.1.2 BACTERIAL SURFACE STRUCTURES

The cell wall, polysaccharide capsules, pili, flagella, lipopolysaccharide, fimbriae.
Engagement of surface structures with components of the innate and adaptive immune system.
Typing methods based on surface structures.
Examples of important Gram positive and negative pathogens.
Secretion systems of bacteria.

33.1.3 MECHANISMS CONCERNING BACTERIAL VARIATION

Mechanisms for horizontal transfer of DNA in bacteria: transformation, transduction, conjugation.
Impact of horizontally acquired DNA on bacterial phenotypes and virulence
Definition of antigenic and phase variation.
Mobile genetic elements, e.g. plasmids, bacteriophages, transposons, integrons.
Transfer of antibiotic resistance elements.
Exchange of virulence determinants. Evolution of pathogenic *E. coli.*
Role of the bacterial envelope in pathogenesis with reference to core organisms (see **33.5**).
Emergence of MRSA.

Intergenomic *vs*. intragenomic events.
Evolution of virulence in enteric pathogens.
Pilin variation, fimbrial variation.

33.1.4 NORMAL MICROBIOTA AND OPPORTUNISM

Blood, lymph and CSF are normally sterile.
General composition of normal microbiota of skin and mucosae.

Adaptations for growth on skin and in gut.

Highly mixed populations of niche-adapted species.
Commensals or symbiotic organisms are usually harmless.
Small proportion of potentially pathogenic organisms (opportunists).
Predisposition to infection due to disruption of physical barriers and attenuation of active responses e.g. wounds, catheterization, chronic ulcers, foreign bodies, diabetes, immunodeficiency.
Concepts of the immunocompromised and immunosuppressed hosts.
Principles of disinfection & sterilization. Antibacterial action of the following and their use in preventing infection: Pasteurization, autoclaving, hypochlorite, halogenated phenols, gamma-irradiation.

Functional interactions between microbiota and host immune systems in health and disease (see also **32.3.1.2**).

33.2 TREATMENT OF BACTERIAL INFECTION

(Note: for immunisation, see **38**)

33.2.1 PHYSICAL METHODS

Surgical drainage e.g. of abscesses.
Debridement e.g. in necrotizing fasciitis.

33.2.2 PRINCIPLES OF ANTIBIOTIC ACTION

You should be able to illustrate core concepts by reference to the various *classes* of antibiotics.
Mechanisms of action of different classes of antibiotics:
Concept of selective action.

- inhibition of cell wall synthesis: e.g. β-lactams (such as penicillin; amoxicillin; benzylpenicillin; flucloxacillin).
  block peptide cross-linking in growing cell wall; bactericidal.
- Isoniazid blocks long-chain mycolic acids (unique to Mycobacteria), bactericidal to growing organisms, otherwise bacteriostatic.
- inhibition of bacterial protein synthesis by binding to bacterial ribosomes: e.g. macrolides (such as erythromycin), aminoglycosides (such as gentamicin, neomycin and streptomycin), chloramphenicol (inhibits peptidyl transferase). Tetracycline (binds to the bacterial 30S ribosome and prevents translation).
- inhibition of transcription: e.g. rifamycins (such as rifampicin).
- inhibition of folate metabolism and hence of DNA synthesis: e.g. 2,4-diaminopyridines (such as trimethoprim).
- inhibition of DNA synthesis by binding to DNA gyrase: quinolones (such as ciprofloxacin).
- Sulphonamides (antifolates) now rarely used because of resistance.

Derivatives with different spectra of activity, bioavailability, and adverse effects.

33.2.3 PRACTICAL CONSIDERATIONS FOR ANTIBIOTIC USE

Choice of antibiotic with appropriate spectrum of activity before and after microbial diagnosis.
Ability of antibiotic to reach infected site.
Dangers of indiscriminate use: drug resistance, elimination of normal microbiota.
Synergism and antagonism between antibiotics.
Hypersensitivity to antibiotics.

33.2.4 MECHANISMS OF ANTIBIOTIC RESISTANCE

Genetic mutation; effect of selection pressure. Antibiotic-resistance is most often determined by plasmids.
Multiple drug resistance.
Medical and veterinary sources of antibiotic selection pressure.
Recombination.
Mechanisms of antibiotic resistance:
- Target-site insensitivity, e.g. changes to ribosome in erythromycin resistance.
- Enzymatic inactivation, e.g. β-lactamases in penicillin resistance, phosphotransferases in aminoglycoside resistance.
- Gyrase mutations in quinolone resistance.
- Development of cell wall impermeability, e.g. mutant porins in Gram-negative bacteria.
- Drug export, multi-drug efflux system.

33.3 BACTERIAL DIAGNOSIS

(Note: This is taught mostly through the practical course – see the practical class notebooks).

33.3.1 ISOLATION OF PRESUMPTIVE PATHOGEN

Safe handling of potentially pathogenic micro-organisms.
Isolation, culture and purification of bacteria from clinical specimens.
Koch’s postulates.
The use of selective and indicator media in the diagnostic laboratory (e.g. MacConkey's agar).

33.3.2 PRINCIPLES OF IDENTIFICATION

Gram staining, and colony and cellular morphology in preliminary identification (exemplified by reference to pathogens in **33.5**).

Tests for antibiotic sensitivity.

Knowledge of the appropriate use of catalase, coagulase, oxidase tests, Streptococcal carbohydrate antigen grouping and MacConkey agar to discriminate core pathogens listed in **33.5** (as detailed in the diagnostic flowchart in the Class Practical Book).

33.3.3 ROLE OF THE DIAGNOSTIC LABORATORY

Making and confirming diagnoses, monitoring treatment, antibiotic susceptibility testing, bacterial typing, provision of information for local, national and international epidemiology.

Concept of presumptive diagnosis (based on clinical signs, patient history, local epidemiology) and associated empirical therapy. Diagnosis and treatment refined following lab tests.

33.4 BACTERIAL PATHOGENESIS

33.4.1 PRINCIPLES OF COMMENSALISM AND VIRULENCE

Definition of virulence.
Molecular Koch's postulates.
Definition and examples of bacteraemia, septicaemia and septic shock.

33.4.2 ATTRIBUTES NECESSARY FOR VIRULENCE

Tropism e.g. adhesion of bacteria to body surfaces, cell invasion, example: role of the Type 1 pilus.
Elicit host cell damage via exotoxins and endotoxin from Gram negative bacteria.
Immune evasion e.g. host mimicry, antigenic variation, recruitment of immune modulators, subversion of immune responses.
Examples of strategies employed by *Neisseria meningitidis* and *Staphylococcus aureus.*
Acquisition of nutrients e.g. iron.
Host-to-host transmission.

33.4.3 INTRACELLULAR PATHOGENS

Intracellular life cycle as a means to avoid immune responses. Induction of cellular uptake by bacteria.

Invasion of cells by *Shigella* and *Salmonella.* Manipulation of the host cytoskeleton by *Listeria.*
Role of bacterial secretion systems during entry.
Avoidance of lysosomal function and other intracellular killing mechanisms, e.g. *Mycobacterium tuberculosis.* Subversion of phagolysosomal function.
Interactions with autophagy.

33.4.4 EXTRACELLULAR PATHOGENS

Toxin mediated disease:
Superantigens.
Clostridial toxins.
Endotoxic shock.
AB toxins, pore forming toxins, specificity of targets of bacterial toxins.
TSSTs produced by *Staphylococcus*.
Examples of extracellular pathogens: *Neisseria meningitidis.*

33.4.5 REGULATION OF VIRULENCE GENE EXPRESSION

e.g. two-component systems, quorum sensing, thermosensors in pathogens.

33.5 SPECIFIC PATHOGENIC BACTERIA

33.5.1 GRAM-POSITIVE ORGANISMS

Streptococcus pneumoniae: primary lobar pneumonia.
Streptococcus pyogenes: (Group A Strep.) pharyngitis; cellulitis; rheumatic fever and glomerulonephritis.
Expression of virulence determinants may be regulated by environment: e.g. in group A Streptococci by CO_2.
Staphylococcus aureus: abscesses, surgical wound and burn infections, food poisoning.
Examples of adhesins, aggressins (e.g. toxins) and antibiotic resistance genes carried by mobile genetic elements (in Staphs & Streps).
Methicillin-resistant *Staphylococcus aureus* (MRSA).
Clostridia spp. *Clostridium difficile* and *Clostridium tetani*: anaerobe; spore-former.

