



**UNSW**  
SYDNEY



**Phase 3**  
**Biomedical Sciences Manual**

**2025**

**Medicine and  
Arts/Medicine**

# UNSW Medicine

## Phase 3 Biomedical Sciences Manual

2025

### Preface

This is the 18th edition of the Phase 3 Biomedical Sciences Student Manual produced by the Faculty of Medicine and Health at the University of New South Wales. It contains a large amount of information relevant to the Biological Sciences component of Phase 3 of the Medicine program.

**Learning Objectives for the Biological Sciences component of the Phase 3 curriculum are set out for each Theme in this Manual, and in the presentations at the Campus Day program.**

In 2025, the Campus Day program has been enhanced by additional teaching session on diseases and technologies with increasing prevalence and integration in medical practice. Please see the Campus Day program for further information.

This Manual contains a number of learning resources for students, including trial exam questions for each topic area, clinicopathological case protocols, and information regarding the assessment of Biomedical Sciences in Phase 3 of the Medicine program at UNSW.

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## Guide to Biomedical Sciences in Phase 3

### 1. Biomedical Sciences Syllabus

The Phase 3 Biomedical Sciences program stresses understanding the Biomedical Sciences in the context of clinical scenarios. The focus is on clinical presentations, and an approach to diagnosis and management that is justified by correlation with the underlying anatomical structures, pathophysiological processes and appropriate pharmacological treatments. The purpose is to help you develop confidence in your clinical reasoning and clinical decision making.

The Phase 3 program builds upon your learning in Phase 1 and Phase 2. Topics that were comprehensively covered in earlier Phases are assumed knowledge and are not dealt with in detail in Phase 3. **Please note that the Biomedical Sciences Viva at the end of 5th Year may reference knowledge from all Phases. For example, Pharmacology stations often relate to learning activities in Phase 2 of the Medicine program.**

This Manual describes in detail the aims and objectives of the program. The Manual is a useful guide to the depth of knowledge and understanding that you are expected to achieve.

Formal teaching in the Biomedical Sciences is NOT comprehensive. Some topics and case protocols are not covered in the hospital-campus teaching sessions in any detail. Some of these may be dealt with in the Campus Day program. Other topics that you are advised to review are listed in this Manual. (See: Topics not covered by formal teaching resources).

### 2. Structure of Phase 3 Biomedical Sciences Teaching

The Biomedical Sciences teaching program in Phase 3 runs over 16 weeks, and is offered twice per year, in STP/TP1 and TP2/TP3, coinciding with the Year 5 clinical terms in Medicine and Surgery.

Teaching in the Biomedical Sciences consists of:

- Hospital-based tutorials
- Campus Days, which include Anatomy Labs, Medical Imaging Seminars, Pharmacology Seminars and Multidisciplinary Seminars
- Pathology laboratory visits
- Online resources and self-directed learning

#### 2.1 Hospital-Based Tutorials

During Year 5 Medicine and Surgery terms, you will attend 24 x 1.5-hour hospital-based biomedical science tutorials.

For **Metro-based campuses**, these tutorials occur twice weekly in STP and TP1, and are then repeated in TP2 and TP3 at metropolitan hospitals. You attend while you are doing your Medicine and Surgery terms. Each Metro-based campus and each main Rural Clinical School campus will organise its own local timetable. (NB students based at Sutherland Hospital will be covered by St George Hospital for these tutorials.)

Most tutorials are held in person (face-to-face), however some campuses may decide to hold the tutorials online. The tutorials are not recorded.

If you are rostered to undertake a 4-week rural clinical placement during your Medicine or Surgery terms, then if your metropolitan “home” hospital offers hybrid tutorials, you may be able to join these during your rural attachment. However, if the tutorials at the “home” hospital are face-to-face only, it is incumbent upon you to make up the eight tutorials that you would otherwise miss by attending tutorials at your “home” hospital, either before (for those students with rural setting placements in TP2 or TP3) or after your rural attachment (for those students with rural setting placements in STP or TP1).

The hospital-based tutorials are centred around one or more case protocols (see below) and are led predominantly by staff specialists and conjoint members of academic staff in the Departments of Anatomical Pathology, Clinical Chemistry, Microbiology and Haematology at each of the metropolitan teaching hospitals. *Please note that some tutors may choose not to include all or any of the allocated case protocols in their tutorials, in which case it is up to you to work through these yourselves.*

**This Manual contains the learning objectives and case protocols associated with each tutorial topic. The tutorials are supplemented by a series of 21 self-learning modules contained in the P3 Biomedical Science Modules Moodle course. Self-enrolment is required via the following link: <http://moodle.telt.unsw.edu.au/course/view.php?id=14483> (student enrolment key: P3BMS).**

You should complete the relevant online self-learning module(s) before attending the tutorial, and prepare for each tutorial by reading through the learning objectives and associated case protocols, consulting your biomedical science texts and other resources.

The topics for hospital-based tutorials are as follows (timetables will vary between hospitals; please note that some campuses will hold tutorials around individual case protocols rather than around the tutorial topic):

Tutorial Topic	Case Protocols (Number in Manual)
Chronic cough & dyspnoea	11
Chest pain & vascular disease (modules)	9, 10, 38
Haematuria (module)	17, 37
Hepatitis & chronic liver disease	22, 36
Cerebrovascular disease	34, 40
Back pain & bone tumours (modules)	5, 6, 14, 35
Acute dyspnoea & haemoptysis (modules)	3, 19, 39
Gynaecological malignancies	1, 2
Glomerulonephritis & renal failure (modules)	18, 27, 32
CNS tumours and CNS infections (modules)	20, 21, 41
Opportunistic infections & AIDS	26
Multisystem disease & polyarthritis (modules)	24, 30
Endocrine disease (module)	25
Breast lumps	7
Scrotal masses	33
Bleeding disorders	8
Dysphagia & haematemesis (module)	13, 16
Inflammatory bowel disease	12
Complications of diabetes	31
Anaemia (module)	28
Allergy and anaphylaxis	4
Gallbladder & pancreatic disease (module)	15, 43
Leukaemia & myeloproliferative disease (module)	29, 42
Lymphoma (module)	23

Case protocols 44 and 45 focus on mental health and pharmacology and are currently not associated with a hospital-tutorial at most campuses. However, there will be a Campus Day that covers related material. Some hospital-campuses may offer an additional tutorial to further explore these case protocols.

## 2.2 Campus Days and Medical Imaging Seminars

Campus Days and Medical Imaging Seminars are scheduled on selected Tuesdays in STP and TP1 and will be repeated (again on Tuesdays) in TP2 and TP3.

Metro-based students are expected to attend all campus day activities in person, except in special circumstances. Rural-based students attend the sessions online. Links to sessions are available to rural students via eMed. Metro-based students have to apply for the session links if they are unable to attend in person. (See Moodle announcements before each session for information about how to apply for the link.)

The Anatomy sessions will be held in the Anatomy Lab 08A on Level 1 of D26 Biological Sciences North and are hybrid for rural students. The other campus day activities are held at various university campus venues. Refer to eMed for the latest roster, and check Moodle for announcements before each campus day.

Unless otherwise advised, the Campus Day sessions will be recorded. The recordings are made available at the completion of the program (i.e. at the end of TP1 and at the end of TP3).

The Biomedical Sciences **Campus Days** will be based on the following themes:

- Clinical Genetics
- Obesity and Cardiovascular Disease
- Infectious Diseases
- Acute Surgical Emergencies and Post-Surgical Care (including fluid replacement, analgesia and fluid balance), and
- Head and Spinal Injury
- Diabetes (new in 2025)
- Omics and Personalised Medicine in Oncology (new in 2025)
- Mental Health (Expanded in 2025)

**Diagnostic Imaging Seminars** are incorporated into the Phase 3 Biomedical Sciences program. These seminars will be delivered by experts in the field and are based on the following themes:

- Chest Imaging
- Head and Spinal Imaging
- Abdominal Imaging
- Cancer Imaging
- CT and MRI brain cases (introduced in 2024)

## 2.3 Pathology Laboratories Visits

During Year 5, you must visit the Anatomical Pathology laboratory and at least **two** additional Pathology laboratories to observe and discuss investigations or procedures performed by that laboratory.

You must document a summary of each procedure in your *Clinical Procedural Skills Acquisition Logbook*, and your attendance must be confirmed by the signature of a supervising scientist or doctor for each procedure documented in your logbook.

Questions related to your documented Laboratory Investigations and Macroscopic Pathology Demonstrations and are included in the Phase 3 Biomedical Sciences Viva (Station B and Station C respectively). You must complete and document the Laboratory visits to be eligible to sit the viva.

### 2.3.1 Macroscopic Pathology Demonstrations

During the year, you must visit an Anatomical Pathology laboratory at least once, to observe and document the 'cut-up' of **four (4) surgical specimens**. The 'cut-up' refers to how a macroscopic surgical specimen is described and sampled for histological examination, usually by a Pathology registrar. **Alternatively**, you may attend and document findings from a hospital or coronial **autopsy** performed by a pathologist or pathology registrar.

Recommended resource to prepare for your visit:

<https://www.rcpa.edu.au/Manuals/Macroscopic-Cut-Up-Manual/General-Information>

### 2.3.2 Hospital Laboratory Investigations

You must document at least four (**4**) procedures attended and observed in **hospital laboratories** (e.g., Clinical Chemistry, Haematology, Molecular Genetics, Immunology, Microbiology, Anatomical Pathology. Note that you can attend the Anatomical Pathology laboratory again to document procedures other than the cut-up.)

Preferably, you should observe procedures carried out in the course of investigation of patients *that you have clerked*. In some cases it will be appropriate to document how a **specimen** is shared between several laboratories.

Examples of recommended tests/procedures to document in your Logbook are listed in: **Error! Reference source not found..**

### 2.3.3 Viva Learning Objectives for Laboratory Visits

You should be able to describe and discuss:

- Application or use of the test
- Specimen to be collected
- Collection, transport, accession to LIS, storage
- Sample to be tested
- Sample preparation
- Test principle
- Outline of the steps used in the test procedure
- Sensitivity and specificity
- Errors, confounders, quality control and quality assurance
- Test results and interpretation
- Report to clinician

## Biomedical Sciences Resources

- **Textbooks:** Prescribed textbooks for the Biomedical Sciences disciplines from your earlier phases
- **This Manual:** Learning objectives, case protocols and reference materials
- **P3 Biomedical Science Modules** (a standalone Moodle module). A series of 21 self-learning modules. Self-enrolment is required via the following link:  
<http://moodle.telt.unsw.edu.au/course/view.php?id=14483> (student enrolment key: P3BMS)
- **BEST Network and Images of Diseases:** An online collection of macroscopic, histopathology and diagnostic imaging resources on the BEST Network at <https://slice.best.edu.au>; or the “**Images of Disease**” macroscopic image databank of specimens at the UNSW Museum of Human Disease at <http://iod.med.unsw.edu.au>. zID and zPass are required to access these.
- **Phase 3 Medicine 2025 Moodle:** A series of online tutorials and other resources linked from the Phase 3 Moodle module, including
  - **Radiology/ Diagnostic Imaging Tutorials** and **RANZCR Education Modules**. The online tutorials cover **chest X-rays, CT scans, MRI, ultrasound and molecular imaging**.
  - **Anatomy resources** (Clinical Case Histories, Anatomy videos and other online material)
  - **Clinical Pharmacology** online learning modules made available via the National Prescribing Service (NPS) website (username and password available from your Clinical School – see <http://learn.nps.org.au>). **You must complete these by the end of the year.**
  - **Clinical correlation tutorials** on common management issues, correlating with the Campus Day themes (Fluid Management, Pain Management)
  - **Pathology resources** (online tutorials on Chemical Pathology, Haematology, Immunopathology)
  - **Pathology cut-up videos** Nine videos of macroscopic Pathology demonstrations (surgical and autopsy pathology videos) via the following link:  
<https://moodle.telt.unsw.edu.au/mod/page/view.php?id=7208579>

There are additional resources on Moodle not highlighted here – please explore the relevant sections in the Phase 3 Moodle module, and refer to **Error! Reference source not found.** for a complete list of the online tutorials available.

- **RCPA Resource Manual:** <https://www.rcpa.edu.au/Manuals/RCPA-Manual> the Royal College of Pathologists of Australasia Manual to guide selection and interpretation of investigations
- **SydPath Test Database** <https://sydpath.com.au/test-offered/> Instructions for collection and handling, as well as reference ranges for a wide variety of laboratory tests

### 3. Phase 3 Biomedical Sciences Correlation Viva

This barrier examination tests your ability to explain clinical scenarios by applying the Biomedical Sciences.

You will be examined at four (4) stations:

Station A	Anatomy focus
Station B	Clinical Laboratory OR Clinical Genetics focus
Station C	Anatomical Pathology focus
Station D	Pharmacology focus.

At each station you have 8 minutes to answer four (4) questions. There will be two examiners at each station: usually one is a campus-based biomedical scientist or doctor, and the other a hospital-based doctor.

Students who fail **one** station (average mark <50%) at their first attempt will be re-examined as soon as practicable i.e., will be offered to attend a *remedial* viva station. The remedial viva station will be an unseen question of the same station-type, A, B, C or D. If you pass this remedial viva, your mark for that station is capped at 50% (unless special consideration applies) and you pass the viva overall.

Students who fail two or more stations (regardless of their total mark), or who fail the remedial viva question, will be deemed to have failed the examination and will be given a supplementary examination at the end of TP1 the following year. At the supplementary exam, students must sit and pass all 4 stations. Students who require a supplementary examination will be encouraged to attend Biomedical Science teaching in STP and TP1 of the following year.

The viva is a barrier exam: you will not graduate until you have successfully completed it.

Further detail regarding the format and timetabling of this examination will be provided during the year.

#### 3.1 Viva Grading and Marks

Each of the four (4) questions at each station is graded P+, P, P- or F, and these grades are converted into numerical marks (F = 30, P- = 50, P = 70, P+ = 90). The marks are averaged to obtain a mark for each station and an overall mark for the exam. Each station is of equal value.

#### 3.2 Viva Examinable Content and Station Structures

**Viva questions will be based on learning activities and/or supporting materials in the Phase 3 Biomedical Sciences curriculum, including (but not limited to):**

- Hospital-based tutorials and their associated case protocols in this Manual
- Online learning modules in the *P3 Biomedical Sciences Modules* Moodle site (<http://moodle.telt.unsw.edu.au/course/view.php?id=14483>; self-enrolment key: P3BMS)
- Phase 3 Campus Day activities
- Mandatory attendance at hospital-based diagnostic laboratories and macroscopic Pathology Demonstrations, as documented in your Clinical Skills Acquisition Booklets. **Note that completion of the laboratory visits is a pre-requisite to sitting the viva.**

Some of the clinical scenarios used in the viva may be new to you, while others may be modified versions of the case protocols contained in this Manual. The basic concepts of the Biomedical Sciences disciplines covered in Phase 1 and Phase 2 of the Medicine program is assumed knowledge and will also be assessed in this examination.

Each station is based on a clinical scenario.

##### Station A

- **Q1-4:** emphasis on clinically relevant Anatomy;
- May include interpretation of commonly used imaging investigations, anatomical models, images or diagrams.



**Station B**

- **Q1:** Diagnostic laboratory investigations ('Laboratory Visits') documented in your Clinical Skills Acquisition Booklet;
- **Q2-4:** based on a case history focusing either on Laboratory Medicine or on Clinical Genetics.

**Station C**

- **Q1:** Macroscopic 'Pathology Demonstrations' documented in your Clinical Skills Acquisition Booklet;
- **Q2-4:** based on a case history focusing on Pathology, including:
- Clinicopathological correlation – may include an image of a macroscopic or surgical specimen;
- Diagnostic methods – may include interpretation of the results of a laboratory investigation or a commonly used imaging investigation;
- Risk factors, disease mechanisms, complications and disease associations.

**Station D**

- **Q1-4:** emphasis on pharmacological principles underlying the management of common conditions;
- Mechanisms of drug action;
- May include interpretation of the results of a laboratory investigation and/or commonly used imaging investigations.

**3.3 Practice vivas: online formative assessment and the mock viva**

To assist you to prepare for the viva, an example of each type of station is available on the Phase 3 Moodle module as an online formative assessment, including criteria for a P grade and suggested answers.

Additionally, an online **mock viva** is held, in which two volunteer students at each station undertake a demonstration viva with two examiners. The examiners then provide feedback, an indication of how grading criteria are applied, and tips for optimising your marks in the viva. Non-volunteering students may observe the online demonstration and ask questions about the exam content and process.

The mock viva is recorded and made available to your student cohort.

Check Moodle for announcements about dates and times of the mock viva.

## Forensic pathology

Forensic Medicine (Pathology) is the interface between Medicine and the Law. This is an appropriate time to acquaint you with some of the legal obligations of a medical practitioner in respect to the death of a patient.

Technically, a person is not dead until a legally qualified medical practitioner has examined that person and found life is extinct. This doctor is then legally obliged to complete a death certificate and forward the certificate, as soon as practicable, to the funeral director responsible for the disposal of the body or, if no funeral director is so responsible, to a local Registrar of Births, Deaths and Marriages (Registration of Births, Deaths and Marriages Act 1973 (NSW)).

There are, however, certain circumstances under which the doctor who pronounced life extinct may not sign a death certificate. These vary slightly from state to state in Australia, but in New South Wales they include the death of a person who has died:

- (i) a violent or unnatural death;
- (ii) a sudden death, the cause of which is unknown;
- (iii) under suspicious or unusual circumstances;
- (iv) the person died in circumstances where the person's death was not the reasonably expected outcome of a health-related procedure;
- (v) in a mental institution, or while temporarily absent from such an institution;
- (vi) in police or prison custody;
- (vii) in residential care for disabled persons, or who, being disabled, received services to enable independent living in the community; and
- (viii) the death of a child in care, or of a child reported under child protection legislation within the preceding 3 years, or a child who is a sibling of a child reported within the last 3 years, or a child who may have suffered abuse or neglect.

The medical practitioner, who is precluded from signing a death certificate, shall, as soon as practicable after the death, report that death to the officer-in-charge of a police station, who in turn will report the death to the Coroner (*Coroners Act 2009 (NSW)*).

The Coroner must determine the cause of death, manner of death, date and place of death, and the identity of the deceased in all cases, and uses the autopsy as one of their primary tools in reaching those conclusions. Family members can object to the conduct of an autopsy. Notification of objection to autopsy can be either to the Coroner directly or through the police investigating the death for the Coroner. A determination on whether, and to what extent, an autopsy will be performed will then be made by the Coroner. If this determination is objected to, a determination can be made by the Supreme Court.

In NSW, the Coroner will order an autopsy in about 60-70% of deaths referred to them for investigation; for the remainder, an autopsy is not carried out, either because the autopsy is deemed unlikely to add additional information or because of objections by the deceased's family. The Coroner does not perform the autopsy themselves but instructs a specialised forensic (or other suitably qualified) pathologist to perform the autopsy on their behalf.

## Reference section

### Principles of laboratory investigations - aims, rules and pitfalls

Diagnosis of disease is based on careful clinical evaluation of symptoms and signs, syndrome recognition and laboratory investigation. In many (if not most) diseases the diagnosis is substantiated by direct imaging of organs or tissues or examination of pathological specimens. The pathology laboratory thus plays a vital role in diagnostic medicine.