33.5.2 ENTERIC O-ANTIGEN-POSSESSING GRAM-NEGATIVE BACTERIA

Escherichia coli, *Shigella spp.*, and *Salmonella spp.*: travellers' diarrhoea, dysentery, enteric fevers, food poisoning.
Vibrio cholerae: cholera.

Klebsiella spp.
Pseudomonas spp.
EHEC and EPEC as examples of pathogens.

33.5.3 MYCOBACTERIA

Mycobacterium tuberculosis (Mtb): tuberculosis. *Mycobacterium leprae.*

Slow growth, mycolic acid cell wall, few surface targets, resistance to phagolysosomal killing, macrophage subversion.
Primary infection: Ghon focus formation, granuloma formation (see **31.3.2**).
Reactivation.
Role of T cells in control of replication of Mtb.
Treatment with antibacterial cocktail over long term.
HIV / tuberculosis interactions.
Assessment of immunity / exposure to tuberculosis (TB).
Multidrug resistance.

33.5.4 NON-O-ANTIGEN-POSSESSING GRAM-NEGATIVE BACTERIA

e.g. *Neisseria gonorrhoeae and Neisseria meningitidis.*
N. gonorrhoeae: differences between men and women with respect to asymptomatic carriage.
Haemophilus influenzae.
Bordetella pertussis.
Legionella pneumophila.
Campylobacter jejuni.

Main steps of infection and transmission cycle, key interactions, importance of sialylation and capsule for evasion.

33.5.5 IMPORTANT CAUSES OF HOSPITAL ACQUIRED INFECTIONS

*Mode of transmission and sources of infection in hospitals (see **38.1**).*

34. MYCOLOGY

34.1 FUNGI OF MEDICAL IMPORTANCE

Fungi as a distinct kingdom of eukaryotes with rigid cell walls.
Unicellular and hyphal growth.
Examples of fungal diseases e.g. athletes' foot, thrush, ringworm.
Opportunistic infections, fungal diseases in AIDS patients.

Yeasts e.g. *Candida* (a commensal in the mouth, gut, vagina – cause of thrush); *Pneumocystis* and *Cryptococcus.*
Filamentous fungi such as *Aspergillus.*
Importance of health of host in resistance to fungal infection.
Aspergillus as an example of the effect of the host upon disease: no disease, allergic bronchopulmonary aspergillosis, aspergilloma in lung cavities, invasive aspergillosis in neutropaenics and severely immunocompromised patients.
Chemotherapy of fungal disease.

35. VIROLOGY

35.1 EXAMPLES OF VIRAL DISEASES

Symptoms, pathogenesis, basis of treatment, and prophylaxis in the following examples; replication and structure of the causative viruses.

Influenza (influenza virus).
Covid-19 (SARS-CoV-2).

Poliomyelitis (polio virus).
Human Immunodeficiency Virus (HIV)
Paramyxoviridae: measles virus, mumps virus, respiratory syncytial virus
Coronaviridae:SARS-CoV, MERS-CoV.
Picornaviridae: rhinovirus – common cold.
Rhabdoviridae: rabies virus.
Reoviridae: rotavirus (childhood diarrhoea).
Flaviviridae: Dengue virus, yellow fever virus, West Nile virus.
Togaviridae: rubella virus.
Challenges posed by Dengue and Ebola virus.
RSV
Viral hepatitis (HAV, HBV and HCV; cell killing by cytotoxic T-cells) and hepatocellular carcinoma (HBV).
Papilloma viruses (warts, cervical carcinoma, other carcinomas).
Infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma (Epstein-Barr virus).
Herpesviridae: cytomegalovirus, HSV (labial and genital herpes), varicella-zoster virus (chicken pox and shingles).

New and emerging viruses.

35.2 LABORATORY DIAGNOSTIC METHODS

Viraemia. Detection of virus in blood (or CSF) as an indication of current infection. Methods for detecting virus (or virus fragments): ELISA, PCR (or RT-PCR), plaque assay, infectious centre assay, haemagglutination. Visualisation by electron microscopy.
Serology. Existence of serum antibody to virus as an indication of prior infection. Dependence on specificity of immune response. Methods for detecting specific antibody: ELISA, inhibition of haemagglutination or plaque formation.

35.3 VIRION STRUCTURE AND CLASSIFICATION

Classification on the basis of size, microscopy.

Simplicity of structure: protein and nucleic acid (RNA or DNA) (lipid and carbohydrate). Diversity of structure, host target. and disease.

The role of the nucleocapsid in packaging virion nucleic acid.

Capsomers. Helical symmetry, e.g. rabies virus, influenza virus. Icosahedral symmetry, e.g. polio virus.

The existence of an envelope in some viruses: the origin of the lipid bilayer from host cell; viral attachment proteins; susceptibility to by detergents, e.g. bile.

The presence of RNA or DNA; possible segmentation; positive or negative polarity. Single-stranded (ss) or double stranded (ds).

Linear or circular; size range: 3-300 kb.

Nucleic acid type (and replication strategy); the Baltimore classification. Finer viral classification based on structure, serology and sequence homology.

Families, subfamilies, genera, species, strains. ssDNA viruses.

35.4 VIRUS REPLICATION

Viruses as obligate intracellular parasites, with a unique mode of replication.

The 'eclipse phase' disappearance of extracellular, infectious virus while intracellular replication occurs.

Entry into cells: concept of virus attachment proteins and their cellular receptors, e.g. HIV gp120 and CD4; influenza virus haemagglutinin and sialic acid; SARS-CoV-2 and ACE2.

Particle/pfu ratios.
EBV gp340 and CD21. Polio virus receptor (PVR).

HIV co –receptors (chemokine receptors CXCR4, CCR5).
Relationship between the distribution of cellular receptors for a virus and its tissue tropism.

Modes of penetration:
HIV – pH-independent envelope fusion.
Influenza virus – low pH-dependent envelope fusion in endosomes.
Capsid transformations at cell surface and endosomes (polio virus).

Nuclear localization (flu, HIV, EBV) and integration (HIV).

Viral gene expression:
Principle of subversion of cell metabolism to manufacture virus components, e.g. poliovirus effects on protein synthesis.

Temporal and quantitative control of gene expression.
Latency-associated transcription (EBV).
Tat and Rev in regulation of HIV-1 expression.

Nucleic acid replication:
Involvement of viral polymerases and other viral enzymes (drug targets: see **35.6.4**).
The requirement of RNA viruses for viral RNA polymerases; possession of polymerases in the virion of negative-strand viruses.

Strategy for production of genomic and messenger nucleic acids.
Reliance of small DNA viruses (e.g. HPV) on host replication machinery.

Viral enzymes:
Essential e.g. DNA and RNA polymerases, reverse transcriptase.

Non-essential e.g. thymidine kinase, ribonucleotide reductase, virulence factors.
The need for reverse transcriptase and integrase in retroviruses: importance as drug targets.
Promotion of amino acid variation by genetic diversity leads: immune escape.
High variation resulting from reverse transcriptase-mediated HIV genome mutation.
Influenza virus mutation and genetic reassortment and recombination (antigenic drift and shift).
Assembly and release:
Self-assembly of capsids and virus-like particles.
budding of enveloped viruses (HIV, EBV).
cell lysis to release naked viruses (poliovirus).
Role of viral proteases in virus maturation (poliovirus, HIV-1) and as drug targets (see **35.6.4**).

Prolonged shedding during persistent infections.
Specific lysis proteins.

35.5 CELLULAR AND SYSTEMIC CONSEQUENCES OF INFECTION

The existence of non-pathogenic viruses.
Mechanisms by which viruses produce disease in whole organism.
Outcome of infection influenced by viral and host factors (see following sections).
Effect of host factors on probability of infection: age, health, immunosuppressive drugs (including steroids).

Effect of dose of infectious agent on outcome.

35.5.1 CELL DEATH

Cytopathic effects of polio virus (motor neurons) and HIV (CD4+ cells).
Role of apoptosis (see **31.1**).
Role of cell-mediated immunity in viral hepatitis.

HIV infection and destruction of gut-associated lymphoid tissue and ensuing immune activation syndrome.
Cytoskeletal changes: changes in cell shape, loss of cell adhesion (notable *in vitro*).

35.5.2 CELLULAR TRANSFORMATION

35.5.2.1 Transformation by DNA Viruses

Transformation as a comparatively rare and atypical consequence of viral infection.
EBV as a cause of infectious mononucleosis, and predisposing factor for Burkitt’s lymphoma (BL) and nasopharyngeal carcinoma (NPC). The requirement for other cofactors.

BL as a defective form of EBV latency in B cells; chromosomal translocations in BL: *MYC* with Ig light or heavy chain loci.
Interactions of virus proteins with products of tumour-suppressor genes
Kaposi's sarcoma and HHV 8.

Papilloma viruses as a cause of common warts (benign tumours); predisposition to carcinoma of the uterine cervix and other carcinomas by certain serotypes.
Hepatocellular carcinoma following chronic HBV and HCV infection.
Stimulation of proliferation of cells infected by DNA viruses with small genomes and some RNA viruses to promote viral replication.
Viral transforming proteins:
Papilloma virus E6 & E7; interactions with cell cycle control proteins.
Adenoviridae, E1A and E1B.
Polyoma viruses (SV40 and polyoma) large T antigen

35.5.2.2 Transformation by RNA viruses

Cellular transformation by retroviruses:
Adult T-cell leukaemia/lymphoma (ATLL) as a rare occurrence in carriers of HTLV-1 (lifetime risk ~4%). Activation of cellular growth-promoting genes by Tax, a virally encoded transcription factor.

Retroviruses oncogenic in animals: e.g. RSV, AMV, MLV.

35.5.3 CELLULAR AND CLINICAL LATENCY

Cellular latency as the persistence of viral genomes in cells without overt expression of new viruses. Observed in herpes viruses and retroviruses.
Latent infections by herpes viruses:
HSV (cold sores, genital herpes); EBV mimicry of antigen-dependent B cell activation. Reactivation during immunosuppression, e.g. transplantation surgery. Cytomegalovirus. Varicella-Zoster virus: chickenpox and zoster ('shingles').
Clinical latency as the temporary absence of symptoms in spite of infection, resulting from cellular latency, active immunity, etc.
HIV: transcriptional silencing of the integrated provirus in response to host cell quiescence: formation of drug- and immune-resistant viral reservoirs.

35.5.4 DISSEMINATION IN THE HOST

Local spread:
Symptoms due to cytopathic viruses appear after a short incubation period e.g. influenza, rotavirus.
Spread to local lymph nodes.
Systemic infection:
Viremia enables infection of distant sites.
Effect of virus on distant tissues becomes evident after a longer incubation period, e.g. poliomyelitis.

Restriction of virus replication to local site by polarized shedding to apical surface of epithelium (e.g. flu).
Spread to lymph nodes as free virus or within phagocytes.
Virus in blood may be free in plasma or within leukocytes.
Secondary viremia as a consequence of viral release from secondary sites into the blood.

Penetration of vascular barrier by viruses (to reach secondary sites esp. CNS) may be within recirculating leukocytes or by replication in endothelial cells.

35.5.5 FEVER, MALAISE ETC

Overlapping spectrum of symptoms found in many viral infections. Most symptoms result from release of mediators of inflammation (see **31.2.6-7**).

Arthropathy, myalgia, headaches, vomiting, dizziness, depression. Post-viral syndromes (ME, 'long COVID').

35.5.6 RESOLUTION

Acute infections:
Action and induction of interferons.
Restriction of viral replication by local production of Type I α/β interferons.
Clearance of virus-infected cells by immune system, chiefly CD8+ lymphocytes (see **32.3.2).**
Clearance of free virus by antibody and complement.
Re-infection prevented by plasma IgG and secretory IgA.

Persistent and chronic infections:
HIV: attack on CD4+ lymphocytes leading to immunodeficiency if not treated; antigenic variation.
Epstein-Barr virus: asymptomatic, or glandular fever, both followed by latent infection: role of CMI in control and symptoms (see **35.5.3**).
Immunomodulatory viral proteins of EBV, other herpes and pox viruses: blockage of complement, interferon, inflammation, fever, MHC I-Ag presentation.
HBV - leading possibly to liver cancer.
Measles, subacute sclerosing panencephalitis (SSPE).

35.6 POPULATION VIROLOGY

35.6.1 PERSISTENCE AND TRANSMISSION

Availability of hosts, population density, multiple different hosts

35.6.2 ROUTES OF TRANSMISSION

Feco-oral route (polio). Mammal bites; rabies virus in saliva.
Respiratory droplets or aerosol (influenza, SARS-CoV-2).
Saliva (EBV). Skin scratches (e.g. papilloma).
Arthropod bites: yellow fever; dengue, West Nile viruses.

Concept of animal reservoirs, zoonoses.
Genito-urinary transmission (HIV).
Transfusion, blood products, i.v. drug abuse (HIV, HBV). Transfusion hepatitis (usually HCV).

35.6.3 PREVENTION AND TREATMENT OF INFECTION

Vaccination, e.g. smallpox eradication
Antiviral drugs

35.6.4 VACCINATION (SEE SECTION 37)

35.6.5 ANTIGENIC VARIATION

Mutability of viral genomes (especially those of RNA viruses). Error rates of RNA-dependent nucleic acid polymerises.
Neutralizing antibody and Tc as selection pressures.
Antigenic drift (e.g. influenza, SARS-CoV-2 and HIV).
Antigenic shift (e.g. influenza). Role of avian and porcine hosts in pandemic shifts.
Antigenic conservatism (e.g. polio).
Concept of virus quasi-species.
Implications for vaccination regimes.

Structural constraints on virus evolution.

CTL as selective agents.

35.6.4 THERAPY OF VIRAL DISEASES

35.6.4.1 Antiviral therapy

Limited choice of targets compared to bacteria (intimacy of parasitism).
Viral target enzymes:
HIV reverse transcriptase: two classes; chain terminators e.g. zidovudine (AZT); direct RT inhibitors, e.g. nevirapine.
HIV protease (e.g. saquinavir) and integrase (e.g. raltegravir) inhibitors.
HIV entry inhibitor binds CCR5 (maraviroc).

Anti-retroviral therapy (ART): use of combinations of 2 or 3 anti-retroviral drugs to minimise drug resistance that results from high HIV mutation rate.
Inhibition of influenza neuraminidase (zanamivir e.g. Relenza, oseltamivir (e.g. Tamiflu). Possibility of interfering with virus/cell receptor recognition.
Influenza virus - M2 ion channel – amantadine.
Herpes - prodrug (aciclovir) conversion by viral thymidine kinase into a guanosine analogue.

Interferons e.g. Type I IFN α in HCV.
Cytokine therapy.

35.6.4.2 Palliative therapy

Problem of lack of effective drugs.
Problem of lack of specific diagnosis: similarity of symptoms.
Anti-inflammatory drugs (see **31.5**).

36. PARASITOLOGY [PATH]

Global world health; worldwide significance of protozoal and helminth infections.
Obstacles to development of modern drugs and effective vaccines.
Protozoa: basic life cycle and pathogenesis. *Plasmodium* spp, Chloroquine and its mode of action. Other protozoan parasites: amoebae, *Toxoplasma*, *Giardia,* Entamoeba, *Leishmania* spp, *Trypanosoma* spp., *Schistosoma* spp.

Pathogenicity factors e.g. antigenic variation.

Taenia spp., *Echinococcus* spp.
Helminth parasites.
Anti-parasite chemotherapy and vaccine development.

37. IMMUNISATION AGAINST INFECTIOUS DISEASE

37.1 PASSIVE IMMUNIZATION

Intravenous immunoglobulin (IVIg), e.g. for rabies, Hepatitis B.

Anti-venom therapy.
Advantage: instant effectiveness.
Disadvantage: short-lasting, serum sickness (response to foreign protein).

37.2 ACTIVE IMMUNIZATION

37.2.1 LIVE ATTENUATED VACCINES

Attenuated form of virulent organism (e.g. measles, Sabin polio vaccine, BCG). Advantages in terms of lifespan, inexpensive manufacture, ease of administration, induction of both cell-mediated and antibody response.
Disadvantages in terms of rare reversion to virulence, severity of reaction
Immunologically related organism (e.g. *vaccinia*).

Other examples of attenuated organisms: rubella, yellow fever 17D vaccine.

(life-threatening infections in immune-incompetent), vaccine shedding into environment, storage difficulty due to heat lability.
Immunisation with virulent organism (variolation).

37.2.2 KILLED AND SUBUNIT VACCINES

Chemical treatment of antigen preparation to inactivate infectivity and toxicity of whole organisms, e.g. cholera, pertussis, seasonal flu vaccine.
Advantages in terms of safety and improved stability in storage.
Disadvantages in terms of expense, less cell-mediated immunity, need for multiple administrations, adjuvants, boosters to offset shorter-lasting immunity.
Subunit vaccines derived from genetically engineered protein subunit e.g. HBV, HPV.
Vaccines against *Streptococcus pneumoniae*.
Inactivated exotoxin e.g. tetanus toxoid.
Composition of vaccines.
Types of antigens; MMR vaccine issues.
Development of conjugate vaccines targeting carbohydrate antigens (illustrating the principle of linked recognition); vaccine escape.