Before embarking on (increasingly!) expensive and often invasive and painful tests, it is important to be aware of the basic principles that govern the use of such investigations. The three aims of investigations are to:

1. **substantiate the provisional diagnosis.**
2. **exclude relevant differential diagnoses.**
3. **evaluate complications and prognosis.**

One of the most vexing problems facing new medical graduates is the rational ordering and interpretation of laboratory tests. Ordering a battery of investigations where one would have sufficed is wasteful and possibly detrimental to the patient if the redundant tests entail significant risk or discomfort. There are several rules or priorities that are important to observe in ordering investigations. These are to perform:

1. **diagnostic rather than non-diagnostic tests.**
2. **painless before painful tests.**
3. **non-invasive before invasive tests.**
4. **inexpensive rather than expensive tests.**
5. **simple rather than complicated tests.**
6. **low risk rather than high risk tests.**
7. **tests that may indicate hazards prior to more invasive tests (e.g. tests of coagulation before liver biopsy).**

Careful consideration should be given to these "aims and rules" before ordering pathology tests. "Screening tests" should be avoided and the cost of investigations to the patient minimised. Please attempt the case studies available via eMed to compare your use and interpretation of diagnostic investigations to that of experts in the field.

**Remember:** Laboratory investigations are no substitute for a carefully obtained history and examination. It is important to be aware of the sensitivity and specificity of tests and to be critical of all results that are inconsistent with the clinical situation or with other laboratory results. All laboratories make mistakes (but rarely)!

## Interpretation of commonly ordered laboratory tests

### Introduction

An abnormal value (i.e. one outside a given reference range) obtained by a laboratory test on a patient's blood, serum or other body fluid (urine, CSF etc.) usually reflects a disease process. However, before the clinician responds to such a result, it should be considered in the light of the clinical picture and the possibility of error. If the laboratory report does not fit the patient's condition, the possibility of error should first be investigated. Once satisfied that there is no laboratory error, a re-evaluation of the patient's signs and symptoms is in order as well as further assessment of other laboratory investigations.

### The Possibility of Error

Factors that may lead to errors and inappropriate interpretation of laboratory results include:

#### 1. Reference Interval (= Reference Range)

Reference intervals or "normal" ranges for laboratory investigations are based on an assumption that these values are normally distributed throughout the healthy population. Therefore, values two standard deviations on either side of the population mean for any measured parameter represent the reference interval, i.e. includes 95% of the values for that population. Those values falling outside the reference interval are said to be abnormal, i.e. they are more than two standard deviations away from the mean. It should be remembered that there is a 5% probability that any value outside the reference interval is obtained purely by chance in a normal individual and not caused by a derangement in the homeostasis of the patient. Indeed, it is logically correct to say that if twenty different laboratory parameters are measured for the same patient at any given time, there is a 62% ( $1 - [0.95]^{20}$ ) probability that one reading will be abnormal purely by chance!

Most laboratories supply only one reference interval for a given test, but there are a number of biological factors that influence the reference interval. These include age, sex, physical size, pregnancy and time of sampling. For example, normal plasma creatinine is dependent upon lean body mass, hence it will be lower in children and small women, and higher in body builders. Although the reference interval for plasma creatinine in adult males is 60-110 µmol/L, a small elderly woman may have a creatinine of 50 µmol/L. If her glomerular filtration rate falls significantly, the plasma creatinine may jump to 100 µmol/L yet remain inside the reference interval for adult males. For this reason, her plasma creatinine is better interpreted using a reference interval for adult females. The reference range of plasma creatinine in adult females is 45 – 90 µmol.

#### 2. Analytical Error is a Measure of Reproducibility

If a laboratory test is re-run a number of times on the same sample, different values will be obtained because of the inherent error of the method. Analytical error is a measure of the reproducibility (precision) of the method. The analytical error may be expressed in absolute units or as a percentage, e.g. for plasma sodium it may be 3 mmol/L or 2%. Therefore, if the measured value of plasma sodium is 135 mmol/L, the true plasma sodium lies in the range 132-138 mmol/L. This is important in the assessment of changes over time. For instance, if the measured sodium levels on two consecutive days were 135 mmol/L and 130 mmol/L, then the true plasma sodium concentrations would be in the ranges 132-138 mmol/L and 127-133 mmol/L. Because of the overlap in these values, there is no certainty that a true change in sodium levels occurred.

#### 3. Artefactual Results

Most abnormal laboratory tests are expected in that they reflect some known or suspected pathophysiology. Occasionally a value may be totally unexpected or discordant with the patient's clinical state. In such circumstances, artefactual causes should be considered before taking any action, and it may be wise to obtain another sample for re-analysis.

Artefactual results may be caused by the patient's clinical condition, diet, drug therapy or excessive exercise; the method of obtaining the specimen, its container and method of transport.

Some common causes of artefactual results are shown in the following table.

### Common causes of artefactual results:

Plasma component	Effect	Cause
Albumin	Increased	Prolonged time of tourniquet
Bilirubin	Decreased	Prolonged exposure to light
Bicarbonate	Decreased	Prolonged exposure to air
Calcium	Increased Decreased	Prolonged time of tourniquet Collected into EDTA container
Cortisol	Increased	Prednisolone therapy; stress
Creatinine	Increased	Diabetic ketoacidosis
Glucose	Increased Decreased	Patient not fasting No fluoride preservative
Phosphate	Increased	Prolonged contact with red cells
Potassium	Increased	Prolonged contact with red cells; Collected into EDTA container; Haemolysis
Sodium	Increased Decreased	Contamination by IV infusion Hyperlipidaemia; Contamination by IV infusion

### Sensitivity, specificity and predictive values - measures of accuracy

No diagnostic test is 100% accurate. The predictive value of any test depends upon its sensitivity and specificity.

**Sensitivity** = The number of people with the disorder who test positive, divided by the number of people with the disorder. For example, if a test has a sensitivity of 99% for detecting a certain disorder, only one person in one hundred with the disorder will return a negative test (i.e. there is a 1% chance of a falsely negative result).

**Specificity** = The number of people without the disorder who test negative, divided by the number of people without the disorder. For example, if a test has a specificity of 99% for detecting a certain disorder, only one person in one hundred without the disorder will return a positive test (i.e. there is a 1% chance of a falsely positive result).

With any laboratory investigation, there is a trade-off between sensitivity and specificity. For example, it may be possible to achieve 95% sensitivity and 90% specificity for a certain test. If 99% sensitivity is desired, it may be achievable but only at the cost of an increased false-positive rate (i.e. the specificity may fall below 90%).

**POSITIVE PREDICTIVE VALUE (PPV)** is the proportion of those with a positive test result who actually have disease, i.e. the number of true positive tests for a disorder, divided by the number of true positive plus false positive tests.

**NEGATIVE PREDICTIVE VALUE (NPV)** is defined as the proportion of those with a negative test result who do not have disease, i.e. the number of true negative tests for a disorder, divided by the number of true negative plus false negative tests.

Please note that the PPV is proportional to the prevalence of the disorder, while NPV is inversely proportional to prevalence. Therefore, a highly sensitive and specific test for a rare disorder will result in a low PPV, but high NPV.

## Key performance metrics for diagnostic tests

**Prof Stacy Goergen**

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A reminder about the definitions of the key diagnostic test performance metrics.

They are derived from the 2 X 2 table representing disease state and the results of tests with binary outcomes (i.e. normal / abnormal, positive negative).

	Disease +	Disease -	Calculations
<b>Positive test result</b>	TP	FP	PPV = TP / (TP + FP)
<b>Negative test result</b>	FN	TN	NPV = TN / (TN + FN)
<b>Calculations</b>	Sens = TP / (TP + FN)	Spec = TN / (TN + FP)	Accuracy = (TP + TN) / (TP + TN + FP + FN)

**Definitions:**

- True positive (TP) = number of patients in whom the test result is positive when disease is present
- False positive (FP) = number of patients in whom the test result is positive when disease is not present
- False negative (FN) = number of patients in whom the test result is negative when disease is present
- True negative (TN) = number of patients in whom the test result is negative when disease is not present
- Sensitivity = proportion of patients WITH disease who have a positive test result
- Specificity = proportion of patients WITHOUT disease who have a negative test result

## Likelihood ratios

$$LR+ = \frac{\text{proportion of patients WITH disease who have a positive test result (SENSITIVITY)}}{\text{proportion of patients WITHOUT disease who have a positive test result (1 - SPECIFICITY)}}$$

$$LR- = \frac{\text{proportion of patients WITH disease who have a negative test result (1 - SENSITIVITY)}}{\text{proportion of patients WITHOUT disease who have a negative test result (SPECIFICITY)}}$$

**Note:**

- High quality diagnostic tests have  $LR+ > 10$  and  $LR- < 0.1$
- A  $LR+$  or  $LR- = 1$  is associated with no change in the post-test probability of disease and therefore is not diagnostically useful



## Reference intervals for commonly ordered laboratory investigations

### Haematology

#### Full Blood Count

Values are for whole blood

Haemoglobin (Hb)	Adult male 130 - 180 g/L Adult female 115 - 165 g/L
Red Cell Count (RCC)	Adult male 4.5-6.5 x 10 <sup>12</sup> /L Adult female 3.8-5.8 x 10 <sup>12</sup> /L
Packed Cell Volume (PCV)	Adult male 0.40-0.54 Adult female 0.37-0.47
Mean Cell Volume (MCV)	80-100 fL
Mean Cell Haemoglobin (MCH)	27-32 pg
Mean Cell Haemoglobin Concentration (MCHC)	300-350 g/L
Reticulocyte Count	10-80 x 10 <sup>9</sup> /L (0.2-2.0%)
Leucocytes (White Cell Count)	4.0-11.0 x 10 <sup>9</sup> /L
Neutrophils	2.0-7.5 x 10 <sup>9</sup> /L
Lymphocytes	1.5-4.0 x 10 <sup>9</sup> /L
Monocytes	0.2-0.8 x 10 <sup>9</sup> /L
Basophils	<0.1 x 10 <sup>9</sup> /L
Eosinophils	0.04-0.4 x 10 <sup>9</sup> /L
Platelet Count	150-400 x 10 <sup>9</sup> /L
Erythrocyte Sedimentation Rate (ESR)	Child 2-15 mm/hr Male 17-50 years 1-10 mm/hr Male >50 years 2-14 mm/hr Female 17-50 years 3-12 mm/hr Female >50 years 5-20 mm/hr

### Tests of Haemostasis

Values are for citrated plasma

Activated Partial Thromboplastin Time (APTT)	25-35 seconds
Therapeutic Range for continuous IV heparin	1.5-2.5 x baseline
Prothrombin Time (PT)	13-17 seconds
International Normalised Ratio (INR)	0.9-1.1
Therapeutic Range for oral anticoagulants	2.0-4.5
Fibrinogen	1.5-4.0 g/L

#### In vivo test

Bleeding time (Simplate II with experienced operator)	<9 minutes
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## Chemical Pathology

### Arterial blood gases

pH	7.35-7.45
pO <sub>2</sub>	75-105 mm Hg
pCO <sub>2</sub>	32-45 mm Hg
Bicarbonate	24-31 mmol/L
Base Excess	-3<BE<3 mmol/L
O <sub>2</sub> Saturation	95-100%

Values are for plasma or serum, unless otherwise indicated

### Iron Studies

Iron	Adult 10-30 µmol/L
Total Iron Binding Capacity (TIBC)	45-75 µmol/L
Transferrin	1.7-3.0 g/L
Transferrin saturation	15-45%
Ferritin	Male 30-300 µg/L Female 15-200 µg/L

### Vitamin B12 and Folate

Vitamin B <sub>12</sub>	120-680 pmol/L
Folate	Red cell 321-1645 nmol/L Serum 5.5-33.3 nmol/L

### Urea, Electrolytes and Creatinine

Sodium	135-145 mmol/L
Potassium	Serum 3.6-5.1 mmol/L Plasma 3.5-5.0 mmol/L
Chloride	95-107 mmol/L
Bicarbonate (Total CO <sub>2</sub> )	24-32 mmol/L
Urea	3.0-8.0 mmol/L
Creatinine	60-110 µmol/L
Osmolality	280-300 mmol /kg water

### Blood Sugar Level

Glucose (plasma)	Fasting 3.0-5.5 mmol/L Random 3.0-7.8 mmol/L
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### Urate

Urate	Male 0.20-0.45 mmol/L Female 0.15-0.40 mmol/L
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### Liver Function Tests

Bilirubin	Total 2-20 µmol/L Direct (conjugated) <7 µmol/L
Alkaline Phosphatase	Adult, non-pregnant 38-126 U/L Growing child 80-500 U/L Bone isoenzyme (adult) 10-20% Liver isoenzyme (adult) 40-60%
Gamma Glutamyl Transferase (GGT)	Male <50 U/L Female <30 U/L
Aspartate Transaminase (AST)	<45 U/L
Alanine Transaminase (ALT)	<45 U/L
Albumin	33-48 g/L
Globulin	25-35 g/L
Total Protein	62-80 g/L



**Blood Lipids**

Triglycerides (National Heart Foundation recommendation)	<2.0 mmol/L
Total Cholesterol (National Heart Foundation recommendation)	<4.0 mmol/L
HDL Cholesterol (National Heart Foundation recommendation)	>1.0 mmol/L
LDL Cholesterol (National Heart Foundation recommendation)	<2.5 mmol/L

**Measures of Myocardial Injury**

Troponin I (TnI)	<34 ng/L (high sensitivity assay but method and sex dependant)
Troponin T (TnT)	<14 ng/L (high sensitivity assay)
Creatine Kinase (CK) – <i>Largely superseded by cardiac troponins</i>	Total: Male 60-200 U/L Female 30-125 U/L MB Isomer: <15 U/L

**Calcium, Phosphate and Magnesium**

Calcium	Total 2.10-2.55 mmol/L Ionised 1.10-1.30 mmol/L
Phosphate	0.80-1.50 mmol/L
Magnesium	Neonate 0.6-0.9 mmol/L Adult 0.8-1.0 mmol/L

**Miscellaneous Electrolytes**

Copper	13-22 µmol/L
Zinc	12-20 µmol/L

**Miscellaneous Enzymes**

Prostate Specific Antigen	Age 20 - 49: 0 - 2.50 U/L Age 50 - 59: 0 - 3.00 U/L Age 60 - 69: 0 - 4.00 U/L Age 70 - 79: 0 - 5.50 U/L Age ≥80: 0 - 6.50 U/L
Acid Phosphatase	Total 5-11 U/L Prostatic 0-4 U/L
Alpha-1 antitrypsin	0.9-1.7 g/L

**Urinary Electrolytes**

Sodium	40-220 mmol/24 hours
Potassium	40-120 mmol/24 hours
Chloride	100-250 mmol/24 hours
Urea	420-720 mmol/24 hours
Creatinine	6-18 mmol/24 hours
Calcium	2.5-7.5 mmol/24 hours
Phosphate	10-40 mmol/24 hours
Urate	Male 2.2-6.6 mmol/24 hours Female 1.6-5.6 mmol/24 hours
Osmolality	50-1200 mmol/kg

**Urinary Protein Excretion**

Protein	<0.15 g/24 hours
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## Endocrinology

### Thyroid Function Tests

Thyroxine	Total (T4) 65-130 nmol/L Free (FT4) 10-25 pmol/L
Free Thyroxine Index (FT4I)	75-150 nmol/L
Triiodothyronine	Total (T3) 0.9-2.7 nmol/L Free (FT3) 4-8 pmol/L
Thyroid Stimulating Hormone (TSH)	0.4-4.0 mU/L

### Miscellaneous Tests of Endocrine Function

Cortisol (peak diurnal)	155-600 nmol/L
Prolactin	Male 0-372 mU/L Female 0-536 mU/L

## Immunology

Values are for serum

Immunoglobulins	
IgG	6.5-16.0 g/L
IgA	0.6-4.0 g/L
IgM	0.5-3.0 g/L
IgD	<0.4 g/L
Rheumatoid Factor (Nephelometry)	<30 IU/L
Complement Factor 3 (C3)	0.9-1.8 g/L
Complement Factor 4 (C4)	0.16-0.50 g/L
C-reactive Protein	<5.0 mg/L (High sensitivity assays 0.2-3 mg/L)

### Lymphocyte Typing (lymphocyte subsets)

Values are for whole blood

Surface Antigen	Cell Type	% Blood Lymphocytes	Absolute Numbers
CD3	Total T-cells	55-90	0.6-2.4 x 10 <sup>9</sup> /L
CD4 (T4)	T-helper/inducer	30-63	0.5-1.4 x 10 <sup>9</sup> /L
CD8 (T8)	T-suppressor/cytotoxic	10-35	0.2-0.7 x 10 <sup>9</sup> /L
CD19	B-cells	3-25	0.04-0.5 x 10 <sup>9</sup> /L

T4:T8 ratio	1.0-3.2
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## Analysis Of Special Fluids

### Cerebrospinal fluid analysis

Appearance	Clear / Colourless
Cell Count	<5 mononuclear white blood cells x 10 <sup>6</sup> /L No red cells or neutrophils
Glucose	2.5-5.5 mmol/L
Protein	Adult 0.15-0.45 g/L Neonate (full term) 0.10-1.20 g/L

### Synovial fluid analysis

Appearance	Clear / Colourless
White Cell Count	10-180 x 10 <sup>6</sup> /L (60% monocytes, 25% lymphocytes, 10% neutrophils)
Glucose	3.0-6.0 mmol/L



***Stool analysis***

Fat (on diet containing $\geq 50\text{g}$ fat/day)	0-20 mmol/day (on at least 3 consecutive days)
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**References**

Royal College of Pathologists of Australasia Manual – <http://www.rcpamanual.edu.au>

See also test databases for hospital laboratories, e.g., SydPath: [http://www.sydpath.stvincents.com.au/spec\\_db/](http://www.sydpath.stvincents.com.au/spec_db/)

**Weight range of normal adult organs**

Organ	Weight (grams)	
	Male	Female
Brain	1300-1500	1150-1350
Heart	280-340	200-280
Right Lung	400-650	375-625
Left Lung	350-550	325-525
Liver	1400-1600	1200-1400
Pancreas	70-140	60-120
Spleen	150-200	140-190
Kidney	125-170	115-155
Pituitary Gland	0.5	0.5
Adrenal Gland	5-10	5-10
Ovary		5-7
Testis	10.5-14	
Prostate	17.5-22.5	
Thymus (M & F)	12-15 (birth) 30-40 (puberty) 10-15 (60 and over)	
Thyroid Gland (M & F)	20-30 (coast); 35-50 (hills)	

## Acid base balance

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**PLEASE NOTE:** Associate Professor Naidoo's notes are not intended to be a complete summary of the topic.  
This material is intended for use as an adjunct to your private study.