Antigen, adjuvant and excipients.
Serogroup switching in the meningococcus.
Serotype replacement in the pneumococcus.

37.2.3 VECTORED VACCINES

Use of non-pathogenic viral vectors (e.g. adenovirus, pox virus) to carry genetic material encoding vaccine antigens (eg. HIV *gag. SARS-CoV 2 spike protein*).

37.2.4 mRNA VACCINES

Nucleoside-modification to enhance stability of mRNA encoding antigenic protein; delivery in lipid nanoparticles (e.g. BioNTech or Moderna vaccines encoding spike protein of SARS-CoV 2).

37.2.5 ADJUVANTS

Role of adjuvants as a depot of antigen.
Inclusion of PAMPs to stimulate innate immunity via PRRs.
Examples of experimental adjuvants e.g. complete Freunds adjuvant (CFA).
Examples of clinically approved adjuvants eg Alum salts.

38. EPIDEMIOLOGY AND POPULATION HEALTH

38.1 KEY CONCEPTS

The infection cycle and routes of transmission.
Incubation period, infectious period, latent period.
Epidemic, outbreak, pandemic.
Measures of transmissibility: attack rate, secondary attack rate.
Methods in epidemiology: case control studies, cohort studies, randomised controlled trials.
The three phases of clinical trials and their purposes.
Epidemiology and risk factors for human infection with pathogenic bacteria, viruses and protozoa, with particular reference to TB, HIV and malaria.
Hospital-acquired infections in the UK: nosocomial and iatrogenic transmission, e.g. MRSA, *C. difficile*, norovirus.
Impact of immunisation on morbidity and mortality.
History of vaccine development. Vaccine efficacy. Direct and indirect effects of vaccines. Ideal vaccines and challenges in their development.

Pre- and post-exposure prophylaxis.
Early intervention.

38.2 GLOBAL HEALTH

Leading causes of infant and childhood mortality and morbidity in resource-limited health care systems, including vaccine-preventable diseases, and infection due to resistant pathogens, e.g. antimicrobial resistance (AMR) in *Streptococcus*, pneumonia, and malaria.

Success of Expanded Programme on Immunization (World Health Organisation EPI) and challenges of implementing new vaccine programmes e.g. MenAfriVac.

38.3 PREVENTION AND CONTROL OF COMMUNICABLE DISEASE

Relative importance of surveillance, prophylaxis, treatment, immunisation. and other public health measures, e.g. public education in the control of communicable disease. Concept of notifiable diseases.
Standard schedules for childhood immunisations.
Herd immunity, basic reproduction number, critical vaccination percentage.
Vaccine side effects: risk to individual versus benefit to population.
Determination of effectiveness of vaccination by randomised controlled trial.
Prevention of exposure, quarantine. Role of contact tracing, carriers.

Control of reservoirs, vectors.

Rationale for timing. Degenerative disease transmissibility: cultural, iatrogenic, genetic determinants of transmission in vCJD.

Incentives for high vaccination uptake. Ethics of compensation.
Procedures for introduction of new vaccines. Regulatory issues for trials.

38.4 STATISTICAL METHODS FOR POPULATION PATHOLOGY

Variables, including continuous, discrete, dependent, independent.
Estimation: confidence intervals for a single proportion, the difference between two proportions and an odds ratio.

Hypothesis tests: test of statistical significance for comparing two proportions (z-tests and chi-squared tests).

39. IMMUNOPATHOLOGY

Concept that immune responses can cause harm to the host and are central to many clinically important diseases.

39.1 HYPERSENSITIVITY

39.1.1 ANAPHYLACTIC (TYPE 1)

Morphology and distribution of mast cells.
Allergic responses: hay fever, asthma, food allergies.
Central role of IgE in triggering mast cell degranulation; FcRε on mast cells.
Origin and effects of histamine, leukotrienes and prostaglandins on smooth muscle of blood vessels and bronchi and on mucosae.
Physiology of anaphalaxis.
Treatment:
Immediate: anti-histamines, adrenaline.
Long-term: cromoglycate, leukotriene receptor antagonists, glucocorticoids, anti-histamines.

Other triggers of degranulation: C5a and C3a, trauma.

Genetic basis of allergies and asthma.
Relationship to Th2 responses.

39.1.2 CYTOTOXIC (TYPE 2)

Cytotoxic effects mediated by antibody binding to surfaces ± complement leading to cell lysis or opsonisation.
Transfusion reactions - the ABO and Rhesus blood groups.
Haemolytic disease of the new-born; pathogenesis and prevention.
Hyperacute allograft rejection.

39.1.3 IMMUNE COMPLEXES (TYPE 3)

Activation of complement by antigen/antibody complexes to initiate acute inflammation.
Local and diffuse complexes: local complexes at specific sites: e.g. inhaled antigen - farmer’s lung; diffuse circulating complexes with deposition in microvasculature of joints, kidneys e.g. systemic lupus erythematosus (SLE), with involvement of autoantibodies.

39.1.4 DELAYED TYPE HYPERSENSITIVITY 'DTH' (TYPE 4)

The role of T cells and absence of a role for antibodies; slow development with cell accumulation.
Roles of T cells and activated macrophages.
Role of persistent antigen: e.g. Mycobacteria in tuberculosis, self-antigen in autoimmunity. Mantoux test; contact sensitivity.

Details of pathogenesis of contact sensitivity

39.1.5 STIMULATORY HYPERSENSITIVITY (TYPE 5)

The role of autoantibodies acting as agonists on cell surface receptors
e.g. Graves' disease (hyperthyroidism).

40. IMMUNE DEFICIENCY AND IMMUNOSUPPRESSION

40.1 IMMUNE DEFICIENCY

40.1.1 T-CELL DEFICIENCIES

Enhancement of susceptibility to infections by viruses and facultative intracellular pathogens.
Inherited: e.g. thymic aplasia (lack of T cells). Adenosine deaminase (ADA) deficiency.
Acquired: e.g. loss of $CD4^+$ T cells due to HIV resulting in AIDS.

Loss of cell-mediated immunity due to measles.

40.1.2 B-CELL DEFICIENCIES

Enhancement of susceptibility to pyogenic infections.
Inherited: e.g. agammaglobulinaemia.

40.1.3 DEFICIENCIES OF THE INNATE IMMUNE SYSTEM

Enhancement of susceptibility to pyogenic infections.
Cellular defects e.g. involving PMN.
Chronic granulomatous disease; Chédiak-Higashi syndrome.
Deficiencies of secreted molecules, e.g. of a complement component.

40.1.4 TREATMENT

Replacement therapy e.g. immunoglobin treatment.
Bone-marrow transplantation.
Chemotherapy e.g. in AIDS.

Gene therapy (e.g. attempted correction of ADA deficiency).

40.2 TRANSPLANTATION

Definition of allograft, xenograft, isograft.
Tissue typing; major and minor histocompatibility antigens.
Basis of graft-versus-host disease (GvHD).
Pathological mechanisms of acute and chronic graft rejection.

40.3 IATROGENIC AND THERAPEUTIC IMMUNOSUPPRESSION

As a complication of the use of cytotoxic drugs or irradiation in tumour therapy (neutropenic sepsis).
Therapeutic immunosuppression (i.e. intentional) after transplantation surgery or to control auto-immune disease.

41. CARDIOVASCULAR PATHOLOGY

41.1 HAEMOSTASIS

A knowledge of haemostasis will be assumed as contained in the first-year syllabus **10.3.**

41.2 THROMBOSIS

"Haemostasis in wrong place".
Differences between arterial and venous thrombosis.
Deep vein thrombosis (DVT).
Risk factors in venous thrombosis. Evolution of a thrombus.
Effects of thrombosis: Stenosis, ischaemia, infarction, embolism, venous leg ulcers.
Factor V Leiden.

41.3 EMBOLISM

Types of embolism: thrombi (others: fat, air, pus, material from atheromatous plaque).
Main consequences of pulmonary embolism.
Systemic embolism: infarction.
Possible healing reactions in an embolised thrombus.

41.4 ATHEROSCLEROSIS

This section assumes knowledge of lipoprotein metabolism and cholesterol transport as contained in the first-year syllabus **44.6.4**

Epidemiology: age, sex, geographical distribution.
Cellular and molecular mechanisms of pathogenesis.
Animal models of atherosclerosis e.g. apoE and LDLR knock-out mice,
Risk factors: smoking, diabetes, genetic (LDL receptors), endocrine (sex), hypertension, hyperlipidaemia (raised LDL as opposed to HDL), oxidised LDL. Human genetics of cardiovascular disease.
Clinical manifestations: angina pectoris, myocardial infarction, claudication, embolism, aneurysm, ischaemic stroke.

41.5 PREVENTION AND TREATMENT OF CV DISEASE

Lifestyle choices: smoking, obesity, physical activity, blood pressure, diet.
Key epidemiological studies e.g. Framingham, MRFIT.
Key clinical trials e.g. 4S statin trial.
Anti-thrombotic drugs: aspirin and its action; GpIIb and IIIa inhibitors; thrombolytic agents e.g. streptokinase, tPA (e.g. Alteplase).
Anti-coagulant drugs: heparin and warfarin; their action and reversal.
Lipid-lowering drugs: action of the statins, e.g. simvastatin.
New drugs that alter plasma cholesterol and lipoprotein levels e.g. ezetimide and anti-PCSK9 antibodies.
Surgical intervention: balloon angioplasty, stenting, coronary bypass.

New anticoagulants, e.g. apixaban.

42. DEGENERATIVE DISEASE DUE TO AMYLOID

42.1 PATHOGENESIS OF AMYLOID DISEASES

Amyloid as fibrillar deposits of abnormally folded host protein that provoke degenerative reactions. The variety of amyloid diseases, dependent on the identity of the protein involved, site of deposition, pathological consequences and causative or risk factors.
Pathological consequences of changes in protein conformation
Histological identification: Congo Red stain, birefringence.

Identity and normal function of proteins involved in amyloid diseases.
Structural basis of amyloid formation, including α-helix to β-sheet transition and fibril formation.

42.2 DISEASES OF AGEING

Alzheimer's disease (senile dementia): slow progressive, irreversible neuronal loss; progressive cholinergic deficit; intermittent but inexorable cognitive decline (see **25.3.2**).
Parkinson's disease.

αβ peptide, APP, homocysteine, acetyl and butyryl cholinesterase.
Senile systemic amyloidosis (cause of congestive heart failure; transthyretin).
Sporadic CJD.

42.3 SEQUELAE OF CHRONIC DISEASES

Secondary (peripheral) amyloidoses in chronic inflammatory diseases (esp. seen in developing countries).
Type II diabetes (multifactorial, esp. obesity (see **56.3**).

Serum amyloid A precursor protein.
Dialysis-associated amyloidosis (β2-microglobulin).

42.4 GENETIC

Mutations affecting protein folding, stability and processing.
Familial CJD. Fatal familial insomnia.

42.5 INFECTIOUS – PRION DISEASES

vCJD (PrP).

Iatrogenic CJD; BSE.

43. NEOPLASIA: THE MOLECULAR & CELLULAR BASIS OF TUMOUR GROWTH

43.1 PATHOLOGY

Note: this section assumes knowledge of the characteristics of neoplastic growth (and distinction from hyperplasia): see first year syllabus **1.12.1.2-3.**

43.1.1 GENERAL

A simple overview of the range and nomenclature of benign and malignant tumours.
Cancer screening.LL

43.1.2 BENIGN TUMOURS

Characteristics of benign tumours.
Examples of benign tumours; papilloma (warts); gliomata; adenoma (e.g. colonic polyps); leiomyoma (e.g. uterine fibroids); lipoma.
Possibility of damaging effects e.g. bleeding, pressure, endocrine toxicity, and possible progression to malignancy.

Teratoma, hydatidiform mole.

43.1.3 MALIGNANT TUMOURS (I.E. ‘CANCER’)

Examples of malignant tumours; squamous cell carcinoma; adenocarcinoma. Characteristics of malignant tumours including invasion, metastasis and progression (see first-year syllabus). Aberrant differentiation; pleomorphism and anaplasia; distinction from benign tumours.
Cancer cell morphology.
Karyotypic variability and its significance.

Tumour imaging.

43.1.4 SPREAD OF MALIGNANT TUMOURS

Local invasion: routes for invasion (including infiltration and permeation)
Metastasis; common and serious problem (but variable).
Routes for metastasis.
Common sites of secondary tumours; anatomical view, and the concept of ‘seed and soil’.
Experimental study of metastasis: Epithelial to mesenchymal transition.
The inefficiency of metastasis, the steps involved and specific interactions that may influence it.

43.1.5 CONSEQUENCES OF MALIGNANT TUMOURS

Local effects; pressure, occupation of space (e.g. intra-thoracic or intra-cranial), obstruction of vessels or ducts, intussusception of the gut, haemorrhage, infection.

Systemic effects; cachexia (weight loss, nausea, anorexia, lethargy); hormonal effects (over-secretion, ectopic secretion, or destruction of endocrine tissue); marrow destruction in leukaemias leading to infection (neutropenia), bleeding (thrombocytopenia), or anaemia. Role of TNFα in cachexia.

43.1.6 TUMOURS AND THE IMMUNE SYSTEM

Immunodeficiency or immunosuppression associated with emergence of lymphomas, digestive tract tumours and virus-associated tumours.

Immunisation against papillomavirus-associated carcinomas.

Proteins abnormally expressed on or secreted by some tumours, their use for the histological detection of tumour cells and to monitor tumour progression and relapse after remission.

43.2 REGULATION OF CELL GROWTH IN TUMOURS

Note: this section assumes knowledge of normal cell growth, hypertrophy & hyperplasia, and its control: see first year syllabus**: 1.10, 1.11.**

Note the difference between cell growth and cell proliferation.

The concept of cellular transformation, comparison with normal cell growth.

In particular:

Independence from mitogens (growth factors).

The potential for unlimited cell division ('immortality'). Telomerase.

The Warburg effect (shift to aerobic glycolysis), its impact on tumour metabolism and importance for tumour imaging by PET.

Transformation as a contributor to (yet alone insufficient for) malignancy.

Experimental assays for tumorigenic cells.

Concept of cancer stem cells – a small proportion of tumour mass that uniquely possess the ability to grow as a tumour xenograft.

Factors that limit tumour cell proliferation: many cells in a typical tumour are not actively proliferating, cellular differentiation, death (necrosis or apoptosis), cell loss (e.g. from skin and gut, or shedding into the circulation).

Cell cycle analysis *in vitro* and in tumours *in vivo.*

43.3 GENETIC BASIS OF MALIGNANCY

43.3.1 ONCOGENES

The concept of viral oncogenes as cancer-inducing genes within oncogenic viruses (e.g. Rous Sarcoma Virus, SV40). Integration of viral oncogenes into cellular DNA, and their role in the maintenance of transformation *in vitro* and tumorigenicity *in vivo*.

Cellular proto-oncogenes: genes with normal roles in the regulation of cell growth, death or differentiation, but which contribute to malignancy as oncogenes when mutated, or inappropriately over-expressed. Detection of 'morphologically transforming' oncogenes in tumour cell DNA by the 3T3 transfection assay.

Examples of oncogenes and the functions of their products in intracellular mitogenic or anti-apoptotic pathways.

Demonstration of oncogene co-operation in the transformation of normal fibroblasts.

43.3.2 SOMATIC MUTATION AND MALIGNANCY

Rarity of tumours expressed on a per cell basis.

Monoclonality of tumours.

Experimental evidence for monoclonality and ongoing evolution of tumour genomes as a consequence of selection *in vivo*.

Age-incidence data; the requirement for the accumulation of several independent genetic events.

Epidemiology of tumours in man; examples indicating the importance of chemical and physical mutagens.

The Ames test. Role of metabolism in conversion of pro-carcinogens (e.g. alcohols) to mutagenic 'ultimate carcinogens'.

Implication that malignancy develops through cells in the body accumulating changes to their genes e.g. activation of oncogenes, and loss of tumour suppressor genes. Examples of accumulated genetic and epigenetic changes in carcinogenesis e.g. the development of carcinoma of the colon.

Cancer genome projects and the identification of cancer-relevant mutations.

43.3.3 TUMOUR-SUPPRESSOR GENES

Roles of tumour suppressor genes in normal growth and development; the significance of their mutation or absence in the development of malignant tumours.

Evidence for tumour suppressor genes; recessivity of tumorigenicity in hybrid cells made by fusing normal and malignant cells.

Examples of tumour suppressor genes and suggested roles of their products: evidence from mouse models.

Inherited tumour predisposition resulting from germline mutation of a tumour suppressor gene and subsequent somatic loss of heterozygosity (e.g. inherited retinoblastoma). Identification of tumour suppressor genes (linkage and positional cloning; association of protein product with viral oncoprotein).