**Normal Extracellular pH = 7.35 –7.45**

Metabolism → Acid Production

\* H<sup>+</sup> production: 50 000 mmol/day from fat

30 000 mmol/day from glucose

Elimination by oxidation to water

Hypoxia → Lactic Acidosis

### **Non-volatile acids**

- Sulphur & phosphorous containing proteins
- Phospholipids
- Organic acids

Eliminated by kidney as titratable acid and NH<sub>4</sub><sup>+</sup>  
50 - 100 mmol/day

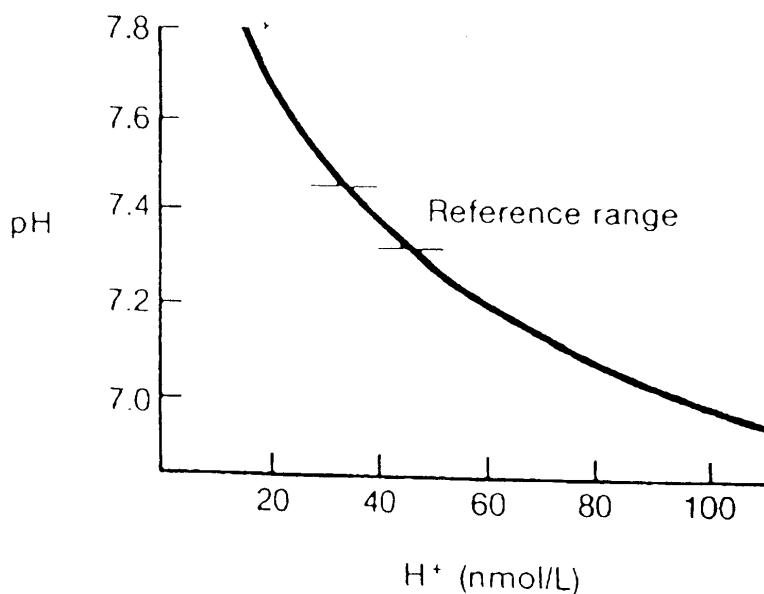
### **Volatile acids**

\* CO<sub>2</sub> production: 22 000 mmol/day

Transport and elimination without acidification

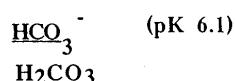
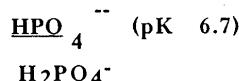


The relationship between pH and  $H^+$  concentration is shown in the Figure below.



Intracellular      Proteins

Extracellular      Proteins



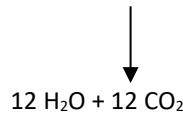
$\text{HCO}_3^-$  buffer is the major ECF buffer.

$$\text{pH} = \text{pK} + \log \frac{\text{HCO}_3^-}{\text{H}_2\text{CO}_3} \quad (2.4) \quad (\text{Kidneys}) \quad (1.2) \quad (\text{Lungs})$$

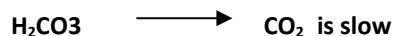
$$* \text{ pCO}_2 \times 0.03 = \text{H}_2\text{CO}_3$$

## Acid Base Homeostasis

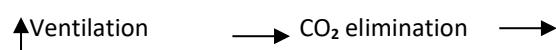
Add 12 mmol HCl per L of ECF:



$$\text{ECF pH} = 6.1 + \log \frac{12}{1.2 + 12} = 6.1 + \log \frac{12}{13.2} - \text{pH} = 6.06$$

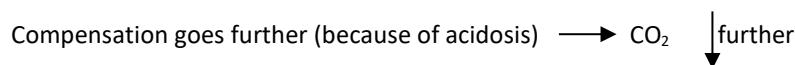


\* Buffering = 1st defense mechanism [12 mmol HCl + H<sub>2</sub>O → pH = 1.92]



$$\begin{aligned} \text{Thus in fact ECF pH} &= 6.1 + \log \frac{12}{1.2} \\ &= 6.1 + \log 10 \\ &= 7.1 \end{aligned}$$

\* Respiratory Compensation = 2nd defense mechanism

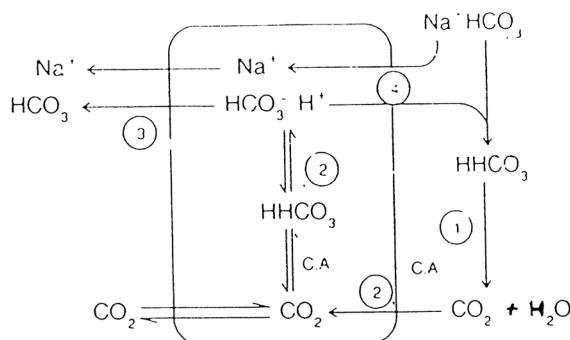


$$\begin{aligned} \text{Thus ECF pH} &= 6.1 + \log \frac{12}{0.6} \text{ (Assuming pCO}_2 = 20 \text{ mm Hg, hence } 20 \times 0.03 = 0.6) \\ &= 6.1 + 1.3 \\ &= 7.4 \end{aligned}$$

Plasma and  
Interstitial Fluid

Tubular Cell

Glomerular Filtrate



\* KINET = 3rd defence mechanism

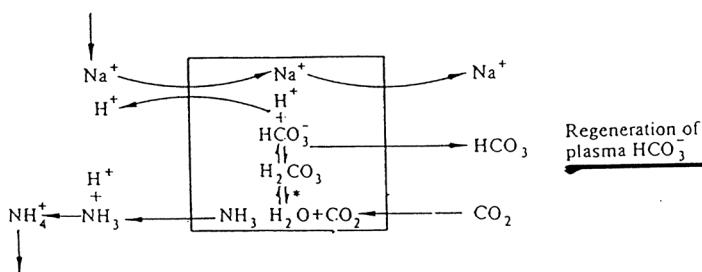
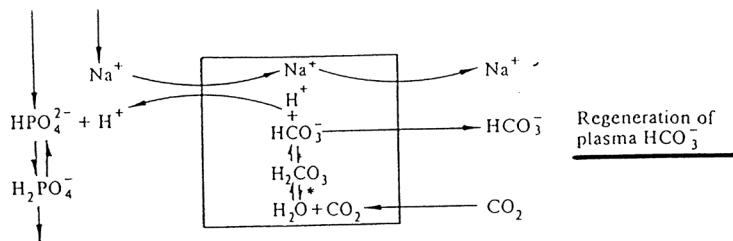


FIG. 6.1. The acidification of urine. The processes are divided into three parts, for purposes of explanation, but this does not necessarily mean that they go on in different types of cell. The points of action of carbonic anhydrase are indicated (\*); in the proximal tubule (top diagram), the enzyme is on the brush border.

## Acidosis

pH = < 7.35

Decreased HCO<sub>3</sub> = Metabolic Acidosis

Increased pCO<sub>2</sub> = Respiratory Acidosis

### **Metabolic Acidosis**

Increased Intake - rare (e.g. NH<sub>4</sub>Cl poisoning)

Increased Production:

- ketoacidosis
- lactic acidosis

Decreased Excretion – e.g. chronic renal failure

HCO<sub>3</sub> Depletion – e.g. diarrhoea

### **Causes of Ketoacidosis**

- Diabetes mellitus
- Alcoholism
- Post-exercise (transient)
- Prolonged fasting / starvation
- Genetic metabolic disease (Glycogen storage disease, Maple syrup urine disease)

### **Causes of Lactic Acidosis**

- A. Increased lactate/pyruvate ratio
  - 1. Anoxia
    - a. Acute respiratory failure
    - b. Inadequate perfusion (shock)
    - c. Anaemia
  - 2. Alcohol
  - 3. Phenformin
  - 4. Tumours
- B. Decreased lactate/pyruvate ratio
  - 1. Thiamine deficiency
- C. Normal lactate/pyruvate ratio
  - 1. Diabetes mellitus
  - 2. Glycogen storage disease

### **Respiratory Acidosis**

CO<sub>2</sub> Retention:

- cerebral disease
- respiratory disease (COPD)
- drugs



**Alkalosis**

pH = &gt; 7.45

Increased HCO<sub>3</sub> =

Metabolic Alkalosis

Decreased pCO<sub>2</sub> =

Respiratory Alkalosis

***Metabolic Alkalosis***Increased intake - HCO<sub>3</sub> infusion/ingestion

Loss of acid - vomiting, N/G suction

Severe hypokalaemia

***Respiratory Alkalosis***

Hyperventilation

- Psychiatric
- Hypoxia
- Ventilators
- Drugs (Salicylates)

**Interpretation of Arterial Blood Gases**

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
pH	7.10	7.63	7.25	7.40	7.31
pCO <sub>2</sub>	35	20	60	26	80
pO <sub>2</sub>	80	90	55	82	65
HCO <sub>3</sub>	12	22	18	16	35

Patient 1
Patient 2
Patient 3
Patient 4
Patient 5

## Glomerulonephritis

*Original notes by Prof D.J. Davies (minor edits have been made)*

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## Glomerular reaction to injury I

### 1. Introduction

The kidney is affected by a wide variety of diseases. Some are similar to those which occur in other tissues and organs of the body but others, particularly those affecting glomeruli, are unique. This is probably because of the complex architecture of the glomerulus and because it is a capillary bed which functions under pressure which is more usually found within arterioles. Some of the processes which damage glomeruli are due to systemic diseases which also affect capillary beds elsewhere in the body but others, which are frequently known by the collective name of "glomerulonephritis", have structural effects which are confined only to this specialised region of the kidney, although they may possibly reflect a systemic disturbance which frequently is immunological.

Before dealing with the pathology of different glomerular disorders there are a few general principles and problems that require consideration to be followed by a summary of the way in which diseases of the glomerulus declare themselves clinically. Then after reviewing the structure of the glomerulus a classification of the principal glomerular diseases is presented.

### 2. Problems and principles in kidney pathology

#### 2.1 Nomenclature and classification

Up until the mid-1950's classification of most kidney diseases, particularly glomerulonephritis was based on the clinical features and there was considerable confusion. With increasing use of renal biopsy for diagnosis of kidney disease, the whole subject has now been put on a more secure footing with a pathological classification. As a result, the names now given to glomerular diseases are mainly based on their appearance by the light microscope, although in some instances this may be qualified by features detected by the specialised methods of immunohistology and electron microscopy.

However, in contrast to diseases of many other organs, there are considerable limitations to the diagnosis of kidney disease by its examination with the naked eye. While this is adequate for recognising tumours and inflammation with abscess formation, in the specialised glomerular diseases, any macroscopic changes in the kidney usually only reflect consequences of the glomerular disease that have secondarily affected the tubules. Seldom can anything be recognised which identifies the primary process affecting the glomerulus.

#### 2.2 Correlation of clinical features and pathology

In many organs different pathological processes can produce the same clinical features. This concept is easily accepted, for example in the heart, where both ischaemic and valvular heart disease can produce a clinically identical state of congestive cardiac failure. The same situation applies in the glomerulus: different pathological processes can all have the same functional effect, for example causing excessive loss of protein in the urine or producing kidney failure.

On the other hand the same pathological processes can give rise to different functional effects depending on the stage in the evolution in the disease. Early on there may be a selective defect in the glomerulus causing either haematuria, proteinuria or both, but later, as the pathological process progresses and disease becomes more widespread, these clinical features will be replaced by the picture of chronic renal failure.

#### 2.3 Correlation of tissue changes with aetiology and pathogenesis

Just because tissue changes look the same under a microscope in two different patients, it does not necessarily mean that in each the lesions have been caused by exactly the same agent acting in the same way. In some organs we have no problems with this concept; for example, in the lungs bronchopneumonia can be caused by a number of different infectious agents, all of which cause a similar type of inflammatory lesion. However, in the glomerulus, some individuals seem to have difficulty in accepting the fact that a variety of aetiological agents and pathogenetic events can give rise to similar changes in the structure of the glomerulus. Sometimes special methods of tissue examination, such as immunofluorescence, or associated clinical features, or the results of laboratory tests, can give a clue about the cause. However, this is not always the case and it should not be

assumed that just because two lesions in different patients look the same under the microscope that they have been caused in the same way.

### **3. Effects of glomerular disease**

To avoid repetition when talking about individual glomerular disorders, it is useful to have a general idea of the different ways in which glomerular disease can present clinically.

In general, when the disease is mild or early in the course of its evolution, the effects are selective to the glomerular tuft but, as the extent and the severity of the disease increases, more complex systemic effects may ensue. Initially this may only alter the composition of the urine but subsequently there may be a systemic effect of selectively altered glomerular function, e.g. due to loss of plasma protein. Later, as the disease progresses, there may be a more general disturbance affecting the total homeostatic function of the kidney causing either acute or chronic renal failure with death in uraemia.

#### **3.1 Urinary abnormalities**

Microscopy and simple chemical examination of the urine are among the simplest of laboratory investigations and are often done as an adjunct to most medical consultations. In addition, they are a standard part of routine employment and insurance medical examinations and, in quite a number of instances, glomerular disease is first detected by urinalysis before the individual has any other symptoms.

The principal abnormalities are:

##### **3.1.1 Proteinuria**

In carrying out its physiological function of preparing an ultrafiltrate of plasma, the glomerular capillary wall normally retains within the capillaries the plasma proteins, particularly plasma albumin, which has a molecular weight of 66,300 Da. The nature of this glomerular permeability barrier has been the subject of considerable discussion and research and appears to involve a variety of factors, including "pore size" and effects of electrostatic charge. Regardless of the exact site of the permeability barrier, it is now becoming clear that, for this barrier to be effective, all the structural components of the glomerular capillary wall have to be intact and changes affecting any of them can lead to leakage of protein into the ultrafiltrate. Tubules have a limited capacity for protein absorption and if glomerular damage is extensive this is soon exceeded and most of the filtered protein appears in the urine. Therefore, detection of plasma proteins in the urine, particularly plasma albumin, is an early and sensitive indicator of diffuse glomerular damage.

The detection of protein in urine however is not completely specific as an indicator of glomerular disease. First, inflammation of the lower urinary tract may cause the appearance of a small amount of plasma protein in the urine, although the distinction from glomerular disease can usually be made clinically and with the aid of other laboratory investigations and the amount present usually is small. Secondly, abnormal low molecular weight proteins may be filtered in the absence of any glomerular damage. The most common instance of this is excretion of immunoglobulin light chains into the urine as Bence-Jones protein in patients with the plasma cell neoplasm, multiple myeloma.

##### **3.1.2 Haematuria (blood in the urine)**

The observation of blood in the urine by a patient is an alarming symptom, which usually causes them to seek medical attention promptly. Bleeding of degree that is recognisable, either to the patient or the medical attendant is described as 'macroscopic haematuria'. Frequently however, the quantity of blood present is insufficient for it to be recognised in this way and it is detected only on examination of the urine, either chemically or by microscopy. The blood can, of course, enter the urine at any point from the glomerulus down to the end of the urethra so that haematuria is a symptom of a wide variety of lesions. From a practical point of view, it is important to distinguish bleeding into the urinary tract from "surgical lesions" (such as tumours situated either in the bladder or elsewhere in the urinary tract), from bleeding caused by so-called "medical diseases" of the kidney, which affect some or all of the glomeruli. This distinction cannot be made macroscopically or chemically. However, with the assistance of phase contrast microscopy, it is possible to distinguish between erythrocytes which have originated from glomerular bleeding from those which have entered the urine lower in the urinary tract, because the former show a great degree of structural deformity.

### 3.1.3 "Casts"

These are abnormal structures recognised on microscopy of urine. Casts are made up of protein, erythrocytes, leucocytes, renal parenchymal cells, or a mixture of all of them. The main thing to know about them is that their presence in urine, particularly in large numbers, is indicative of intra-renal, usually glomerular, disease.

## 3.2 Syndromes of Glomerular Disease

A "syndrome" is a collection of symptoms and signs and, sometimes, a specific abnormal laboratory result. It usually characterises disease in a particular location, although there may be a variety of underlying pathological processes, e.g. Cushing syndrome due to increased steroids can be due to a basophil adenoma of the pituitary and functioning benign or malignant tumours of the adrenal cortex.

There are two important "glomerular" syndromes:

### 3.2.1 The "nephrotic" syndrome

The features of this are heavy proteinuria (at least 3.5 grams per day per  $1.73m^2$  body surface area), hypoproteinaemia and generalised oedema, usually associated with increased blood lipids, particularly cholesterol, and the presence of lipids in the urine.

The fundamental defect is a profound and extensive disturbance of glomerular permeability causing loss of plasma albumin, either alone or in company with higher molecular weight proteins, into the ultrafiltrate in Bowman space and eventually into the urine. For a short time such loss of plasma protein can be compensated by increased production by the liver but eventually the concentration of albumin and the other plasma proteins falls and, as a secondary consequence, there is a drop in plasma protein osmotic pressure. This disturbs the Starling's forces across capillaries throughout the body and leads to the widespread oedema, which is the main feature of this condition. The development of oedema also involves retention of sodium in the body this syndrome by processes that are still far from clear but may be due to excessive production of aldosterone. Lipid abnormalities are probably secondary to loss of the plasma albumin but there is some argument about this.

The nephrotic syndrome can be caused by a wide variety of different pathological processes but they all involve all glomeruli in both kidneys producing injury of mild to moderate severity.

### 3.2.2 The "nephritic" syndrome

With this syndrome patients feel generally ill and frequently there is facial oedema, most often noticed early in the morning. Characteristically there is haematuria (blood in the urine) the quantity is usually small and the macroscopic appearance is sometimes described as "smoky".

Microscopy shows blood and casts in the urine. The blood pressure is increased; this can be mild but sometimes may reach dangerous levels.

There is some protein in the urine, but the quantity is less than in the nephrotic syndrome ( $<3.5$  g/day) and plasma protein concentrations are not reduced. Glomerular filtration rate, however, is impaired and there may be some increase in the plasma concentration of nitrogenous products of metabolism such as urea and creatinine.

Classically this syndrome is produced by a disease called acute proliferative glomerulonephritis in which there is a marked cellular reaction with swelling and proliferation of cells in the tuft causing reduction in glomerular capillary blood flow and filtration. Nephritic syndrome may be encountered in other disorders, usually ones with well-developed cellular reaction in the glomerulus. The pathophysiology of this condition is far from fully worked out but there seems to be a component of sodium retention, which probably plays a part in causing the oedema (which, however, is not due to protein loss).



### 3.3 Systemic effects

Frequently disease of the renal glomeruli presents in a way which does not always draw immediate attention to the kidney as the source of the problem.

There are two principal ways in which kidney disease may produce systemic effects:

#### 3.3.1 Hypertension

Elevation of the systemic blood pressure, both systolic and diastolic, is a common clinical event and no medical examination is complete without its measurement. Most commonly, the cause is so-called essential hypertension, that is hypertension where the primary cause is unknown, but in a small proportion of cases this may be the way in which a number of primary glomerular diseases may present. The possibility of primary renal diseases, particularly glomerulonephritis, should be borne in mind as a cause of hypertension especially if it is detected in childhood or in young adults and if there are pronounced associated urinary abnormalities.

#### 3.3.2 Renal failure

The principal function of the kidney is maintenance of the constancy of the composition of the internal environment. As you will have learned from anatomy and physiology, this is done by ultrafiltration of plasma in the glomerulus followed by modification of the volume and composition of the ultrafiltrate by reabsorption and secretion by the renal tubules.

So far the functional abnormalities produced by glomerular damage that I have described can be attributed to disturbance of the permeability barrier of the glomerulus which allows blood components to escape into the urine. If, however, destruction of glomeruli is sufficiently severe or extensive, all aspects of renal function are affected and homeostasis becomes impaired leading eventually to a state of intoxication known as uraemia, which literally means urine in the blood. The patients become drowsy, apathetic and may develop lesions in a number of organs in the body including the entire length of the gastrointestinal tract, which may be ulcerated, and in the pericardium where there may be acute fibrinous pericarditis.

Depending upon its speed of onset, renal failure can be of two forms, acute or chronic:

##### (a) Acute renal failure - now known as "Acute kidney injury"

This is caused by disease affecting both kidneys that has a sudden onset. Characteristically, there is an abrupt increase in the concentration of creatinine and urea in the blood, often accompanied by disturbances of water and electrolyte metabolism and of acid-base balance. Frequently, though not invariably, there is a marked reduction in urine output to less than 400 mL per day, a state that is described as oliguria.

Acute kidney injury has a wide variety of causes; some of them may be pre-renal, caused by a disturbance of renal blood flow, post-renal caused by acute obstruction of the urinary tract but it can also be caused by diffuse kidney disease. Most often it is due to so-called 'acute tubular necrosis' in states of hypotension and shock but occasionally acute renal failure is caused by fulminating disease affecting all glomeruli.

##### (b) Chronic renal failure - now known as "Chronic kidney disease"

This is caused by a slow progressive loss of nephrons over a period of weeks, months or even years. The cause is usually some form of renal disease, commonly glomerulonephritis, in an advanced stage. It may have been preceded by one of the other syndromes referred to above or it may arise without any evidence of previous disease. As with acute kidney injury, the fundamental event is loss of power to control the constancy of the internal environment, so that there is a rise in plasma creatinine or urea. Frequently there are disturbances of water and electrolyte metabolism and of acid base balance. When prolonged there may also be disturbances of calcium and phosphorous metabolism, leading to a variety of secondary metabolic bone diseases. In contrast to acute kidney injury, urine output is usually increased to three to four litres per day but its concentration cannot be varied effectively to meet the metabolic needs of the body. The cause of the polyuria has been something of a puzzle but is now attributed to the few nephrons that survive, operating under conditions of osmotic diuresis.

#### 4. Structure of the normal glomerulus

While this is a subject with which you should already be familiar, it is worth repeating a few points that are relevant to the nature and distribution of the various pathological processes about to be described.

The basement membrane is a convenient point of reference, both in the normal and the diseased glomerulus. It covers the capillary loops but does not encircle them entirely. It is instead reflected from one loop to the next over an intercapillary area, the mesangium. As a result there are two types of cell enclosed within the glomerular basement membrane. The first is the endothelial cell that lines the capillary and the second the mesangial cell, which lies in the extracellular mesangial matrix, situated in the intercapillary area.

The endothelial cell has a large nucleus surrounded by a small quantity of cytoplasm and over the rest of the capillary is spread as a thin layer within which there are multiple small gaps known as fenestrae.

The mesangial cell has a centrally placed "kidney-shaped" nucleus surrounded by cytoplasm which is relatively rich in organelles from which stellate processes radiate through the substance of the mesangium.

The outer surface of the glomerular basement membrane is covered by complex specialised cells - the visceral epithelial cells or podocytes. The nucleus is located in the body of the cell situated some distance from the glomerular basement membrane but from the cell body there extends complex branching primary and secondary cytoplasmic processes, terminating as tertiary pedicels or foot processes which cover the entire external surface of the glomerular basement membrane. The foot processes of adjacent podocytes interdigitate to form a complex intercellular junction and the gap between them is known as the filtration slit, which is thought to be the final part of the route through which the glomerular ultrafiltrate passes.

In addition, the glomerulus may also contain some cells from the blood: erythrocytes, neutrophil leukocytes and mononuclear cells. Normally these are few but their numbers are greatly increased in pathological states.

Earlier when talking about proteinuria, mention was made of the glomerular permeability barrier, which retains the plasma proteins within the capillary lumen. There has been considerable argument about the precise site of this. Current knowledge makes much of this argument mis-directed, because it is becoming increasingly evident that for the permeability barrier to be effective, the integrity of all components of the glomerular capillary wall must be maintained. Therefore, compromise of the structure of any of them may lead to the leakage of plasma protein and, if the defect is large enough, erythrocytes from the lumen of the capillary into Bowman space and thence into the urine. In recent years a number of specific proteins have been identified in the foot process component of the filtration barrier; their structure is genetically determined, and genetic disorders have now been identified as causes of glomerular disease in early childhood.

#### 5. Pathology of glomerular disease

##### 5.1 Methods of investigation

Percutaneous core biopsy of kidney is sent fresh (ie not in formalin fixative) to the Anatomical Pathology (AP) laboratory. The biopsy is used to prepare specimens for:

- light microscopy, immunofluorescence and electron microscopy (AP lab)
- (in some cases) cytogenetics, flow cytometry (haematology or immunopathology lab)
- frozen storage

##### 5.2 Terminology

(how many glomeruli are abnormal on histopathology)

diffuse              virtually all glomeruli are affected

focal              a glomerulus is picked out here and there leaving others apparently unaffected

(how much of each glomerulus is abnormal on histopathology)

global              the whole glomerulus is abnormal

segmental          only part of the glomerulus is abnormal

In practice, processes that are diffuse usually affect the glomerular tuft globally; and focal processes most often are segmental.

## Glomerular reaction to injury II

The classification of glomerular disease is primarily based on the structural changes evident in glomeruli by light microscopy (histopathology). The classification adopted here is a fairly standard one although the order in which the different conditions are presented may vary a little. For convenience of presentation these are divided into two major groups:

- primary glomerulonephritis, in which structural changes are limited to the glomerulus
- secondary glomerular lesions occurring as part of systemic disease when there are generally similar lesions in other organs of the body which usually affect small blood vessels.

Each of these two groups can be further subdivided :

- a marked cellular reaction in the glomerulus
- cellular changes are inconspicuous and the major abnormality involves the extra cellular structures of the glomerulus, particularly the basement membrane and the mesangium.

This classification is shown below.

### ***Classification of glomerular disease:***

#### **1. Primary disease - mostly 'glomerulonephritis'**

##### **1.1 With cellular reaction**

- 1.1.1 Acute diffuse proliferative glomerulonephritis
- 1.1.2 Mesangial proliferative glomerulonephritis
- 1.1.3 Membrano-proliferative glomerulonephritis
- 1.1.4 Focal and segmental glomerulonephritis
- 1.1.5 Crescentic glomerulonephritis

##### **1.2 Without cellular reaction**

- 1.2.1 'Minimal change' disease
- 1.2.2 Focal and segmental sclerosis and hyalinosis
- 1.2.3 Membranous nephropathy
- 1.2.4 'Thin basement membrane disease'

#### **2. Secondary disease - involvement by systemic disease**

##### **2.1 With cellular reaction (mostly) - usually 'vasculitis'**

- 2.1.1 Systemic lupus erythematosus (SLE) - various lesions
- 2.1.2 Microscopic polyangiitis nodosa
- 2.1.3 Henoch-Schönlein purpura
- 2.1.4 'Focal embolic nephritis' (in bacterial endocarditis)

##### **2.2 Without cellular reaction**

- 2.2.1 Diabetic glomerulosclerosis - nodular and diffuse
- 2.2.2 Amyloid
- 2.2.3 Hereditary disorders - various

#### **3. 'Chronic glomerulonephritis' causing end-stage renal disease (advanced chronic kidney disease)**

## Glomerular disease - summary of features

\*Please note: this table is included purely as a reference resource, and to familiarise you with the terms. You are **NOT** expected to commit this information to memory.

### 1. Primary glomerular disease

Disease	Usual clinical features	Light microscopy	Immunohistology	Electron microscopy
<b>Acute diffuse proliferative glomerulonephritis</b>	1. Nephritic syndrome - usually post-infectious (rare in adults) 2. Macroscopic haematuria 3. Rapidly progressive GN	Swollen, hypercellular glomerular tufts, with or without polymorphs; "humps" on trichrome stain	Irregular coarse granular deposits in capillary walls and mesangium - strong C3 ± weak IgG, IgM, IgA and/or C1q, fibrin in capillaries	Tuft packed with mononuclear cells with or without polymorphs; subepithelial "humps" and other deposits
<b>Mesangial proliferative glomerulonephritis</b>	1. Isolated proteinuria and/or microscopic haematuria 2. Recurrent haematuria (may occur with viral URTI in <i>IgA nephropathy</i> ) 3. Nephrotic syndrome (uncommon)	Increase in mesangial cells and matrix ± mesangial deposits	1. <i>IgA nephropathy</i> - strong mesangial IgA ± weaker IgG, IgM, C3 and/or fibrin 2. No IgA - negative or IgM, C3	Increase in mesangial cells and matrix ± mesangial deposits
<b>Membranoproliferative glomerulonephritis</b> (also known as <i>mesangiocapillary glomerulonephritis</i> )				
<b>Type I</b> - subendothelial deposit variety	Various: 1. Nephrotic syndrome 2. Acute nephritic syndrome 3. Isolated proteinuria and/or microscopic haematuria 4. Hypertension / proteinuria 5. Occasionally rapidly progressive GN	Type I - Increase in mesangial cells and matrix; reduplication of basement membrane ("double contours"), subendothelial deposits	Type I - Coarse elongated deposits in capillary walls and some in mesangium; subendothelial deposits	Type I - Increase in mesangial cells and matrix; mesangial interposition in capillary walls; subendothelial deposits
<b>Type II</b> - "dense deposit disease"		Type II - Ribbon-like thickening of glomerular and other renal basement membranes	Type II - Moderate ribbon-like staining of basement membrane for C3, strong staining for coarse C3 in mesangium; no IgG or C1q	Type II - Dense deposits in glomerular and other renal basement membranes
<b>Type III</b> – uncommon – one form has proliferative change and features of membranous glomerulonephritis				

Disease	Usual clinical features	Light microscopy	Immunohistology	Electron microscopy
<b>Focal and segmental glomerulonephritis</b>	1. Proteinuria and/or microscopic haematuria 2. Recurrent macroscopic haematuria (may be <i>IgA nephropathy</i> ) 3. Hypertension, proteinuria 4. Occasionally nephrotic or nephritic syndromes	Focal and segmental proliferative lesions ± necrosis ± crescents	1. <i>IgA nephropathy</i> - strong mesangial IgA ± weaker IgG, IgM, C3 and/or fibrin 2. No IgA - various combinations, or negative except for fibrin	Focal increase in mesangial matrix and cells ± mesangial deposits; necrosis and fibrin; crescents and fibrin
<b>Crescentic glomerulonephritis</b>	Rapidly progressive glomerulonephritis, often with systemic disease	1. Cellular crescents in >80% of glomeruli 2. Cellular crescents in >80% of glomeruli superimposed on associated glomerulonephritis (e.g. membranoproliferative GN)	1. Strong linear IgG ± C3 in tuft and fibrin in crescent ( <i>Goodpasture syndrome</i> ); or negative in tuft and fibrin in crescent 2. Fibrin superimposed on typical features of underlying form of glomerulonephritis	Inflammatory cells in tuft and crescent cells in Bowman space; disruption of basement membrane; fibrin in tuft and crescent; various deposits; necrosis
<b>Minimal change disease</b>	1. Proteinuria 2. Nephrotic syndrome (usually steroid responsive)	Nil or minor increase in mesangial matrix or cells	Nil or sparse C3 (children) or IgM (adult)	Extensive spreading of podocyte foot processes
<b>Focal and segmental hyalinosis and sclerosis</b>	1. Nephrotic syndrome (usually steroid resistant) 2. Proteinuria 3. Hypertension and proteinuria	Focal and segmental hyalinosis and sclerosis (PAS +ve masses) - focal lesions may be missed on biopsy	Moderate to strong segmental or diffuse mesangial IgM + C3; or negative; or "IgA disease" (see above)	Extensive spreading of podocyte foot processes; focal epithelial cell disruption; segmental hyalinosis and sclerosis
<b>Membranous glomerulonephritis</b>	1. Nephrotic syndrome 2. Isolated proteinuria and/or microscopic haematuria	Subepithelial deposits with intervening basement membrane "spikes", progressing to chain-like arcades in "late" lesions	Strong IgG, uniform and finely granular capillary wall staining; weaker C3 ± IgM or IgA; occasional fibrin; IgG occasionally pseudolinear	Subepithelial deposits between projections of basement membrane; overlying spreading of podocyte foot processes
<b>Thin basement membrane "disease"</b>	Recurrent microscopic or macroscopic haematuria	Doubtful or minor increase in mesangial matrix and/or cells	Nil or minor IgM ± C3	Abnormally thin glomerular basement membrane

**2. Secondary glomerular disease**

Disease	Usual clinical features	Light microscopy	Immunohistology	Electron microscopy
<b>Diabetic glomerulosclerosis</b>	1. Proteinuria 2. Nephrotic syndrome; ± hypertension ± renal failure + evidence of diabetes	1. Nodular - mesangial nodules of various sizes (Kimmelstiel-Wilson nodules) 2. Diffuse - generalised thick mesangial matrix + severe arteriolosclerosis	Negative or weakly positive albumin, immunoglobulin or complement in mesangium ± basement membranes	1. Nodular - local thickening of mesangium 2. Diffuse - generally thickened mesangium + thick basement membrane
<b>Systemic lupus erythematosus</b>	1. Haematuria, proteinuria 2. Nephrotic syndrome 3. Renal failure + various extra-renal features and antinuclear antibodies	Mimics most common primary glomerular lesions; often proliferative ± necrosis ± deposits	Various but often “full house”: IgG, IgM, IgA, C3, C1q	Various - often proliferation, necrosis and extensive disease; subepithelial and/or subendothelial deposits
<b>Lung haemorrhage with nephritis (Goodpasture syndrome)</b>	Haematuria ± proteinuria + rapidly progressive glomerulonephritis + systemic illness - lung haemorrhage	Focal and segmental or crescentic glomerulonephritis	Linear IgG ± C3 (anti-basement membrane antibody)	Proliferation (no special features)
<b>Henoch-Schönlein purpura</b>	1. Haematuria 2. Renal impairment (rare) + systemic illness: purpura, GIT bleeding	Focal and segmental necrotising or, rarely, diffuse proliferative or crescentic glomerulonephritis	Mesangial IgA, fibrin	Mesangial deposits and proliferation
<b>Polyarteritis nodosa (microscopic)</b>	1. Haematuria, proteinuria 2. Rapidly progressive glomerulonephritis + systemic illness and focal extra-renal lesions, often respiratory; anti-neutrophil cytoplasmic antibody (ANCA)	Focal and segmental necrotising or crescentic glomerulonephritis	Usually fibrin only; immunoglobulins and complement usually absent or minimal	Proliferation, necrosis; deposits absent or minimal
<b>Focal glomerulonephritis in systemic disease e.g. “Focal embolic nephritis” in bacterial endocarditis</b>	Haematuria + systemic illness and bacterial endocarditis	Usually focal and segmental or, less often, diffuse proliferative glomerulonephritis	Various: IgG ± IgM ± IgA ± C3 - mesangial or capillary wall	Proliferation, deposits in some cases - mesangial ± subendothelial
<b>Amyloid</b>	1. Proteinuria 2. Nephrotic syndrome; + renal failure ± various extra-renal features	Thickening of mesangium and basement membrane; Positive staining with Congo red	Various - usually weak; occasionally specific light chain	Characteristic meshwork of beaded fibrils in mesangium and basement membrane

Disease	Usual clinical features	Light microscopy	Immunohistology	Electron microscopy
<b>Hereditary nephritis</b>	1. Haematuria; proteinuria; nephrotic syndrome; renal failure 2. Extra-renal: nerve deafness, eye signs	Various - usually low-grade proliferative lesions and mesangial thickening	Nil or minor IgM ± C3	Characteristic “splitting” of basement membrane
<b>Fabry disease</b>	Proteinuria, renal failure + skin lesions	Podocytes swollen, “foamy” cytoplasm containing abnormal lipid	Nil or minor IgM ± C3	Characteristic “myelin” figures in podocytes

## Common causes of anaemia

### *Pathological classification of anaemia*

#### **Hypochromic Microcytic**

Fe deficiency  
Thalassaemia  
Anaemia of Chronic Disease (severe)

#### **Normochromic normocytic**

Blood loss or haemolysis  
Marrow failure  
Anaemia of Chronic Disease / Inflammation (mild)

#### **Macrocytic**

Megaloblastic: Vit B12 or Folic acid deficiency  
Others: Alcohol, Liver Disease, Hypothyroidism

## Differential diagnosis of hypochromic anaemia

- **Defect in haem synthesis**
  - A. Iron deficiency anaemia
  - B. Anaemia of chronic disease, including chronic inflammation, chronic infection, and malignancy.
  - C. Sideroblastic anaemia
- **Defect in globin synthesis**
  - A. Thalassaemia syndromes.
  - B. Other haemoglobinopathies.

N.B. Serum ferritin levels are typically employed to measure total body iron stores (i.e. low ferritin levels always indicate iron deficiency). However, in the setting of chronic inflammation, circulating cytokines such as IL-1 and TNF- $\alpha$  result in production of IL-6 by macrophages. In turn, IL-6 induces hepatocytes to produce increased amounts of ferritin, as part of the acute-phase response. Thus, in the setting of co-existing chronic inflammation and iron deficiency, ferritin levels may be within the reference range. In that situation, measurement of serum soluble transferrin receptor concentration (sTFR) may be used to diagnose iron deficiency. sTFR rises in iron deficiency, and is unaffected by the acute-phase response.

In anaemia of chronic disease / inflammation, IL-6 induces hepatocytes to produce increased amounts of hepcidin, which blocks the action of ferroportin. Ferroportin is important in enabling iron transfer and recycling (e.g. from gut epithelial cells to transferrin, and from bone marrow macrophages to erythrocyte precursors). Thus, increased levels of hepcidin play an important role in the pathogenesis of anaemia of chronic disease / inflammation.

## Causes of folic acid deficiency

Inadequate intake	Poor diet, edentulous individuals, alcoholism
Impaired Absorption	Disorders of the small intestine, sprue and malabsorption syndromes, intestinal short circuits, surgical resection, steatorrhoea, infiltrative lesions of the small intestine, such as malignant lymphoma, Whipple disease etc.
Drugs	Anticonvulsants, oral contraceptives
Increased Requirement	Infancy or pregnancy, chronic haemolytic anaemias, myeloproliferative disorders, lymphoproliferative disorders, neoplastic diseases, skin diseases including psoriasis and exfoliative dermatitis, renal dialysis
Blocked Activation	Folic acid antagonists such as methotrexate, pyrimethamine and pentamidine.