Testing for predisposition to tumour development.

Role of somatic loss of heterozygosity in the occurrence and progression of non-inherited tumours.

Mechanisms of loss of heterozygosity, and evidence for its importance.

43.4 CANCER THERAPY

Note that the other major therapies for cancer are surgery and radiotherapy.

43.4.1 CYTOTOXIC DRUGS

Principles of action of cytotoxic drugs used against neoplasms:
- Alkylating agents (chemically damage DNA), e.g. cyclophosphamide, cisplatin.
- Antimetabolites (metabolic inhibition of DNA synthesis), e.g. methotrexate.
- Microtubule poisons (block mitosis), e.g. vinca alkaloids such as vincristine.
- Anti-tumour antibiotics (bind DNA, inhibit topoisomerase, cause DNA breaks) e.g. doxorubicin.

Adverse effects due to limited selectivity; problem of low therapeutic index:
- Reversible cytotoxic effects (e.g. damage to bone marrow, lymphoid tissue, GI epithelium, hair).
- Irreversible toxicity to organs with little/no cell growth (kidney, nerves, heart & lungs). Vinca alkaloids are given intravenously only – severe neurotoxicity (intrathecal administration is lethal; see **19.3**).

Importance in tumour progression of the development of drug resistance.
- Strategies for avoidance of resistance: use of maximum tolerated dose, use of combination therapies.

Mechanisms of resistance to chemotherapy:
- Decreased drug entry into cells.
- Altered expression or mutation of target enzymes.
- Improved DNA repair activity.
- Decreased likelihood of apoptosis.
- Increased detoxification.
- Drug extrusion (multi-drug resistance).

43.4.2 TARGETED CANCER THERAPIES

Principle of molecular targeted therapy of tumours; lower toxicity c.f. cytotoxic drugs.

Endocrine: e.g. tamoxifen (anti-estrogen) and aromatase inhibitors (block extra-ovarian estrogen synthesis in post-menopausal women; used for breast cancer); reduction of testosterone to treat prostatic tumours (orchidectomy, drugs to depress LH release, anti-androgens).

Principes of immunotherapies harnessing T cells.

Inhibitors of growth signal transduction: therapeutic antibodies against growth factor receptors (e.g. trastuzumab; breast cancer); small molecule inhibitors (e.g. imatinib, blocks the abnormal BCR-ABL protein tyrosine kinase driving cell growth in chronic myeloid leukaemia).

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 knowledge of the syllabus below.

47.7 STATISTICS FOR RESEARCH

Overview of clinical and epidemiological research: clinical vs. statistical significance, iterative loop of research, fundamental equation of error.
Topic preparatory to critical appraisal: Types of observational study; intervention studies including randomized and cross-over trials; introduction to meta-analysis.

47.8 GRAPHICAL METHODS FOR CLINICAL AND BIOLOGICAL DATA

Graphical methods for clinical and biological data including histograms and scatterplots, survival curves, forest plots etc.

47.9 OTHER SITUATIONS

Other situations: Lognormal distribution, Poisson distribution, use of t-tables for smaller samples.

47.10 NONPARAMETRIC STATISTICS

Nonparametric statistics: Summary measures for non-normal data, introduction to nonparametric hypothesis tests.

47.11 LINEAR REGRESSION

Simple and multiple linear regression.

APPLIED PHYSIOLOGY AND PHARMACOLOGY

The second-year course and examination assume a core knowledge of Physiology and Pharmacology in the first year syllabus.

51. ELECTROLYTES AND FLUID BALANCE

51.1 REGULATION OF BODY FLUID OSMOLARITY AND VOLUME

Regulation of osmolarity by alterations in water balance.
Regulation of volume by alterations in Na^+ balance.

Abnormalities of water balance and regulation.
Dehydration associated with hyperventilation at altitude.

51.2 REGULATION OF PLASMA POTASSIUM

Normal dietary balance. Distribution and total body content of potassium.
Normal plasma concentration at rest and during exercise.
Consequences of hypo/hyperkalaemia; muscle weakness and cardiac dysrhythmias.
Renal handling of potassium. Fine-tuning of potassium reabsorption /secretion in the distal tubule; reciprocity of potassium and hydrogen ion fluxes.
Hormonal control of renal mechanisms.
Potassium sparing and potassium losing diuretics.
Non-renal handling of potassium. Redistribution of potassium under hormonal effects on Na-K ATPase (insulin, catecholamines, exogenous β_2-agonists (e.g. salbutamol).
Abnormalities of potassium balance, including diarrhoea and renal failure.

Protective effect on the myocardium of high adrenaline concentrations during exercise-induced hyperkalaemia.
Specific effects on the ECG of hyper/hypokalaemia.

Presence of hypokalaemia in *Conn's syndrome* and *Cushing's syndrome*

51.3 REGULATION OF EXTRACELLULAR CALCIUM

Distribution and total body content of Ca^{2+}: plasma Ca^{2+} level; cell Ca^{2+}.
Functions of Ca^{2+}: consequences of hypo/hypercalcaemia.
Sources and flux of Ca^{2+}: gastrointestinal absorption; renal reabsorption/excretion.
Formation and reabsorption of bone. Roles of osteoblasts, osteocytes and osteoclasts.
Hormonal regulation: parathyroid hormone, Vitamin D, calcitonin.
Special considerations: development, pregnancy, lactation, and aging.
Disorders of Ca^{2+} homeostasis. Osteomalacia, Osteoporosis. Distinction between osteomalacia and osteoporosis. Osteoporosis as a common side-effect of corticosteroid therapy.

The calcium receptor; syndromes in calcium receptor mutations.

Osteoporosis as a common disease of old age, particularly of post-menopausal women. Osteoporosis treatment.

51.4 IRON HOMEOSTASIS

Iron stores, uptake and loss of iron from the body, and the daily rotation of iron via macrophages from senescent red blood cells to production of new red blood cells.
Dietary sources of iron. Role of hepcidin in the control of absorption via ferroportin at gut mucosal cells. Stimulation of iron uptake by hypoxia.
Transport of iron: role of transferrin and transferrin receptors.
Storage forms of iron and role of ferritin.
Loss of iron from the body: Iron deficiency anaemia.

Impact of inflammation or infection on iron haemostasis.
Causes, consequences and treatment of iron overload.
Haemochromatosis.

51.5 ACID–BASE BALANCE

Determinants of extracellular pH.
Respiratory and metabolic disturbances.
Renal contribution to acid-base balance: Cellular mechanisms and their regulation.
Integration of renal and respiratory mechanisms.
Davenport diagrams: Graphical representation of acid-base disturbances.
Blood gas analysis and its interpretation.
The concept of base excess.
Causes and consequences of chronic acidosis and alkalosis.

Alternative interpretations of acid-base balance.

52. HYPERTENSION AND CARDIAC FAILURE

52.1 THE CONTROL OF SYSTEMIC ARTERIAL BLOOD PRESSURE

Short-term control of arterial blood pressure (ABP): Baroreflex control and the circulation as a closed system; high pressure baroreflex afferent and efferent pathways.
Normal stability of ABP independent of local flows to organs and tissues.
Long-term control of ABP by renal pressure natriuresis: Circulation as an open system.
Guyton model (or physical equilibrium model) of long-term control of ABP (see **52.3**).
Normal changes in ABP with age and ethnicity.
Changes in vascular dynamics with age.
Relative risks of mortality according to long-term ABP.
Definition and classification of hypertension.
Risk factors for hypertension.
Factors associated with long-term elevation in systemic arterial pressure: *'essential hypertension', renal disease, phaeochromocytoma.*

Principles of management of hypertension.

Rate sensitivity of carotid sinus baroreceptors.
Effect of arterial chemoreceptor stimulation on the circulation (see **53.2**).
Central pathways of the baroreflex: role of the brainstem.
Factors associated with short-term elevation in systemic arterial pressure: static exercise (see **53.2**), acute stress, sexual intercourse, head injury (Cushing response).
Marked dependence of long-term ABP on daily salt and water intake in some circumstances; consequent importance of salt restriction.

52.2 ENDOCRINE INVOLVEMENT IN SECONDARY HYPERTENSION

Adrenal glands (cortex and medulla).
Influences of aldosterone, cortisol, adrenaline on renal function, vascular tone, and circulating volume.
Renin–angiotensin-aldosterone system (see **51.1**).
Anti-diuretic Hormone (ADH) (see **51.1**).
Vascular receptors for ADH, effects on renal function, vascular tone, and circulating volume.
Angiotensin receptors in kidney & vascular smooth muscle.
Cortisol excess (e.g. *Cushing's syndrome*) and aldosterone excess (*Conn's syndrome*) as causes of hypertension.

Over activity of the renin-angiotensin system as a possible cause of essential hypertension.

52.3 INTEGRATED CONTROL OF CARDIAC OUTPUT

Cardiac output as both a function of and determinant of central venous pressure.
Guyton's model of the circulation and graphical depiction.
Representation of cardiac function by the Starling curve and the systemic circulation by a vascular function curve.
Concepts of arterial and venous compliances, systemic vascular resistance (SVR), mean circulatory pressure (MCP).

Possible limitations of Guyton's model

52.4 PHARMACOLOGY (with focus on mechanisms of action as well as elements of therapeutic indications, side effects and contraindications).

52.4.1 MAIN DRUG CLASSES USED IN THE TREATMENT OF HYPERTENSION:

Diuretics:
- Thiazide, loop and potassium-sparing diuretics.

Vasodilators:
- Alpha-adrenoceptor antagonists (alpha-blockers).
- Angiotensin converting enzyme inhibitors (ACE inhibitors).
- Angiotensin receptor blockers (ARBs).
- Ganglionic blockers (in acute hypertensive emergencies).
- Nitic oxide donors (in acute hypertensive emergencies).
- Ion channel modulators: Ca^{2+}-channel blockers and K^{+}-channel openers.
- Renin inhibitors.

Cardio-inhibitory drugs:
- Beta-blockers.
- Ca^{2+}-channel blockers.

Centrally acting sympatholytic drugs.

Alternative explanations for mechanisms underlying the therapeutic efficacy of anti-hypertensive drugs based on the effects they exhibit on the kidneys.

52.4.2 MAIN DRUG CLASSES USED IN THE TREATMENT OF HEART FAILURE:

Diuretics:
Including thiazide, loop and potassium-sparing diuretics.

Vasodilators:
- Angiotensin converting enzyme (ACE) inhibitors.
- Angiotensin receptor blockers (ARBs).
- Nitric oxide donors.
- Natriuretic peptides.
- Phosphodiesterase inhibitors.

Cardio-stimulatory (inotropic) drugs:
- Digoxin.
- Sympathomimetic drugs (beta-agonists).
- Phosphodiesterase inhibitors.

Cardio-inhibitory drugs:
- Beta-blockers.
- Ca^{2+}-channel blockers.

52.5 CARDIOVASCULAR REGULATION IN CRITICAL ILLNESS

Symptoms, signs, and causes of acute left and right ventricular failure.
Chronic heart failure.
Therapeutic interventions in heart failure.
Symptoms, signs, and causes of shock.

Anaphylactic shock and cardiovascular collapse from spinal anaesthesia. (see **18.1.2**).
Effect on the circulation of pneumoperitoneum for keyhole (laparoscopic) surgery.

Therapeutic interventions for the various types of circulatory shock.
Features of hypovolaemic, cardiogenic and septic shock; autotransfusion; neural and endocrine responses to shock; the acute stress response.
Use of Guyton’s analysis to determine primary changes and physiological responses to shock.

Principles of treatment of shock: use of vasoconstrictors. Potential of steroid therapy.

53. PHYSIOLOGICAL CHALLENGES

53.1 CHANGES IN POSTURE

The orthostatic challenge:
Primary changes in the circulation occurring on going from lying to standing.
Consequences of high pressure in dependent capillaries and of sub-atmospheric pressure in venous sinuses of the skull.
Cardiovascular reflex responses to change in posture.
Role of arterial baroreceptors, the autonomic nervous system and cardiopulmonary baroreceptors in maintaining orthostasis.

Veno-arterial reflex as an axon reflex.
Orthostatic intolerance in peripheral neuropathy (e.g. in diabetes mellitus) and as a side-effect of anti-hypertensive therapy.
Venocaval compression in supine pregnant women.
Effect of changes in posture on arterial blood pressure and V/Q matching in the lung.

53.2 EXERCISE PHYSIOLOGY

Energy metabolism and oxygen consumption during exercise.
Metabolic rate and its different measures; O_2 consumption, CO_2 production, and combined heat and work output.
Power supply: the energy value of basic body fuels; respiratory quotient.
Physiological changes during exercise.
Control of physiological changes during exercise:
Sources of feedforward and feedback control in the regulation of breathing and the circulation during exercise; baroreceptors, arterial & central chemoreceptors, skeletal muscle work (chemo) receptors.
Role of the autonomic nervous system in the cardiovascular response to exercise.
Role of local control of blood flow in muscle.

Measurement of the mechanical efficiency of exercise; different mechanical efficiencies of static and dynamic exercise.

Exercise ECG testing.
Factors limiting exercise in normal subjects and in patients with heart and/or lung disease.
Effects of training on exercise performance in normal subjects.

53.3 LIFE AT HIGH ALTITUDE

Physiological responses and pathological changes in the respiratory and cardiovascular systems at altitude: Role of PO_2.
Chemoreceptor and renal adaptations.
Bohr shift of the oxyhaemoglobin dissociation curve.
EPO and its regulation by hypoxia inducible factor (HIF).
Polycythaemia and its effect on the concentration of oxygen in blood.
Elevation of pulmonary artery pressure.
High altitude pulmonary oedema.
Acute mountain sickness and high-altitude cerebral oedema.
Use of acetazolamide, dexamethasone and nifedipine to prevent and /or treat high altitude sickness.

Changes in the oxygen cascade at altitude.

Fan of curves of the ventilatory response to CO_2.

Cheyne-Stokes breathing and disturbance of sleep at high altitude.

53.4 BODY TEMPERATURE CONTROL

Normal body temperature and its circadian and menstrual rhythms.
Concept of 'core temperature' and the importance of its maintenance.
Brown fat as a thermogenic organ.
Definition of hyperthermia and hypothermia.
Contributions of convection, evaporation, conduction and radiation to heat loss.
Coordination of body temperature control by the hypothalamus (see **55.2**).
Thermoneutral zone and its relation to clothing.
Temperature control in the thermoneutral zone of core temperatures by skin blood flow and piloerection; shivering, sweating. Acclimatisation.
Pyrogen receptors in anterior hypothalamus; NSAIDS and paracetamol as antipyretics.
Peripheral injuries (*frostbite, burns*).

Relation between metabolic rate and body mass in mammals; Kleiber’s rule.
Possible role of bradykinin or Vasoactive Intestinal Polypeptide.

Therapeutic uses of hypothermia.

Pyrexia. Heat stroke. Malignant hyperthermia.

54. ASTHMA AND RESPIRATORY PHARMACOLOGY

54.1 ASTHMA AND ITS PHARMACOLOGY

Asthma vs Chronic Obstructive Pulmonary Disease (COPD).
Asthma: role of inflammatory response.
- Mucus formation and airway epithelial desquamation.
- Eosinophilic vs non-eosinophilic asthma

Maintenance therapy and treatment of acute attack
Measurements to assess therapeutic response.
Bronchodilators (short and long term):
- β_2-adrenoceptor agonists e.g. salbutamol; adrenaline.
- Cholinoceptor antagonists e.g. ipratropium.
- Xanthines e.g. aminophylline.

Bronchodilators: actions and adverse effects
Steroids: eg beclomethasone actions and adverse effects (see **31.5**)

Changes in blood gases in moderate and severe asthma: terminal progression to asphyxia with hypercapnia.
Anti-leukotrienes in asthma therapy.
Monoclonal antibodies (e.g.anti-IL-5).
Inhibition of mast cell degranulation.
Other neurotransmitters acting on the bronchial plexus as possible therapeutic targets.
Use of humidification and mucolytics.
Mechanical ventilation in asthma.

54.2 ANAESTHESIA

Two main classes of general anaesthetic agent:
- Intravenous e.g. propofol and
- Inhalational e.g. isoflurane, sevoflurane;
- Common respective uses of these for induction and maintenance of anaesthesia.