**Causes of vitamin B12 deficiency**

Inadequate intake	Total vegetarianism (vegan)
Impaired absorption	Gastric disorders (decreased intrinsic factor), partial or total gastrectomy pernicious anemia, alkaline reflux gastritis, gastric carcinoma; Pancreatic insufficiency; Disorders causing villous atrophy, including sprue, Whipple disease and coeliac disease; Disorders of the terminal ileum, including regional enteritis, ileal resection, selective malabsorption of vitamin B12; and infiltrative intestinal disease, such as malignant lymphoma.
Drug administration	Para-aminosalicylic acid, neomycin, colchicine, ethanol, etc.
Increased requirement	Pregnancy, neoplastic disease, hyperthyroidism, hyperactive erythropoiesis, as in patients with chronic haemolytic disorders.
Consumption by intestinal parasites or bacteria	<i>Diphyllobothrium latum</i> infestation, Blind-loop syndrome

**Causes of iron deficiency**

Inadequate intake	Vegetarian diet
Impaired absorption	Malabsorption syndromes, gastrectomy, atrophic gastritis
Increased loss	Gastrointestinal (e.g. varices, peptic ulcer, aspirin ingestion, carcinoma, diverticulosis, haemorrhoids, hookworm infestation) Uterine (e.g. menorrhagia, parturition) Renal (e.g. haematuria, haemoglobinuria)
Increased requirement	Pregnancy, breast feeding, infancy, adolescence

**Characteristics of Iron, Vitamin B12 and Folate**

Characteristic	Iron	Vitamin B12	Folate
<b>Natural sources</b>	Meat, fish, soybeans	Animal origin: meat, liver, fish, eggs and milk	Leafy green vegetables, liver, kidney, yeast, mushrooms, nuts and fruits
<b>Normal daily intake (Western diet)</b>	15 mg	3-30 µg	500 µg
<b>Daily requirement</b>	1 mg	1-3 µg	50-100 µg
<b>Total body stores</b>	1000 mg, in bone marrow, liver, spleen	3-5 mg in liver, muscle and kidney	6-20 mg, in liver, red blood cells and other tissues
<b>Normal serum level</b>	75-150 µg/dL	150-450 pg/ml	6-20 ng/ml (serum) 165-600 ng/ml packed RBC's
<b>Site of absorption</b>	Duodenum and jejunum	Ileum	Duodenum and jejunum
<b>Mechanism of absorption</b>	Gastroferrin, hydrochloric acid, pancreatic enzyme	Gastric intrinsic factor and calcium ions	Intestinal conjugase
<b>Binding proteins</b>	Transferrin ( $\beta$ -globulin)	Transcobalamin I and transcobalamin II	Similar to $\beta$ -lactoglobulin
<b>Parent form</b>	Iron	Cyanocobalamin	Pteroylglutamate
<b>Red cell morphology in deficient patient</b>	Microcytic-hypochromic	Macrocytic-normochromic	Macrocytic-normochromic

## Groups at risk of acquired immunodeficiency

- Pregnant women
- Newborns and infants
- Frail elderly
- Immunologically compromised individuals such as:
  - Patients with HIV/AIDS
  - Transplant recipients
  - Cancer patients, particularly leukaemic patients
  - Patients undergoing haemodialysis or with chronic renal disease
  - Diabetics
  - Alcohol abusers and those with non-alcoholic liver disease
  - Injecting drug users
  - Those receiving prolonged treatment with corticosteroids or cytotoxic drugs, or both
  - Those with collagen vascular diseases, e.g. SLE
  - Patients with iron overload

## Blood transfusions

*Updated by A/Prof Robert Lindeman and Dr Susan MacCallum*

### Dept of Haematology, Prince of Wales Hospital

The Red Cross co-ordinates the collection, processing, testing and distribution of blood and blood products throughout NSW. In addition, some blood products, in particular single donor platelets, are collected by hospitals and some autologous collection is performed by both public hospitals and the private sector.

### Donor Screening

It is important to understand that donor screening goes beyond the HIV testing so frequently discussed in public. There are 3 important parts to the process:

- Donor Declaration Form
- Donor Interview
- Donor Testing

### Declaration Form

The declaration form itself identifies high risk, in particular intravenous drug usage and male to male sex. The wording itself is covered by regulation of the NSW Human Tissue Act and if a false or misleading declaration is made, then there is potentially a \$5,000 fine and/or one year in jail.

### Testing

All blood donations are tested for the following:

- HIV 1&2 antibody and nucleic acid test (NAT)
- Hepatitis B surface antigen and NAT
- Hepatitis C antibody and NAT
- HTLV-I antibody
- Syphilis antibody
- Malaria

As well, an ABO and Rh group is performed on every donation and screening is performed for red cell antibodies.

In addition to this screening, some donations are tested as required for CMV antibody. CMV negative products are labelled as such and are issued for patients who are at high risk of CMV infection and its consequences.



### HIV, Hepatitis B and Hepatitis C

There has been only one case of HIV in Australia through blood transfusion since screening began in 1985.

Probably the most frequently asked question of anyone involved in blood transfusion continues to be: "*What is the risk of getting an infectious agent through blood?*" The risks continually change, but generally in a direction towards greater safety.

The current risk rate for HIV 1&2 in Australia is below 1 in 10 million units collected, while the rates of hepatitis B and C are below 1 in 3 million. Nucleic acid testing (NAT) is performed for HIV and hepatitis B and C in addition to serological testing.

Finally, the risk for syphilis is well below 1 in 1 million and, in fact, there has not been a documented case of transmission of syphilis in Australia for at least 3 decades.

### Other Infectious Risks

The list of possible infectious risks is actually very long, however, the combined risk of other infections is very low. The most significant risk not yet discussed would be that of bacterial contamination, particularly from the organism *Yersinia enterocolitica*. This risk, however, would again fall well below 1 in 250,000 units collected. *Yersinia* is a particular problem as it grows well at the temperature of refrigerated blood, may arise in a donation from a donor who remains asymptomatic, and may proliferate extensively in blood without causing obvious discolouration or clot formation in the pack. *Yersinia* is a particular problem in red cell concentrates. Platelet concentrates can also transmit bacteria, but because they are stored at 20-22°C, they tend to harbour different bacteria to red cell concentrates.

All blood collected in Australia is leucodepleted (i.e. passenger white cells are removed) before storage and as such carry as little risk of CMV infection as CMV-negative blood, as borne out in recent studies. Major groups of people who should receive CMV negative blood products are CMV-negative pregnant women, neonates and for intra-uterine transfusion. Some bone marrow transplant centres prefer CMV-negative products.

## Blood Products

### Whole Blood

Whole blood is not currently available in Australia -we use component therapy (red cells, platelets, FFP and cryoprecipitate).

### Red Cell Concentrate

Concentrated red cells have a volume of approximately 350mL. Like whole blood, it is stored at 26°C and can be stored for 35 to 42 days. It is used for the correction of anaemia where transfusion is indicated, including haemorrhage where it is used in conjunction with plasma volume expanders. The transfusion of concentrated red cells increases oxygen carrying capacity.

### Platelets

Platelet concentrates have a volume of 5070 mL and actually consist of concentrated platelets suspended in plasma. They must be stored at room temperature (22°C) and constantly agitated. Storage life is 5 days. Platelets are used for treatment of thrombocytopenia, with particular examples including prophylaxis in bone marrow failure and in haemorrhage and coagulopathies arising from haemorrhage. The number of platelet concentrates used in any given transfusion should be minimised to reduce the number of donors a recipient is exposed to, however, typically 4 random concentrates would be used in a single transfusion episode. Platelets can also be provided from a single donor product collected by apheresis, with this single product being equivalent to approximately 4 of the random concentrates. Routine bacterial testing of platelets is performed, as there is a greater risk of bacterial infection from transfused platelets as a consequence of their storage at room temperature.

ABO antigens are present on the platelet surface and it is prudent to use ABO matched platelets whenever feasible. However, it is not normally necessary to delay a needed transfusion in order to obtain ABO compatible platelets. The recovery of ABO incompatible platelets is somewhat blunted. The D antigen is not detectable on platelets and post transfusion survival of platelets from D positive donors is normal in recipients with anti-D. As platelet concentrates may contain up to 0.5mLs of red cells, ideally they should be matched for Rh type. If this is not possible, consider RhD immunoglobulin.

### Fresh Frozen Plasma (FFP)

FFP has a volume of approximately 200 ml, although this can be quite variable. It is stored below -25°C. It contains all the coagulation factors and, not surprisingly, its principle use is in the correction of coagulation factor depletion. Transfusion of large volumes of FFP can carry with it problems of sodium overload due to the anti-coagulant. FFP is not indicated for volume expansion or as a nutritional source or to enhance wound healing.

### Cryoprecipitate

Cryoprecipitate is prepared from FFP and is a concentrate of high molecular weight plasma proteins that precipitate in the cold, including Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin. It carries high concentration of these factors in a relatively small volume of 20-30 ml., with larger volumes 60-100ml obtained from single-donor apheresis. It is an excellent source of fibrinogen, which is required to support critically bleeding patients and those with coagulopathy such as in liver transplantation.

Cryoprecipitate was the treatment of choice for people with Haemophilia A and von Willebrand disease until specific Factor VIII concentrates became available in the 1970s, and is no longer used for this purpose in Australia.

### Predeposit Autologous

Predeposit autologous blood is only collected from people who have extremely rare blood groups. It is frozen and stored for emergencies, and collected pre-emptively for surgical use.

The routine use of autologous blood prior to surgery has been discontinued due to studies showing that predeposit collection of units of blood resulted in an increased rate of transfusion of any type, probably due to pre-operative anaemia. Crossover of autologous units to the homologous pool cannot be justified as autologous units have a higher frequency of infectious disease markers.

### Directed

Directed, or designated, donations are not promoted by the Red Cross. Directed donors are likely to have at least some subconscious element of coercion as they have been asked by a relative to donate blood. The person who has a high-risk factor and is asked by a brother or sister to donate blood has a difficult decision to make and may go ahead with the donation in preference to disclosing a risk factor previously unknown to the rest of the family.

There are specific circumstances, such as rare blood groups, where family members may be the only donors available. Donor and recipient must be ABO identical and donations from blood relatives needs to be irradiated to avoid the risk of Graft Versus Host Disease. It has been shown that while people believe that getting directed units from relatives and friends is safer, it has been shown that these donations actually carry a greater risk, as the incidence of infectious disease markers is higher in this group of donors. One contributing factor to this is that most directed donors are new donors, as compared to the random blood supply - 90% of the donations come from regular donors who have been screened multiple times.

### Leukodepletion

Leukodepletion (filtering to remove contaminating white cells) or packed red cells has been instituted in NSW. All red cells and platelets are leucodepleted at Red Cross prior to storage. Leukodepletion avoids transfusion reactions, particularly in patients who are multiply transfused. It is also a potential way of preventing alloimmunisation, however, studies are not conclusive on prevention of platelet alloimmunisation / platelet refractoriness. As mentioned earlier, it also provides a vehicle for preventing the risk of CMV infection.

### Compatibility Testing

Units of red cells and whole blood need to be cross-matched prior to transfusion. This requirement is not present for platelets, although platelet transfusions are best given on a group specific basis.

Compatibility testing essentially consists of a check of the ABO and Rh groups and a test of whether the patient serum will react to the red cells of the potential donor units.

Compatibility testing also requires that general screening is made of the recipient's serum for the presence of red cell antibodies; for example, anti-D and anti-Kell.



There is an increasing trend for this cross-matching to be done in a non-physical way; that is, via a computer cross-match. This can only be followed if the patient does not have unexpected red cell antibodies.

### Antiglobulin (Coombs) Test

An important test in blood banking is the antiglobulin, or Coombs, test.

There are 2 variations of this:

- The **indirect test**, which looks for **circulating** red cell antibodies. Such antibodies will occur when a patient has been alloimmunised and, for example, has an anti-D or an anti-Kell. It is important for these antibodies to be identified so that donor blood lacking the corresponding antigens can be selected.
- The **direct test**, which indicates whether **red cells are coated** with either antibody, or complement, or both. The commonest situations in which this occurs are when there is autoantibody, as in autoimmune haemolytic anaemia, or importantly also when there has been an incompatible blood transfusion and antibodies present in the recipient have coated the transfused donor cells.

## Transfusion Reactions

A number of reactions can occur upon the transfusion of blood. However, these are probably best divided into major and minor reactions.

### Major

Three principle types of major reaction can occur. They are:

- **Haemolytic transfusion reaction**: generally caused through ABO incompatibility. Incompatibility in other blood groups can cause problems, but rarely causes severe acute reactions. Clerical error resulting in ABO incompatibility remains the most common cause of life-threatening haemolytic transfusion reaction
- **Bacterial sepsis**: for example, following transfusion of platelet concentrates as storage at room temperature favours bacterial growth. Red cells rarely may be heavily contaminated with *Yersinia* or other organisms, such as *Pseudomonas* or *Klebsiella*. Transfusion of such units may result in a sudden onset of septic shock, with mortality rates up to 30%.
- **Anaphylactic reaction**: exemplified by the transfusion of blood products into a patient who is IgA-deficient and has anti-IgA antibodies.

### Minor

With regard to minor transfusion reactions, the commonest are: febrile non-haemolytic transfusion reactions, which occur in approximately 2% of recipients; and allergic reactions which, again, are frequent in multiply transfused patients and manifest as urticaria.

### Other Complications

There are many other potential complications of blood transfusion which include:

- **Alloimmunisation**: which is very common in multiply transfused patients, and generally is due to formation of HLA antibodies. This can cause subsequent difficulty in finding compatible red cell units
- **Transfusion-associated Cardiac Overload (TACO)**: affects about 1% of blood products transfused due to volume overload.
- **Transfusion Related Acute Lung Injury (TRALI)**: results from the transfusion of blood products (most commonly plasma) containing donor neutrophil antibodies. The pathophysiology is not well understood, but the consequence is a condition resembling pulmonary oedema occurring after a transfusion that can be life threatening in vulnerable recipients. The risk of TRALI has reduced since Australia has switched to predominantly male plasma (due to less HLA-Antibodies)
- **Graft Versus Host Disease (GVHD)**: this occurs in severely immunocompromised recipients as a consequence of viable remaining lymphocytes among the transfused cells. GVHD is prevented by irradiating blood products administered to these individuals (patients undergoing stem cell transplantation, infants, patients with Hodgkin lymphoma, patients treated with purine analogues).
- **Metabolic factors**: which have a particular risk of occurring in massive transfusions, such as hypothermia, hypocapnia and citrate toxicity, with the massive transfusion context also at risk of depleting coagulation factors if platelet and plasma components are not administered
- **Iron overload** as a longer-term risk as there is 250 mg of iron in each unit transfused, with patients who have received over 100 units of red cells are likely to become iron overloaded.

### Investigation of Transfusion Reactions

Investigation of transfusion reactions is obviously of importance in establishing the cause of a given reaction. Initially, it should be decided whether the transfusion reaction is minor; such as a febrile haemolytic transfusion reaction, in which case slowing the unit of blood may be sufficient. Or, in the case of a major transfusion reaction, a number of investigations need to be urgently performed. In the case of significant reactions, the following are important:

Firstly, check for clerical errors - in particular, identification of both the pack and the patient. The pack itself should be examined for evidence of clots or discolouration or other problems.

A number of laboratory investigations should be carried out.

In particular, the blood packs must be kept and returned to the cross-matching laboratory, together with appropriate post transfusion specimens. Urinalysis should be performed and in cases of suspected bacterial sepsis, blood cultures and a gram stain should be performed. Other tests include an urgent re-crossmatch, Coombs test, FBC, coagulation studies, haemolysis screen, and urine for haemosiderin.

### Treatment Of Major Transfusion Reaction

In the case of major transfusion reactions, it is paramount that the intravenous line is not removed as it may be difficult, or impossible, to regain venous access.

Clearly, volume replacement should be carried out as appropriate.

Specific therapies should also be instituted, as appropriate, depending upon the nature of the reaction. For example; if bacterial sepsis is suspected, antibiotics should be administered after appropriate cultures have been taken; in the case of anaphylaxis, subcutaneous adrenaline should be part of the treatment regime.

### Treatment of Hypovolaemia

Treatment of a hypovolaemic patient will vary somewhat depending on the cause of the hypovolaemia and the choice of products available.

Clearly, in the situation of a haemorrhage, whole blood or packed cells in combination with other fluids is the appropriate therapy of choice.

In general, the fluids that are available for restoring blood volume can be divided into crystalloids; for example, normal saline and similar solutions, and colloids.

#### Colloids

The currently approved colloid available is Albumin made by CSL from plasma by Red Cross. The product that is generally available is Albumex 4%, or Albumex 20%.

Previously available starches such as Gelofusion and Haemaccel are no longer used due to renal toxicity and allergy.



## Monitoring drug concentrations

**Dr Richard Day**

Professor of Clinical Pharmacology, St Vincent's Hospital & UNSW

### When:

- Medicines with low therapeutic index (ratio of toxic to therapeutic doses)
- When effect is hard to measure e.g. prevention of seizures in an epileptic patient
- When there is substantial intersubject variability in pharmacokinetics
- When there is a non-proportional relationship between dose rate changes and steady state concentrations e.g. phenytoin
- When drug interactions are suspected
- When drug-induced toxicity is suspected
- When a therapeutic concentration range has been established
- At the extremes of age
- When clearance organs are impaired, e.g. liver or kidney failure
- Suspected drug abuse
- Failure to respond

### Which Medicines:

- Aminoglycosides
- Vancomycin
- Lithium
- Immunosuppressants e.g. cyclosporine, tacrolimus, sirolimus
- Antiretroviral drugs
- Phenytoin, carbamazepine, valproate, lamotrigine
- Digoxin
- Fluocytosine
- Amiodarone
- Perhexiline
- Aspirin/Salicylate
- Isoniazid
- Methotrexate
- Paracetamol
- Dicloxacillin, flucloxacillin (when poor absorption suspected)
- Itraconazole, Fluconazole, Voriconazole
- Antipsychotics – risperidone, haloperidol, clozapine
- Tyrosine kinase inhibitors - imatinib

### When to measure:

- Critical to know and record time of blood sample in relationship to the last dose
- Trough concentrations (i.e. just before next dose) are generally optimal
- Concentrations after 'steady state' has been achieved generally optimal (after dosing has exceeded 5 half-lives)

### Pitfalls:

- Forgetting that the 'therapeutic range' for a drug is different from the 'normal range' for an analyte such as plasma creatinine. The 'therapeutic range' is that concentration range for a drug, usually at the trough of the dosing interval, where the **probability** for efficacy without toxicity is most likely.
- Forgetting that a normal or near normal plasma creatinine concentration in an elderly, light weight patient usually **does not** mean a normal glomerular filtration rate. This is critical for drugs such as gentamicin (<http://www.sydpath.stvincents.com.au/tests/Aminoglycosides.htm>)

## Campus day multidisciplinary case-based seminar outlines

### Campus Day Program

You are required to attend the Campus Days and Medical Imaging Seminars during your Medicine and Surgery clinical terms. You should check eMed for the most current roster, and Moodle for announcements regarding updates to scheduling, and the mode of delivery. Most sessions are delivered hybrid; however, some will be completely online. Metro-based students are expected to attend in person unless they have a valid reason for attending online.

### 1. Clinical genetics

#### Aim

The aim of this day is to explore a range of principles relevant to Clinical Genetics, with particular reference to genetic testing.

#### Learning objectives

On completion of the Clinical Genetics Campus Day and associated activities, you should be able to:

1. Take a complete genetic family history, construct a pedigree chart and use it to identify key Mendelian genetic disease inheritance patterns
2. Describe commonly used genetic tests and understand the limitations associated with each testing strategy
3. Explain the importance of pre- and post-test counselling and utilise relevant guidelines and policies regarding consent for testing and sharing of information
4. Interpret the language and nomenclature used in the reporting of genetic test results
5. Explain when to refer a patient with a confirmed or possible genetic diagnosis to healthcare professionals with appropriate expertise
6. Describe the roles of different healthcare professionals involved in the management of patients/families with confirmed or possible genetic disorders and discuss how these roles are likely to evolve in the future.

#### Resources / Pre-reading

A pre-session adaptive tutorial will be made available via the Phase 3 Moodle module. Additional online resources will be shared with you prior to each Campus Day. The provisional schedule for the day is given below:

10:00-10:05	Introduction
10:05-10:35	Future of Genetics and Genomics in Medicine
10:35-11:15	Different Testing Scenarios
11:15-11:30	Morning Break
11:30-12:00	Different Genetic Tests
12:00-12:50	Interpreting Genetic Test Results
12:50-13:20	Lunch
13:20-14:00	Genetic Treatments
14:00-16:00	DMD Case Study with Breakout Sessions



## 2. Obesity and cardiovascular disease

### Aim

The aim of this seminar is to review Biomedical Sciences principles relevant to obesity and cardiovascular disease.

### Learning objectives

At the completion of this seminar, you should be able to:

1. Assess absolute cardiovascular risk for individuals and advise appropriate CVD screening activities related to heart disease, obesity and diabetes
2. Understand the pathophysiology of hypertension and vascular disease
3. Understand the biochemical processes in obesity, lipid disorders and diabetes
4. Describe pathogenesis of ischaemic heart disease and the range of clinical syndromes arising from myocardial ischaemia
5. Outline appropriate pharmacological and non-pharmacological treatments for smoking, obesity, lipid disorders, ischaemic heart disease and impaired glucose tolerance
6. Understand the mechanisms of action of pharmacological treatments, relevant pharmacokinetics, and effects of co-morbidities, e.g. renal impairment and concomitant medications on dosing schedules.

### Resources / pre-reading:

1. Goodman & Gilman's The Pharmacological Basis of Therapeutics, 13th ed. (2018). Available online through UNSW Library at: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013386250001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013386250001731?auth=SAML)
2. Australian Medicines Handbook. Available online through UNSW Library at: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013388100001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013388100001731?auth=SAML)
3. National Heart Foundation – Guide to Management of Hypertension in Adults 2016 (<https://www.heartfoundation.org.au/for-professionals/clinical-information/hypertension>)
4. Rang & Dale's Pharmacology, 10th ed. (2024). Hard copy available at UNSW Library; and also available online: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013388730001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013388730001731?auth=SAML)
5. Ambrose, J.A., Barua, R.S. (2004). The pathophysiology of cigarette smoking and cardiovascular disease: an update. *Journal of the American College of Cardiology*, 43(10), 1731-7. Available through UNSW Library. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013394340001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013394340001731?auth=SAML)

### Case History

Laura Anderson, a 66-year-old, recently retired Marketing Consultant, is brought by ambulance to the Emergency Department. She has experienced 30 minutes of central chest pain not relieved by sublingual glyceryl trinitrate. She has had intermittent angina for 7 years.

On examination:

General appearance:	She is in considerable distress, sweaty and grey Height 1.65m, Weight 93kg, BMI 34
Heart rate:	100/min
Blood pressure:	162/94
Respiratory rate:	20/min
Temp:	36.4°C

### Questions

1. What is the most likely diagnosis?
2. What are the possible outcomes? Outline the underlying pathology of each possible consequence.

If we could go back in time, could we have helped Laura avoid this predicament? Further information about Laura's case will be revealed during the seminar.

### 3. Infectious diseases

#### Aim

The aim of this seminar is to review Biomedical Sciences principles relevant to approaching a patient with fever of unknown origin (FUO).

#### Learning Objectives

At the completion of this seminar, you should be able to:

1. List the most common causes of FUO
2. Outline your approach to history and physical examination of a patient with fever
3. Develop a logical approach to the investigations of a patient with fever
4. Complete a laboratory request form
5. Understand the appropriate approach to treatment following diagnosis, including how to prescribe antibiotics such as gentamicin safely and effectively.

#### Resources / Pre-reading

1. Harrison's Principles of Internal Medicine, 21st ed. (2022). Fever of Unknown Origin. Chapter 20. Available online through UNSW Library at:  
[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013412370001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013412370001731?auth=SAML)
2. Brown I, Finnigan NA. Fever of Unknown Origin. [Updated 2022 Aug 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from:  
[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013416330001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013416330001731?auth=SAML)
3. Fernandez C, Beeching NJ. Pyrexia of unknown origin. Clin Med (Lond). 2018 Mar;18(2):170-4. doi: 10.7861/clinmedicine.18-2-170. Available from:  
[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013417000001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013417000001731?auth=SAML)
4. David A, Quinlan JD. Fever of Unknown Origin in Adults. Am Fam Physician. 2022 Feb 1;105(2):137-143. Available from:  
[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013417440001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013417440001731?auth=SAML)
5. eTG complete (Therapeutic Guidelines 2021 edition): Antibiotic. Available online through UNSW Library at:  
[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013417890001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013417890001731?auth=SAML)

#### Case History

Linda, a 45-year-old schoolteacher, presents to the Emergency Department with a 3-week history of fever, especially in the afternoon and evening, and night sweats. Her appetite has been poor but she denies weight loss. She has had mild abdominal discomfort. Physical examination revealed a temperature of 38.5°C, a regular heart rate 88/min and a BP of 130/80. There is mild diffuse abdominal tenderness. Examination is otherwise unremarkable.

#### Questions

1. Outline the steps involved in the pathogenesis of fever. Consider:
  - Initial stimuli
  - Cellular targets of these stimuli
  - Circulating endogenous mediators
  - Target tissue of these mediators and its key product
  - How the brain then controls body temperature.
2. What questions should the doctor ask Linda?
3. What is particularly important to check in the physical examination?

Further developments in Linda's case will be revealed during the seminar.

## 4. Post-operative care

### Aim

The aim of this seminar is to investigate post-surgical care, including the importance of hospital acquired infection, antibiotic prescribing and pain management.

### Learning objectives

At completion of this seminar you should be able to:

1. Understand post-surgical fluid balance, replacement and prescribing (includes discussion of fluid chart use)
2. Prescribe post-operative pain relief safely and effectively
3. Identify the important features and management of common hospital acquired infections (including antibiotic prescribing and quality and safety issues).

### Resources / Pre-reading

#### Pain Management

1. Therapeutic Guidelines: General principles of acute pain management. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013450290001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013450290001731?auth=SAML)
2. The Oxford Pain Internet Site hosted by Bandolier: <http://www.bandolier.org.uk/booth/painpag/index.html>
3. Online tutorial: Pain Management (see Phase 3 Moodle) <https://moodle.telt.unsw.edu.au/mod/h5pactivity/view.php?id=7208564>

#### Fluid management:

1. Online tutorial: Fluid Balance – Clinical Assessment and Management (see Phase 3 Moodle) <https://moodle.telt.unsw.edu.au/mod/h5pactivity/view.php?id=7208560>
2. Scott N, Squibbs J, Lake A, Guha A. Risks of intravenous fluid therapy by first year residents—a prospective study. Br J Med Med Res. 2016;15(4):1-13. doi: 10.9734/BJMMR/2016/25456. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013454360001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013454360001731?auth=SAML)
3. Lyons I, Furniss D, Blandford A, Chumbley G, Iacovides I, Wei L, Cox A, Mayer A, Vos J, Galal-Edeen GH, Schnock KO, Dykes PC, Bates DW, Franklin BD. Errors and discrepancies in the administration of intravenous infusions: a mixed methods multihospital observational study. BMJ Qual Saf. 2018 Nov;27(11):892-901. doi: 10.1136/bmjqqs-2017-007476. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013455470001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013455470001731?auth=SAML)
4. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, Christophi C, Leslie K, McGuinness S, Parke R, Serpell J. Restrictive versus liberal fluid therapy for major abdominal surgery. New England Journal of Medicine. 2018 Jun 14;378(24):2263-74. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013461470001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013461470001731?auth=SAML)
5. Bhonagiri D, Lander H, Green M, Straney L, Jones D, Pilcher D. Reduction of in-hospital cardiac arrest rates in intensive care-equipped New South Wales hospitals in association with implementation of Between the Flags rapid response system. Intern Med J. 2021 Mar;51(3):375-384. doi: 10.1111/imj.14812. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66027706430001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66027706430001731?auth=SAML)
6. Hughes C, Pain C, Braithwaite J, Hillman K. 'Between the flags': implementing a rapid response system at scale. BMJ Qual Saf. 2014 Sep;23(9):714-7. doi: 10.1136/bmjqqs-2014-002845. [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013459890001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013459890001731?auth=SAML)

#### Hospital-acquired infection:

- Ausmed. (2018). Central Line Associated Blood Stream Infections (CLABSI). <https://www.ausmed.com.au/learn/articles/central-line-associated-bloodstream-infections>
- Haddadin Y, Annamaraju P, Regunath H. Central Line Associated Blood Stream Infections. [Updated 2022 Nov 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK430891/>
- Patel, P. K., Gupta, A., Vaughn, V. M., Mann, J. D., Ameling, J. M., & Meddings, J. (2017). Review of Strategies to Reduce Central Line-Associated Bloodstream Infection (CLABSI) and Catheter-Associated Urinary Tract Infection (CAUTI) in Adult ICUs. Journal of Hospital Medicine, 13(2), 105–116. <https://doi.org/10.12788/jhm.2856> <https://pubmed.ncbi.nlm.nih.gov/29154382/>
- Antibiotic prescribing: Please access Therapeutic Guidelines online via UNSW Library: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013450290001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013450290001731?auth=SAML)

Antibiotic: Sepsis and bacteraemia (including Principles of managing sepsis and septic shock, and Empirical regimens for sepsis or septic shock). Limit to adults and take special note of the section on Hospital-acquired sepsis or septic shock, source not apparent.

- Principles of vancomycin use:

[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66177710370001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66177710370001731?auth=SAML)

### **Relevant local study on peripheral cannula issues:**

- Alexandrou, E., Ray-Barruel, G., Carr, P. J., Frost, S., Inwood, S., Higgins, N., ... Rickard, C. M. (2015). International prevalence of the use of peripheral intravenous catheters. *Journal of Hospital Medicine*, 10(8), 530–533. doi: 10.1002/jhm.2389.

[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66013473270001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66013473270001731?auth=SAML)

### **Related news report:**

- Aubusson, K. (August 21, 2018). Patients jabbed in the wrong places: Botched, painful catheters rife. *Sydney Morning Herald online*.

[https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66027678390001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66027678390001731?auth=SAML)

### **Case History:**

*George, a 75-year-old man with a history of biventricular heart failure, comes to hospital for a sigmoid colectomy following diagnosis of colon cancer. His heart failure is currently well controlled on irbesartan, frusemide and perindopril. He also takes rosuvastatin and can climb one flight of stairs without stopping. He looks after himself at home and walks to the local shops. He weighs 80 kg.*

### **Stages in the case scenario**

The basic case scenario is provided to you as pre-reading with the other resources listed above. During the seminar, the facilitators will take you through the case by asking the questions and highlighting the discussion points suggested along the way.

### **Questions**

#### **Pre-operative assessment**

1. As the surgical intern, you are required to clerk George, and to make a pre-operative assessment with regard to:
  - a) Previous surgery
  - b) Peri-operative fluid management
  - c) Planning for pain relief.
2. Please outline your approach to these three aspects of his care.



**Case continued...**

*At induction of general anaesthesia George is given 2g Cephazolin and 500mg Metronidazole. The operation proceeds well, and during the three hours he is anaesthetised, he receives two units of packed cells (to replace operative blood loss) and a total of three litres of crystalloid (two litres of Hartmann's solution and 1 litre of normal saline) to maintain arterial blood pressure and urine output.*

*At the end of the operation, he is woken and extubated before being moved to the recovery ward. On arrival there he is alert and responding to questions, pulse rate 76 and regular, arterial BP 140/70. He is complaining of some abdominal pain, but it is not severe, and he is relatively comfortable. He is prescribed an Oxycodone Pain Protocol for use in Recovery, and an oxycodone PCA is commenced for use on the ward.*

*As the surgical intern on the ward, you are called to see him on the surgical ward at 8 pm on the evening of surgery (he is 6 hours post-operative). He has passed only scant amounts of urine for the past three hours. He has been charted for 150 ml/hr of Dextrose 4% plus 1/5N Saline, but due to an error in reading the chart, he has been receiving only 50 ml/hr.*

**Question:**

3. What steps do you take to analyse and resolve the situation?

*Further developments in George's case will be revealed during the seminar.*

## 5. Head and spinal injury

### Aim

The aim of this seminar is to review the pathophysiology of trauma, with particular reference to head and spinal injuries.

### Learning objectives

At the completion of this seminar you should be able to:

1. List the likely causes of death following trauma to the head, neck, thorax and abdomen.
2. Explain the underlying anatomical basis of nerve and spinal cord injuries following head and neck trauma.
3. Compare and contrast the pathophysiology and clinical consequences of epidural, subdural, subarachnoid and intracerebral haemorrhage.
4. Outline the Glasgow Coma Scale, and its utility in the assessment of patients following head injury.
5. Describe the clinical manifestations, complications and emergency management of raised intracranial pressure.
6. Describe the emergency management and possible neurological consequences of fracture of the cervical spine.

### Resources / Pre-reading

1. Moore, K.L., Dalley, A.F., & Agur, A.M.R. (2018). Clinically Oriented Anatomy, 8<sup>th</sup> ed. Wolters Kluwer. **Hard copy** available at UNSW Library.
2. Drake R.L., Vogl A.W., Mitchell A.W.M. (2020). Gray's Anatomy for Students, 5<sup>th</sup> ed. Elsevier. available online through UNSW Library at: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/65302844220001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/65302844220001731?auth=SAML)
3. Kumar, V., Abbas, A.K., & Aster, J.C. (2023). Chapter 23 (Central Nervous System) in Robbins Basic Pathology (11<sup>th</sup> ed.). Elsevier. Available online through UNSW Library at: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/65302844740001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/65302844740001731?auth=SAML)
4. Vella MA, Crandall ML, Patel MB. Acute Management of Traumatic Brain Injury. *Surg Clin North Am.* 2017 Oct;97(5):1015-1030. doi: 10.1016/j.suc.2017.06.003. Available from: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66158393120001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66158393120001731?auth=SAML)
5. Stocchetti N, Zanier ER. Chronic impact of traumatic brain injury on outcome and quality of life: a narrative review. *Crit Care.* 2016 Jun 21;20(1):148. doi: 10.1186/s13054-016-1318-1. Available from: [https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW\\_INST/citation/66063715490001731?auth=SAML](https://unsw.alma.exlibrisgroup.com/leganto/public/61UNSW_INST/citation/66063715490001731?auth=SAML)

### Case History

*A 16-year-old boy was brought by ambulance to the Emergency Department. His mother, who accompanied him in the ambulance, revealed that he was kicked in the right side of the head during a football match one hour previously. The boy was unconscious for a short period of time after the injury but quickly regained consciousness on the field. St. John's ambulance officers ensured that he remained still and fitted a neck brace before moving him to the sidelines on a backboard. A few minutes later he complained of a severe headache and became increasingly drowsy and confused, as well as vomiting several times. Examination in the Emergency Department revealed that the boy was irritable and confused, with a tender swelling over the right temporal region. There was tenderness over the cervical spine and weakness of the left arm.*

<b>Vital Signs</b>	
Heart rate (b/min)	60
Blood pressure (mm Hg)	140/60
Respiratory rate (/min)	10
<b>Temperature (°C)</b>	36.3

### Questions

1. What is the most likely diagnosis?
2. If untreated, what would you predict would happen to this boy?

*Further developments in this boy's case will be revealed during the seminar.*

## Hospital-based tutorial topics

The topics that may be covered in hospital-based Phase 3 Biomedical Sciences tutorials are listed below. This list of topics is not meant to be an exhaustive one, and tutors at each hospital may choose to combine, separate or in other ways alter topics. The topics listed, together with the learning objectives, are a guide to the scope and depth of knowledge that is expected.

The onus is on you to ensure that you are able to address adequately the learning objectives stated below.

**Each 90-minute tutorial will focus on a case protocol (or protocols) relevant to the topic, and any associated modules in the *P3 Biomedical Science Modules* Moodle course. Self-enrolment is required via the following link: <http://moodle.telt.unsw.edu.au/course/view.php?id=14483>**

**Student enrolment key: P3BMS**

In the short listing below, each tutorial topic is shown together with the types of diseases that may be considered in that tutorial. This short listing is followed by a more detailed list of learning objectives for each topic. **Please note that where there is a selflearning module (or modules) associated with a tutorial topic, it is expected that you will have explored the relevant module(s) prior to attendance at the tutorial. It is also expected that you should prepare for each tutorial by reading the learning objectives and associated case protocols, as well as consulting biomedical science texts and other resources.**

Tutorial Topic	Case Protocols (Number in Manual)
Chronic cough & dyspnoea	11
Chest pain + vascular disease (modules)	9, 10, 38
Haematuria (module)	17, 37
Hepatitis & chronic liver disease	22, 36
Cerebrovascular disease	34, 40
Back pain + bone tumours (modules)	5, 6, 14, 35
Acute dyspnoea + haemoptysis (modules)	3, 19, 39
Gynaecological malignancies	1, 2
Glomerulonephritis + renal failure (modules)	18, 27, 32
CNS tumours and CNS infections (modules)	20, 21, 41
Opportunistic infections & AIDS	26
Multisystem disease + polyarthritis (modules)	24, 30
Endocrine disease (module)	25
Breast lumps	7
Scrotal masses	33
Bleeding disorders	8
Dysphagia & haematemesis (module)	13, 16
Inflammatory bowel disease	12
Complications of diabetes	31
Anaemia (module)	28
Allergy and anaphylaxis	4
Gallbladder & pancreatic disease (module)	15, 43
Leukaemia & myeloproliferative disease (module)	29, 42
Lymphoma (module)	23

**Acute dyspnoea:**

Asthma, pulmonary thromboembolism, pulmonary oedema, airway obstruction, acute respiratory distress syndrome, pulmonary collapse, pneumonia

**Allergy and anaphylaxis**

Causes and pathophysiology of shock and anaphylaxis

**Anaemia**

Causes and investigation of anaemia, including haemolysis and anaemia resulting from impaired production (aplastic, myelophthisic, iron deficiency, megaloblastic)

**Back pain**

Intervertebral disc disease and its consequences, vertebral metastases, metabolic bone disease

**Bleeding disorders**

Causes, effects and investigation of bleeding disorders, including hereditary and acquired thrombocytopenia, disseminated intravascular coagulation. Principles of blood banking and complications of blood transfusions

**Bone tumours**

Osteosarcoma, Ewing sarcoma, multiple myeloma, chondrosarcoma, metastases, osteochondroma, giant cell tumour, etc.

**Breast lumps**

Pathological investigation of breast lumps. Carcinoma of the breast, fibrocystic change, fibroadenoma, fat necrosis, breast abscess and mastitis

**Cerebrovascular disease**

Cerebrovascular disease including cerebral ischaemia, cerebral infarction, transient ischaemic attacks and intracranial haemorrhage (extradural, subdural, subarachnoid, intracerebral)

**Chest pain**

Coronary heart disease (angina, unstable angina, myocardial infarction) and its consequences. Diffuse oesophageal spasm, pericarditis, pulmonary infarction, aortic dissection, pleurisy

**Chronic cough and dyspnoea**

Emphysema, chronic bronchitis, small airways disease and chronic airflow limitation; interstitial lung disease

**CNS infections**

Meningitis, encephalitis, brain abscess

**CNS tumours**

Primary and secondary cerebral neoplasms, cerebral abscess, hydrocephalus, intracranial haemorrhage.