Drugs used to induce sleep or sedation (defined in relation to maintenance of verbal contact with a patient, who can still obey commends); benzodiazepines (e.g. temazepam & diazepam).
Definition of minimal alveolar concentration of an inhalational anaesthetic.
Effects of anaesthetic agents on respiratory control.
Effects on the cardiovascular system and body temperature control.
Principles of management of these systems:
fluid therapy, vasoconstrictors e.g. α_1-agonists such as phenylephrine; parasympatholytics e.g. muscarinic antagonists such as glycopyrrolate.
Adjuvant drugs in general anaesthesia and their actions:
- Anxiolytics e.g. temazepam.
- Neuromuscular blocking agents e.g. atracurium, suxamethonium.
- Muscarinic antagonists e.g. atropine.
- Cholinesterase inhibitors e.g. neostigmine.
- Local anaesthetics e.g. lidocaine, bupivacaine.
- Non-steroidal anti-inflammatories e.g. ibuprofen.
- Opiate analgesics e.g. morphine.
- Reversal of opiates: naloxone.
- Antiemetics e.g. ondansetron

Stages of increasing depth of anaesthesia, including analgesia, excitement, surgery. Meyer-Overton correlation for inhalational agents: the potency of agents increases with their solubility in lipid.

Contrasting hypotheses of general anaesthetic action: lipid and protein sites.

Respiratory stimulants e.g. doxapram.

Possible regions of the brain targeted by general anaesthetics.
Possible cellular actions of general anaesthetics, including the possibility of potentiation of synaptic inhibition and depression of synaptic excitation

Reversal of benzodiazepines flumazenil.

55. INTEGRATIVE ROLE OF THE HYPOTHALAMUS

55.1 FUNCTIONS OF THE HYPOTHALAMUS (see **23.1**)

Hypothalamic nuclei (see **23.3.1**).
Roles in homeostasis, rhythms, development (e.g. puberty), metabolism, control of autonomic nervous system (see **55.2**), and endocrine system control.
Monitoring of plasma levels of hormones, metabolites, plasma osmolarity.
Coordination of regulation of blood pressure and volume (see **52.2**).
Body temperature regulation (see **53.4**).
Control of the anterior pituitary by secretion of: Releasing hormones: GnRH, GHRH, TRH, CRH; release-inhibiting factors dopamine, somatostatin.
Negative and positive feedback by peripheral hormones and by metabolic signals.
Local and systemic effects of pituitary tumours
Secretion of oxytocin and ADH from posterior pituitary (see **57.6**).

55.2 HYPOTHALAMIC CONTROL OF THE AUTONOMIC NERVOUS SYSTEM

Neural outputs to brain stem and spinal cord centres.
Effects of hypothalamus/hypothalamic lesions on autonomic functions: In the eye (pupil, lacrimation); osmotic regulation and cardiovascular system;
thermoregulation; alimentary system (salivation, peristalsis); genital system (erection, emission); urinary system; sleep-wake; aggressive behaviour (sham rage).
Autonomic and endocrine components of the stress response (see **55.3**)

Relate effects on autonomic function of stimulation and lesion in anterior and posterior hypothalamus.

55.3 PHYSIOLOGICAL RESPONSE TO STRESS

Stress definition: How stress influences the hypothalamus.
Hypothalamic inputs from brainstem, amygdala, hippocampus.
Acute stress response: Role of the sympathetic nervous system.
Prolonged stress response: Role of the hypothalamo-pituitary-adrenal axis.
Effects of sympathetic nervous system activation, “flight or fight” response.
Effects of glucocorticoids; widespread actions that influence metabolism, brain, cardiovascular, immune and reproductive systems.
Stress-related illness.
Stress and fetal programming of adult health (e.g. hypertension; type II diabetes).

Autonomic failure.
POMC (pro-opio-melano-cortin) as a precursor of ACTH; effects of adrenalectomy on production of melanocyte stimulating hormone (MSH), and effect on pigmentation.

56. METABOLISM, GROWTH AND APPETITE

56.1 METABOLIC HOMEOSTASIS

Growth, malnutrition and obesity.
Prenatal and postnatal growth. Fetal programming by nutrient restriction.
Common pathologies of fetal growth.
Hormonal control of energy metabolism (IGF1, IGF2, insulin, Growth Hormone). Human placental lactogen.
Substrate provision and utilisation during short and long term fasting.
Metabolic responses to chronic malnutrition. Assessing severity of malnutrition.
Energy balance and body weight regulation, hormonal control of body weight.
Dynamic role of adipose tissue in energy homeostasis, adipose tissue as an endocrine organ, production and secretion of leptin (see **56.2**).
Differences in the roles of visceral and subcutaneous fat deposits.
Obesity and its consequences. Adipose inflammation in obesity.
Obesity and type II Diabetes (see **56.3**).

Inflammatory infiltrates in adipose tissue in obesity.
Other adipokines: adiponectin, acylation stimulating protein, TNFα.

56.2 CONTROL OF APPETITE

Ventromedial nucleus ‘satiety centre’, lateral hypothalamus ‘feeding centre’.
Arcuate nucleus as an integrative centre for peripheral signals.
Signals from alimentary tract hormones: Ghrelin, insulin.
Other gastrointestinal hormones affecting feeding behaviour: Cholecystokinin (CCK) via vagal inputs; pancreatic polypeptide (PYY); glucagon-like-peptide-1 (GLP-1).
Signals from adipose tissue: leptin.
Leptin and leptin receptor deficiency as a rare cause of major obesity.
Central signals: Neuropeptide Y (NPY), αMelanocyte Stimulating Hormone (αMSH), mesolimbic reward system, social cues.
Eating disorders (see **25.4**).

Fröhlich’s syndrome.

Stimulus-specific satiety; ‘Cafeteria effect’.

Role of melanocortin 4 (MC4) receptor; orexins; AgRP.
MC4 receptor mutation; other mutations associated with obesity.

56.3 NUTRITION

Micronutrients: Vitamin D (see **51.3**) and Folic Acid. Roles in pregnancy and development.
Diet and health: Evidence for link to disease e.g. type II diabetes and cardiovascular disease.
Evidence for role of diet in improving health outcomes (see **56.1**).

57. REPRODUCTION

The anatomy, histology and embryology of the reproductive system are all covered by the first-year core syllabus and are assumed knowledge. The main hormones relating to the reproductive system are also covered by the first-year core syllabus. The second-year core focuses on the application of the basic knowledge gained in the first year.

57.1 FERTILIZATION AND IMPLANTATION

Fertilisation: Zona Pellucida binding, acrosome reaction; cortical reaction. Resumption of egg's second meiotic division.
Preparation of the uterus for pregnancy.
The process of implantation.

Status of the fetus as an allograft; mechanisms preventing immune rejection of fetus.
Ectopic pregnancy.

57.2 PREGNANCY

Development, structure and function of the placenta; placental villi (see **57.3**).
Production of estrogen, progesterone, gonadotrophins during pregnancy.
Roles of these hormones in the maintenance of pregnancy.
Placental hormone secretion. Human placental lactogen.
Role of fetal steroids: Concept of the feto-placental unit.
Prenatal diagnosis.
Fetal programming of adult health (hypertension; type II diabetes).

57.3 PLACENTA

Function of structures in the uterine wall, in the placenta and umbilical cord:
Endometrium, amnion, decidua basalis, cotyledon, uterine gland, intervillus space, primary villus, secondary villus, tertiary villus, trophoblast, cytotrophoblast, syncytiotrophoblast,
Umbilical artery and vein. Wharton's jelly.
To relate the structure of the human placenta to the fetal blood supply, fetal nutrition.

Placenta pathology e.g. placenta praevia.
Neonatal physiology

57.4 BIRTH AND LACTATION

Birth: Mechanism of parturition.

BREAST ANATOMY

Position on and in chest wall; nipple & areola; areolar glands; gross structure of breast, axillary tail.
Vessels: arterial supply from axillary artery, internal thoracic artery.
Lymphatic drainage to axillary nodes; internal thoracic nodes.
Breast cancer; spread to lymphatics, sentinel node.

Hormonal control of parturition - role of oxytocin and prostaglandins.
The Ferguson reflex.
Premature and delayed parturition.

Lactation: Breast development in pregnancy and lactation and its hormonal control.
Lactogenesis: Roles of prolactin and other hormones.
Milk-ejection reflex: Role of oxytocin.
Consequences of lactation and raised prolactin levels on fertility.
Galactorrhoea.

57.5 CONTROL OF FERTILITY AND INFERTILITY

Causes of male and female infertility.
Control of fertility by the hypothalamo-pituitary-gonadal axis (see **55.1**).
Suppression of ovulation in starvation, severe exercise, emotional stress.
Puberty onset. Precocious puberty; delayed puberty.
Contraception and strategies for the treatment of infertility in males and females; *in vitro fertilization.*
Ageing of the female reproductive tract; the menopause.

Use of hormone replacement therapy at menopause.

57.6 SEXUAL AND REPRODUCTIVE BEHAVIOUR

Oxytocin and vasopressin: Role in social, reproductive and parental behaviour.

Evidence for oxytocin and vasopressin central effects on social and sexual behaviour.