Pathology of raised intracranial pressure

**Diabetes mellitus - complications**

Causes and diagnosis of diabetes mellitus. Complications, including acute metabolic events and chronic complications (nephropathy, neuropathy, retinopathy, macrovascular disease)

**Dysphagia and haematemesis**

Causes of dysphagia, including carcinoma of the oesophagus, oesophagitis, achalasia, diffuse oesophageal spasm, webs, etc. Peptic ulceration, acute and chronic gastritis, carcinoma of the stomach, Mallory-Weiss tears, oesophageal varices

**Endocrine disease**

Graves disease, simple and multinodular goitre, thyroiditis, carcinoma of the thyroid (papillary, follicular, anaplastic, medullary), adrenal gland disorders, pituitary disorders, parathyroid disorders,

**Gallbladder and pancreatic disease**

Gallstones and their consequences, including bile duct obstruction, cholecystitis and cholangitis, carcinoma of the gallbladder. Acute and chronic pancreatitis and carcinoma of the pancreas

**Glomerulonephritis**

Causes and consequences of acute kidney injury, the nephritic syndrome and proliferative glomerulonephritis (focal and diffuse proliferative, post streptococcal, IgA nephropathy, etc.); nephrotic syndrome - causes and complications, including primary glomerulonephritis (minimal change, focal segmental glomerulosclerosis, membranous, membranoproliferative) and secondary causes (diabetic nephropathy, systemic lupus erythematosus, amyloidosis, drugs, etc.)

**Gynaecological malignancies**

Carcinomas of the cervix, uterus and ovaries

**Haematuria**

Tumours of the urinary tract, including renal cell carcinoma and transitional cell carcinomas, renal calculi

**Haemoptysis**

Carcinoma of the lung, bronchiectasis, lung abscess, tuberculosis, other causes of haemoptysis

**Hepatitis and chronic liver disease**

*Hepatitis - viral, alcoholic, autoimmune. Chronic hepatitis, cirrhosis and its complications*

**Inflammatory bowel disease**

*Ulcerative colitis, Crohn's disease, infective causes of diarrhoea*

**Leukaemia and myeloproliferative disorders**

*Acute and chronic leukaemias (myeloid and lymphoid), polycythaemia vera, myelofibrosis. Differential diagnosis of splenomegaly*

**Lymphoma**

*Non-Hodgkin lymphoma, Hodgkin lymphoma; differential diagnosis of lymphadenopathy*

**Multisystem disease**

*Systemic lupus erythematosus, autoimmune disease, scleroderma, transplant rejection*

**Opportunistic infections and AIDS**

*HIV infection and its complications, other causes of secondary or acquired immunosuppression*

**Polyarthritis**

*Rheumatoid arthritis and its consequences, Sjögren syndrome*

**Renal failure**

*Causes of chronic kidney disease, including chronic glomerulonephritis, hypertensive, diabetic and reflux nephropathies and tubulointerstitial disease; consequences and complications of CKD*

**Scrotal masses**

*Testicular tumours (seminoma and non-seminomatous germ cell tumours), hydrocoele, spermatocele, hernias, epididymo-orchitis, testicular torsion*

**Vascular disease**

*Atherosclerosis, including cerebrovascular disease, peripheral vascular disease, and abdominal aortic aneurysm formation; vasculitic syndromes*

**Topics not covered by formal teaching resources**

In addition to the above topics, you are expected to acquire an understanding of the following areas, which will not be formally covered in teaching sessions or online learning modules:

- causes of hoarseness including laryngeal mass lesions
- causes of weight loss including malabsorption syndromes
- causes of deterioration in higher cerebral functions, including dementia syndromes, slow virus infections and prion diseases
- immunopathology of transplantation and rejection
- causes of skin rashes, including immunologically mediated diseases, e.g. eczema, SLE

## Specific learning objectives for hospital-based tutorials

For each topic, a set of specific learning objectives is outlined below. **If these objectives are not fulfilled within formal teaching sessions, it is your responsibility to achieve the learning objectives through further study.** You should note that each topic is associated with one or more case protocols, which are short clinical scenarios with associated questions that can be found in a subsequent section of this manual. For each topic, trial exam questions have been included. These questions should be attempted, either as preparation for each formal teaching session (preferably), or for revision purposes.

### Acute dyspnoea and haemoptysis

The aim of this topic is to revise the pathological basis, diagnosis, and pharmacological treatment of acute dyspnoea. This topic will also consider the diseases that may cause haemoptysis, including lung cancer, bronchiectasis, lung abscess, pulmonary infarction, and pulmonary oedema.

#### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Define the term "dyspnoea" and describe the pathophysiological conditions that may cause it.
2. Describe the factors that predispose to the development of pulmonary thromboembolism, explain its possible clinical consequences, and outline an appropriate sequence of investigations to confirm the diagnosis. Describe the mechanisms of action of anticoagulant and fibrinolytic medicines.
3. Outline the common causes of heart failure, describe the physiological consequences of left ventricular and right ventricular failure, and relate those changes to the usual radiographic appearances in this condition. Consider the pros and cons of the major pharmacological drug groups used to manage heart failure, namely ACE inhibitors, AII Inhibitors, beta blockers, nitrates, loop diuretics, digoxin.
4. List the factors that may trigger asthma. Describe the pathological changes that occur in this disease, and the effects that these changes have on respiratory function. Understand the pharmacological mechanisms of the 'preventative' and 'relieving' medications used in asthma.
5. Outline the pathological changes seen in the acute respiratory distress syndrome (ARDS). Be aware of the pharmacological modalities used in ARDS and their modes of action.
6. Discuss the role of arterial blood gas analysis in the investigation of acute dyspnoea.
7. List the common diseases that underpin haemoptysis and describe the pathogenetic mechanisms.
8. Describe the scientific evidence linking cigarette smoking to the development of lung cancer. Discuss the socio-demographic determinants of smoking prevalence and implications for preventive strategies. Explain the rationale for, and routes of administration of, nicotine replacement therapies.
9. Compare the biological behaviour of small cell and non-small cell lung cancer and discuss the implications that the differences in behaviour may have for the management of patients.
10. Describe the common modes of spread of lung cancer and relate the pathological changes at each stage of the disease with possible clinical manifestations.
11. Describe the common causes, morphology, and clinical manifestations of bronchiectasis.
12. List the causes of a lung abscess and indicate why such a lesion may produce haemoptysis.
13. Describe the pathogenesis of primary and post-primary tuberculosis and relate this to the typical pathological findings in each stage of the disease.
14. Describe diagnostic procedures appropriate to the investigation of haemoptysis, including the role of sputum cytology.
15. Describe investigations appropriate to the diagnosis of tuberculosis. Discuss what steps you would take following the diagnosis of tuberculosis and outline the recommended therapy.

#### ***Trial exam questions:***

1. Compare and contrast the pathophysiology of allergic and non-allergic asthma.
2. Outline the pathophysiology of fatal pulmonary embolism.
3. Explain the clinical effects of primary bronchogenic carcinoma that are due to local growth and invasion.
4. List the factors associated with reactivation of pulmonary tuberculosis and outline the appropriate diagnostic tests and antimicrobial treatment.
5. Describe how AII inhibitors affect the pathophysiology of cardiac failure.

#### ***Case protocols associated with this topic – 3, 19***

#### ***Other relevant protocol – 39***

## Anaemia

The aim of this topic is to review the common causes and clinical consequences of anaemia.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the normal morphology and function of red blood cells.
2. Outline the ontogeny of erythrocytes from their bone marrow precursors and the factors that regulate this development.
3. Outline a basic classification of the causes of anaemia.
4. Discuss the common causes of microcytic hypochromic anaemia, in particular, the role of iron deficiency in the pathogenesis of this disorder.
5. List the common causes of iron deficiency anaemia and describe the consequences of such deficiency on both the bone marrow and mucosal tissues. Describe the principles of prescribing iron replacement therapy. Describe the hazards of this therapy.
6. Describe the common haemoglobinopathies, especially thalassaemia and sickle cell anaemia.
7. Outline the causes of haemolytic anaemia. In particular, contrast the intra- and extra-corpuscular causes of haemolysis. The clinical features and consequences of haemolytic anaemia should also be discussed.
8. Outline an appropriate sequence of investigations for a patient presenting with anaemia.

### ***Trial exam questions:***

1. Outline the clinical features of iron deficiency anaemia. What are the common underlying causes?
2. Outline the causes and an appropriate sequence of investigations for macrocytic anaemia.

### ***Case protocol associated with this topic – 28***

## Anaphylaxis, allergy and shock

The aim of this topic is to revise the common causes, pathophysiology and pharmacological treatment of shock, with particular emphasis on anaphylaxis and septicaemia.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Define “shock” and describe the clinical features.
2. Classify the causes of shock based on pathophysiology.
3. Explain the pathophysiology, and outline the common causes, of systemic anaphylaxis resulting from both allergic (type 1 hypersensitivity) and non-allergic mechanisms. Describe how the common drug therapies work in patients with systemic anaphylaxis.
4. Appreciate the common factors that predispose to the development of sepsis.
5. Describe the pathogenesis of endotoxin-induced shock.
6. Explain how sepsis can induce multiple organ failure.
7. Outline the pathophysiology of disseminated intravascular coagulation associated with sepsis.
8. Describe the appropriate laboratory investigation of a patient with sepsis. List the specimens that you would collect, the microbiological tests that you would order and the common microorganisms that you would expect to culture under various clinical circumstances, and the haematological and biochemical abnormalities that may be associated with sepsis.
9. Outline the empirical antibiotic therapy that would be recommended in immunocompetent patients (adults and children) with severe sepsis where there is no obvious source of infection.

### ***Trial exam questions:***

1. Discuss the following statement: “Anaphylaxis and septic shock are two examples of shock due to a maldistribution of blood flow.”
2. Discuss the immunopathogenesis and clinical manifestations of common allergic reactions to penicillin.

### ***Case protocol associated with this topic – 4***

## Back pain and bone tumours

The aim of this topic is to alert you to the wide differential diagnosis of back pain (an extremely common symptom). In particular you should become familiar with the pathological processes that may induce back pain, the investigations that can establish the diagnosis, and the pharmacological treatment of osteoporosis.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. List the common sources of back pain, both local and referred.
2. Distinguish between the classical clinical features ("red flags") of mechanical and inflammatory back pain and list the sociocultural risk factors ("yellow flags") for development of chronic back pain. How do the pharmacological approaches contrast?
3. Outline the pathogenesis of lumbar intervertebral disc degeneration and prolapse, and describe the clinical syndromes that may ensue.
4. Define the terms "spondylolisthesis" and "facet joint degeneration", and explain how these disorders may cause back pain.
5. Compare and contrast the clinical features of acute osteomyelitis in children and adults.
6. Discuss the routes by which bone may become infected and list the microorganisms most commonly associated with osteomyelitis. Outline the empirical therapy for pyogenic osteomyelitis.
7. Describe the complications of vertebral osteomyelitis, both pyogenic and tuberculous.
8. Explain the pathophysiology of metabolic bone diseases - in particular osteoporosis (primary and secondary), osteomalacia, hyperparathyroidism, Paget's disease of bone and renal osteodystrophy.
9. Construct a table comparing the biochemical and radiographic abnormalities caused by each of the metabolic bone diseases.
10. Discuss the methods of prevention and the investigation of post-menopausal osteoporosis. What pharmacological options are available for treatment? How do they work? Which are preferred?
11. List the common neoplasms occurring in bone in approximate order of frequency.
12. Name the primary neoplasms that are most likely to metastasise to bone and describe the common locations, clinical effects and investigative abnormalities associated with skeletal metastases.
13. Outline the genetic and acquired risk factors for the development of osteosarcoma.
14. Construct a table that compares the epidemiology, cell of origin, clinical behaviour and radiographic appearances of osteosarcoma, chondrosarcoma, Ewing sarcoma and giant cell tumour of bone.
15. Define the term "multiple myeloma" and discuss the pathophysiology of this disorder in terms of infiltration of bone and the presence of secreted paraprotein in serum and/or urine.
16. Explain the development of renal impairment and immunodeficiency in patients with multiple myeloma.
17. Distinguish between benign and malignant causes of paraproteinaemia, and list the features of "monoclonal gammopathy of undetermined significance" (MGUS).

### ***Trial exam questions:***

1. Discuss the following statement: "The clinical effects of renal osteodystrophy result from a combination of osteoporosis, osteomalacia, hyperparathyroidism and iatrogenic factors."
2. Write notes on Paget's disease and its complications. What are the treatment options? How do they work?
3. List the clinical effects of multiple myeloma resulting from infiltration of bone and monoclonal gammopathy.
4. Write brief notes on the pathogenesis and complications of osteogenic sarcoma.

### ***Case protocols associated with this topic – 5, 6***

### ***Other relevant protocols – 14, 35***

## Bleeding disorders

The aim of this topic is to review the pathophysiology and investigation of common bleeding problems, and to discuss the complications of blood transfusions.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the structure and function of platelets, and their role in haemostasis.
2. Compare and contrast the intrinsic and extrinsic coagulation pathways, and the investigations used to assess them.
3. Describe the common congenital and acquired causes of bleeding disorders, and their typical clinical presentations. What medicines affect platelet function? How?
4. Outline the genetics and pathophysiology of the haemophilias and Von Willebrand's disease.
5. Summarise the common causes of thrombocytopenia. In particular, outline the pathophysiology of idiopathic thrombocytopenic purpura, disseminated intravascular coagulation and infiltrative disease of the bone marrow.
6. Outline the laboratory evaluation of a patient with thrombocytopenia, disseminated intravascular coagulation, and bleeding associated with liver disease.
7. List the indications for blood and platelet transfusions.
8. Outline the basic principles and techniques of cross-matching whole blood prior to transfusion.
9. Describe the main complications of blood, white cell and platelet transfusions, and the pathophysiology of these reactions.

### ***Trial exam questions:***

1. Briefly outline the pathogenetic mechanisms of the common complications of blood transfusions.
2. Outline an appropriate sequence of investigations to determine the cause of spontaneous bruising and recurrent epistaxis.

### ***Case protocol associated with this topic – 8***



## Breast lumps

The aim of this topic is to consider the possible causes of a breast lump, and the ways in which a diagnosis of these conditions may be reached.

### ***Learning objectives***

At the completion of this topic you should be able to:

1. Provide a differential diagnosis of a breast lump, appropriate for the age of the patient.
2. Relate the pathological changes that cause breast lumps to the characteristic clinical features.
3. List in order of importance those factors known to increase the risk of the development of breast cancer.
4. Discuss the significance of axillary lymphadenopathy in the prognosis of a woman with breast cancer.
5. What is the lymphatic drainage of different parts of the breast? What are the anatomical locations of the groups of axillary lymph nodes that are palpable during physical examination? How is the concept of "sentinel lymph node" useful in the management of breast neoplasm?
6. State the common modes of spread of breast cancer, and the likely clinical consequences of such spread.
7. Discuss the methodology, advantages and disadvantages of mammography, ultrasound, fine needle aspiration biopsy, Tru-Cut biopsy, incisional and excisional biopsy, and frozen sections, as they relate to the diagnosis of breast cancer and benign breast lesions.
8. Describe the pathological changes seen in Paget's disease of the nipple
9. Relate the mammographic appearance of breast cancer to the pathological changes seen in these lesions.

### ***Trial exam questions:***

1. What prognostic indicators can the pathologist provide by examination of tissue obtained from a radical mastectomy for carcinoma of the breast?
2. Discuss the role of mammography in (a) screening for breast cancer; and (b) investigation of a breast lump.

### ***Case protocol associated with this topic – 7***

## Cerebrovascular disease

The aim of this topic is to gain insight into the common causes of cerebrovascular disease or “strokes”, with particular emphasis on haemorrhagic, thromboembolic and ischaemic diseases that affect the central nervous system.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Summarise the frequency, morbidity and mortality associated with cerebrovascular disease in the community.
2. Describe the anatomy of the cerebral circulation, particularly the blood supply to the major functional regions of the cerebral cortex, cerebellum and brain stem.
3. Outline the major sensory and motor descending pathways from the cortex to the spinal cord.
4. Compare and contrast the three common stroke syndromes: haemorrhagic, thrombotic and embolic. In particular, outline the common syndromes that result from haemorrhage or infarction in particular anatomical sites.
5. Summarise the factors that predispose to cerebrovascular disease and outline evidence-based interventions to reduce this risk.
6. Outline the major stroke syndromes that result from occlusion of the anterior, middle and posterior cerebral arteries, as well as the effects of occlusion of the vertebral artery and the perforating branches of the lenticulostriate arteries.
7. Outline the common sequelae that result from cerebral infarction.
8. Summarise the effects of raised intracranial pressure.
9. Describe the various types of intracranial haemorrhage, their common sites and factors predisposing to their development. Understand the risks of intracerebral haemorrhage associated with warfarin use and how age affects the risk.
10. Describe the microscopic changes that occur in the brain as a result of ischaemia, and how these changes differ from those found in other organs undergoing ischaemic necrosis.

### ***Trial exam questions:***

1. Outline the clinicopathological consequences of thrombotic occlusion of the left middle cerebral artery.
2. Write brief notes on intracranial haemorrhage.

### ***Case protocol associated with this topic – 34***

### ***Other relevant protocol – 40***

## Chest pain and vascular disease

The aim of this topic is to review the pathological basis of chest pain. While ischaemic heart disease will be emphasised, other conditions such as anxiety disorders, pneumonia, pulmonary infarction, aortic dissection, pericarditis and chest wall pain should be considered.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the events that may lead to occlusion in the coronary circulation, and recognise the macroscopic and microscopic changes that may occur in the myocardium as a result of such an event.
2. Describe the typical clinical syndromes of chest pain, including panic attacks, ischaemic, pleuritic, chest wall and radicular pain, and indicate their pathological and anatomical basis.
3. Discuss the epidemiology of ischaemic heart disease and its associated morbidity and mortality.
4. Outline the common sites of coronary artery atherosclerosis, and describe the relationship between the complications of atherosclerosis and the clinical syndromes of stable and unstable angina.
5. Relate these same changes in the myocardium to the electrocardiographic abnormalities that characterise myocardial infarction.
6. Describe the way in which estimation of serum biomarkers may aid in the diagnosis of myocardial infarction. In particular, outline the time course of changes in serum levels of cardiac troponins following myocardial infarction.
7. What pharmacological treatments are used to limit the extent of a myocardial infarction and what is their mechanism of action?
8. Describe in detail the common complications of myocardial infarction, and their pathological basis. In particular, describe the mechanisms responsible for ventricular and other arrhythmias, cardiogenic shock and cardiac failure, cardiac rupture, pericarditis and pulmonary thromboembolism.
9. Discuss the common causes, typical pathological changes, and clinical consequences of aortic dissection.
10. List the causes of pericarditis, and outline the clinical features and potential complications of this condition.
11. Provide an explanation for the pathogenesis of atherosclerosis that encompasses the key epidemiological and pathological features described above.
12. Describe the natural history of an atherosclerotic plaque, and the diverse physiological and clinical consequences that may arise from a complicated lesion.
13. Describe the pathological changes that may be seen in the arterial tree as a consequence of systemic hypertension.
14. Outline the common causes of aneurysms, and describe the consequences of their development at typical sites within the arterial tree.

### ***Trial exam questions:***

1. Compare and contrast the pathogenesis of typical angina pectoris, unstable angina and myocardial infarction.
2. Write brief notes on the early and delayed complications of myocardial infarction.
3. Describe the mechanisms of action of the medicines used to limit the extent of myocardial infarction.
4. Discuss the pathophysiology of myocardial “reperfusion injury”. How does it differ from “stunned myocardium”?
5. Describe the “response to injury” hypothesis regarding the pathogenesis of atherosclerosis.
6. Discuss the causes and complications of aortic aneurysms.

### ***Case protocols associated with this topic – 9, 10***

### ***Other relevant protocol – 38***

## Chronic cough and dyspnoea

The aim of this topic is to gain familiarity with the common causes of chronic airflow limitation and its clinical consequences. Interstitial lung disease should also be considered.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the anatomical and physiological basis of gas exchange across the pulmonary vascular bed.
2. Describe the normal cellular structure of the bronchial wall and the functional significance of the components.
3. List the most common causes of acute bronchitis and discuss the appropriateness of antibiotic therapy in acute bronchitis and acute exacerbations of chronic obstructive pulmonary disease.
4. Define terms used in relation to chronic cough and dyspnoea, including emphysema, chronic bronchitis, chronic bronchiolitis and chronic airflow limitation. For each of these disorders, describe the concomitant pathological, physiological and/or clinical changes, as well as common causative factors.
5. Describe the characteristic features of the common forms of emphysema.
6. Outline what is known of the pathophysiology of emphysema, particularly with respect to its causation by cigarette smoking.
7. Outline the physiological consequences of chronic airflow limitation, especially on gas exchange and pulmonary arterial resistance.
8. Describe the typical histological features of interstitial lung disease, and relate these to their physiological effects in terms of gas exchange and pulmonary function tests.
9. List factors known to be associated with the development of interstitial lung disease.
10. Delineate groups at risk of inhalation of inorganic dusts such as asbestos, silica and coal, and compare the pathological, radiographic and clinical effects of these agents.

### ***Trial exam questions:***

1. Explain the relationship between the inhalation of cigarette smoke and the destruction of alveolar walls.
2. Outline the adverse effects of cigarette smoking on organs other than the lung.

### ***Case protocol associated with this topic – 11***

## CNS tumours and CNS infections

The aim of this topic is to review the pathophysiology of common intracranial space occupying lesions, particularly primary and metastatic neoplasms, as well as to review the pathophysiology and pathogenesis of meningitis and encephalitis.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the causes of raised intracranial pressure, including neoplasms, abscesses and haemorrhages.
2. Describe the clinical features and complications of raised intracranial pressure.
3. Describe the investigations appropriate for a patient presenting with raised intracranial pressure. How can raised intracranial pressure be managed?
4. Describe the appearance, location and effects of metastatic neoplasms involving the central nervous system.
5. Summarise the major pathological features of glioma, ependymoma, meningioma, acoustic neuroma and pituitary adenoma.
6. Describe the effects of metastatic carcinoma to the vertebrae and spinal cord, with emphasis on the syndrome of spinal cord compression.
7. Outline the common microorganisms that lead to meningitis and encephalitis, particularly viral, bacterial and fungal causes.
8. Outline the common causes of non-infectious meningeal irritation, e.g. subarachnoid haemorrhage.
9. Describe the anatomy of the pain sensitive structures within the cranial vault, principally the blood vessels, meninges and cranial nerves.
10. Explain the pathophysiology of the common clinical features of meningeal irritation, particularly headache, neck stiffness, photophobia, nausea and vomiting.
11. Describe the route of entry of microorganisms into the central nervous system and the variety of lesions that such microbial invasion may cause, including meningitis, encephalitis and brain abscess.
12. Summarise the factors that would predispose an individual to develop meningitis or encephalitis.
13. Describe the epidemiological features of particular types of meningitis, particularly meningococcal meningitis, fungal and viral meningitis. What treatments are recommended for bacterial meningitis?
14. Discuss the role of public health measures in preventing bacterial meningitis epidemics.
15. Describe the pathological changes that occur in the meninges during acute and chronic meningitis.
16. Discuss the laboratory diagnosis of meningitis and construct a table summarising the cerebrospinal fluid abnormalities in patients with bacterial, tuberculous, viral and fungal meningitis.
17. Outline the recommended management of suspected bacterial meningitis prior to hospitalisation and immediately following admission to hospital, including the names of any antibiotics that may be used.

### ***Trial exam questions:***

1. Discuss the common causes and potentially lethal complications of raised intracranial pressure.
2. Outline the range of clinical manifestations of a pituitary adenoma.
3. Discuss the likely causes of death in meningococcal meningitis.
4. Compare and contrast abnormalities of the cerebrospinal fluid would you expect to find in bacterial, viral and cryptococcal meningitis.

### **Case protocols associated with this topic – 20, 21**

### **Other relevant protocol – 41**

## Diabetes mellitus - complications

The aim of this topic is to review the pathophysiology, treatment and long-term consequences of diabetes mellitus.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Define the term “diabetes mellitus”, and indicate the common investigations used in the diagnosis and monitoring of this condition.
2. Distinguish between type1, type 2 and gestational diabetes on epidemiological and clinical grounds.
3. Describe the role of insulin in carbohydrate and lipid metabolism. What broad categories of insulins are available?
4. Describe the pathogenesis of the common forms of diabetes mellitus, and outline the major risk factors for their development.
5. Describe the biochemical basis of the major metabolic disturbances in diabetes, including ketoacidosis and hyperglycaemic coma, and the likely metabolic consequences of these conditions.
6. Describe the macrovascular and microvascular complications of diabetes, with emphasis on diabetic retinopathy and nephropathy. What pharmacotherapy is indicated to slow down the progression of these complications, and why?
7. Discuss the factors that may result in the development of a foot ulcer in an individual with diabetes mellitus.
8. List the microorganisms most commonly associated with foot ulcers in a diabetic patient and outline the treatment strategy that you would recommend.
9. Discuss the nature and pathogenesis of neurological lesions seen in long-standing diabetes mellitus.
10. List the pharmacotherapies that are available for type 1 and type 2 diabetes and discuss their appropriate application.
11. Explain the importance of ongoing monitoring of blood glucose levels in diabetes.

### ***Trial exam questions:***

1. What are “advanced glycosylation end-products”? What is their relationship to the long-term complications of diabetes mellitus?
2. Discuss the pathophysiology and complications of diabetic ketoacidosis.
3. Discuss why combination therapy may be useful in the management of type 2 diabetes.

### ***Case protocol associated with this topic – 31***

## Dysphagia and haematemesis

The aim of this topic is to review the pathophysiology and treatment of dysphagia, with emphasis on reflux oesophagitis and oesophageal carcinoma, as well as to review the pathophysiology and treatment of conditions causing acute and chronic upper gastrointestinal bleeding.

### Learning objectives

At the completion of this topic you should be able to:

1. Describe the normal anatomy of the oesophagus and neuromuscular function during swallowing.
2. Distinguish between dysphagia and odynophagia (pain on swallowing).
3. List mechanical causes of dysphagia, including inflammatory conditions, other non-neoplastic strictures and malignancies.
4. Describe neuromuscular causes of dysphagia, emphasising achalasia, diffuse oesophageal spasm and scleroderma.
5. Discuss the pathogenesis and clinical features of reflux oesophagitis and its complications. In particular, describe the histological features of Barrett's oesophagus. What pharmacological options are available to treat reflux oesophagitis? What are the merits of these treatments?
6. Describe predisposing factors and clinical features of malignant neoplasms of the oesophagus, with an emphasis on squamous cell carcinoma and adenocarcinoma.
7. Outline the role of endoscopy and functional studies such as manometry in the investigation of oesophageal disease.
8. Describe the normal mucosal protective mechanisms in the gastrointestinal tract.
9. Describe the clinical features which suggest the site and severity of gastrointestinal bleeding.
10. Discuss the pathogenesis of important causes of acute upper gastrointestinal haemorrhage, including erosive gastritis, ruptured gastro-oesophageal varices, Mallory-Weiss tears and peptic ulcers. Recognise that any of the listed conditions may be the cause of haematemesis in a chronic alcoholic. How important is drug-induced upper GI bleeding?
11. Explain the aetiological role of *Helicobacter pylori* in gastritis, peptic ulceration and gastric carcinoma, as well as the pharmacological options for eradication of *H. pylori*.
12. Outline the complications of chronic peptic ulcers.
13. List factors predisposing to the development of gastric carcinoma.
14. Describe the clinical presentation and mode of spread of gastric carcinoma.
15. Discuss the advantages of endoscopy in the management of upper gastrointestinal haemorrhage.

### Trial exam questions:

1. Discuss the proposed roles for the known aetiological factors in oesophageal carcinoma.
2. Write brief notes on the pathogenesis and complications of Barrett's oesophagus.
3. List the common causes of haematemesis. What abnormalities might you find at autopsy following death due to massive blood loss?
4. Outline the factors that may predispose to peptic ulceration, and discuss the proposed pathogenetic mechanisms.

### Case protocols associated with this topic – 13, 16

## Endocrine disease

The aim of this topic is to review the pathological basis of endocrine disease. In particular, the pathophysiology and management of diseases affecting the thyroid gland will be emphasised.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Present a differential diagnosis of a lump in the neck, based on its location and other clinical features of the lesion and the individual.
2. Describe the physiological control of thyroid hormone secretion.
3. List the common causes, clinical effects and likely findings on investigation of both hyper- and hypofunction of the thyroid gland.
4. How would you monitor a patient with hypothyroidism on replacement thyroxine therapy?
5. Compare and contrast the pathophysiology of Graves' disease and Hashimoto's thyroiditis.
6. Discuss the mechanisms of action of drugs used to treat Graves' disease
7. List the common causes of a clinically apparent single thyroid nodule, and distinguish between them on the basis of history, examination and results of investigations.
8. Discuss the pathophysiological basis of hyperpituitarism and hypopituitarism.

### ***Trial exam questions:***

1. Discuss the cardiovascular manifestations caused by abnormalities of thyroid function.
2. Outline an appropriate sequence of investigations to determine the cause of a single thyroid nodule.

### ***Case protocol associated with this topic – 25***



## Gallbladder and pancreatic disease

The aim of this topic is to consider the causes and consequences of gallstone formation, and of inflammation of the pancreas.

### ***Learning objectives***

At the completion of this topic you should be able to:

1. Describe the anatomy of the biliary tree, the composition of bile and the factors that maintain cholesterol in solution.
2. Discuss factors predisposing to the formation of cholesterol and bile pigment stones.
3. Outline the pathogenesis, clinical features and complications of disease caused by gallstones within the gall bladder and cystic duct, specifically biliary colic, acute cholecystitis and chronic cholecystitis.
4. Describe the clinical consequences of gallstones within the extrahepatic bile ducts.
5. List other conditions causing bile duct obstruction.
6. Describe the normal exocrine function of the pancreas and its hormonal regulation.
7. Describe the factors predisposing to acute pancreatitis.
8. Outline the clinical features and complications of acute pancreatitis, and the biochemical parameters that indicate a poor prognosis.
9. Describe the pathogenesis, clinical presentation and metabolic consequences of chronic pancreatitis.
10. Discuss the clinical features and complications of pancreatic neoplasms.
11. Discuss the role of imaging techniques in the management of biliary and pancreatic disease.

### ***Trial exam questions:***

1. Outline the acute and chronic complications of cholelithiasis.
2. Discuss the causes and complications of acute pancreatitis.

### ***Case protocols associated with this topic – 15, 43***

## Glomerulonephritis and renal failure

The aim of this topic is to elucidate the pathophysiology of the nephrotic and nephritic syndromes and to review the common causes and pathophysiology of proteinuria, as well as acute and chronic renal failure.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the normal anatomy and physiology of the kidney.
2. Define the terms “oliguria”, “nephritic syndrome”, “nephrotic syndrome”, “acute kidney injury” (acute renal failure) and “chronic kidney disease” (chronic renal failure).
3. Describe the relationship between serum creatinine and glomerular filtration rate.
4. Summarise the common causes of acute and chronic renal disease in Australia.
5. Explain the pathophysiological basis of the features of the nephritic syndrome.
6. For a patient with the nephritic syndrome, outline an appropriate sequence of investigations to determine the underlying lesion.
7. Discuss the common forms of proliferative glomerulonephritis according to pathological features and aetiology.
8. Outline an appropriate diagnostic approach to an individual with acute kidney injury.
9. Describe the common causes and investigation of proteinuria found on urinalysis, and contrast tubular and glomerular forms of proteinuria.
10. List the common causes of the nephrotic syndrome in children, adolescents and adults.
11. List the recognised aetiological agents in membranous glomerulonephritis.
12. Explain the pathogenesis of the main complications of the nephrotic syndrome.
13. Outline the pathophysiology of glomerulonephritis in terms of underlying mechanisms of immunological injury.
14. Discuss the indications for renal biopsy, investigations that should be undertaken prior to the procedure, the complications, and the methods by which the pathologist assesses the biopsy.
15. Describe differences in the pathophysiology of renal impairment due to glomerular and tubulointerstitial processes, and the ways that these differences may manifest clinically.
16. Describe the pathophysiological basis of metabolic acidosis, anaemia, secondary and tertiary hyperparathyroidism, as seen in chronic kidney disease.
17. Summarise the factors that may lead to a deterioration of renal function in patients with stable, chronic kidney disease.

### ***Trial exam questions:***

1. What is “acute renal failure”, and what are the common underlying lesions?
2. Explain the pathogenesis of post-streptococcal acute proliferative glomerulonephritis.
3. What is the “nephrotic syndrome”, and which are the common underlying lesions?
4. Outline an appropriate sequence of investigations to determine the cause of proteinuria.

### ***Case protocols associated with this topic – 18, 27, 32***

## Gynaecological malignancies

The aim of this topic is to elucidate the pathology and clinical features of common gynaecological malignancies, including cancers of the ovary, uterine corpus and cervix.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Review the gross and microscopic anatomy of the female genital tract relevant to the development, clinical features and spread of gynaecological malignancies.
2. Describe the types of primary and secondary ovarian malignancies, including details of histogenesis, clinical features and prognosis of the most common types.
3. List the causes of post-menopausal bleeding per vagina. In particular, describe the predisposing factors, clinical features and prognosis of endometrial carcinoma.
4. Discuss the pathogenesis and prevention of cervical carcinoma, including screening for precancerous lesions of cervical cancer.

### ***Trial exam questions:***

1. Which are the common lesions that cause post-menopausal bleeding per vagina, and what are the appropriate investigations to determine the cause?
2. What methods are available to screen for ovarian malignancy, and how effective are these methods in detecting the disease at an early stage?
3. How does the new National Cervical Screening Program differ from conventional Pap smears? Does vaccination against HPV eliminate the need for screening?

### ***Case protocols associated with this topic – 1, 2***

## Haematuria

The aim of this topic is to review the causes and pathophysiology of haematuria.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe methods for the detection of blood in urine, and describe ways in which the appearance of red cells may differ in relation to the origin of bleeding within the urinary tract.
2. List the causes of haematuria in terms of pre-renal, renal and post-renal causes of blood loss.
3. Describe red blood cell casts and list the common causes.
4. Compare and contrast the pathological and clinical features of renal cell carcinoma and transitional cell carcinoma.
5. Describe the causes and pathophysiology of renal colic.
6. Outline the possible causes of haematuria in a person who in the past has chronically ingested compound analgesics.
7. Summarise the investigation of a patient with persistent haematuria.

### ***Trial exam questions:***

1. List the common causes of haematuria due to pre-renal, renal and post-renal disorders.
2. Outline the clinical features and complications of renal cell carcinoma.

### ***Case protocol associated with this topic – 17***

### ***Other relevant protocol – 37***



## Hepatitis and chronic liver disease

The aim of this topic is to review the common causes of hepatic injury and the metabolic consequences of such disease.

### **Learning objectives:**

At completion of this topic you should be able to:

1. Describe the metabolism of haem and excretion of its breakdown products.
2. Outline the metabolic consequence of hepatic failure.
3. Describe the clinical features of viral hepatitis. Compare and contrast disease caused by the hepatotropic viruses HAV, HBV, HCV, HDV and HEV.
4. Discuss the pathogenesis, clinical features and sequelae of chronic hepatitis, both viral-associated and autoimmune.
5. How does cirrhosis affect the pharmacokinetics of drugs? Use oral morphine and oral diazepam as examples.
6. Outline the spectrum of liver disease associated with alcohol abuse.
7. What pharmacological treatments are available to assist patients to cease abusing alcohol? How do those drugs work, and how effective are they?
8. List factors predisposing to the development of cirrhosis of the liver.
9. Discuss the pathogenesis of the clinical features and complications of cirrhosis.
10. Describe the metabolic consequences of obstruction to the biliary tree.
11. Discuss the common tests used to evaluate hepatic function and the pathophysiological basis of abnormalities detected by these tests.
12. Recognise the usual pattern of liver function test abnormalities observed in hepatitis, hepatic infiltration, biliary obstruction and hepatic failure.

### **Trial exam questions:**

1. Discuss the pathophysiology of four potentially lethal complications of cirrhosis.
2. Describe the epidemiology and clinical consequences of Hepatitis B infection.

### **Case protocol associated with this topic – 22**

### **Other relevant protocol – 36**

## Inflammatory bowel disease

The aim of this topic is to review the nature, consequences and common causes of diarrhoea.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the epidemiology, morbidity and mortality associated with diarrhoea, in particular travellers' diarrhoea and severe epidemic forms of diarrhoeal illness.
2. Outline the difference between secretory and non-secretory diarrhoea.
3. Describe the common causes of diarrhoea and their clinical manifestations.
4. Outline the pathophysiology of cholera. In particular, discuss the mechanisms whereby the exotoxin leads to the development of secretory diarrhoea. The clinical consequences of such illness should be appreciated.
5. Describe the pathogenesis of *Salmonella typhi* infection. In particular, the stages of this disease should be appreciated and the fact that this is more a systemic disease than a gastrointestinal illness.
6. List the common causes of inflammatory bowel disease. In particular, Crohn's disease and ulcerative colitis should be reviewed and the pathophysiology and clinical features of these diseases appreciated.
7. What pharmacological therapies are used for Crohn's disease and ulcerative colitis? What are their mechanisms of action? What role do TNF inhibitors play in the management of these conditions?
8. Describe the common microorganisms that may cause colitis.
9. Outline the pathophysiology of *Clostridium difficile*-induced "pseudomembranous colitis".
10. Indicate the appropriate investigations for patients with suspected microbial diarrhoea.
11. Outline the common metabolic consequences of severe, prolonged diarrhoeal illness.
12. The pathophysiology of irritable bowel syndrome should be addressed

### ***Trial exam questions:***

1. Compare and contrast Crohn's disease and ulcerative colitis with regard to macroscopic pathology and complications.
2. Outline an appropriate sequence of investigations to determine the cause of bloody diarrhoea.

### ***Case protocol associated with this topic – 12***



## Leukaemia and myeloproliferative disease

The aim of this topic is to review the common types of leukaemia and myeloproliferative disorders, and their clinical features.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the different types of leucocytes and their respective functions.
2. Outline the ontogeny of different types of leucocytes. Describe the role of cytokines and growth factors in the development of white blood cells and in their specific differentiation into end stage cells.
3. Outline the causes and consequences of leucopenia. In particular, the causes and consequences of lymphopenia and neutropenia should be understood.
4. Discuss the classification of leukaemia and the rationale for this classification.
5. Describe the major clinical and pathological differences between acute and chronic leukaemia.
6. Describe the clinical and laboratory features of the common types of leukaemia, including acute myeloid, acute lymphoid, chronic myeloid and chronic lymphoid forms.
7. Outline the factors, both genetic and acquired, that predispose to leukaemia.
8. Discuss the pathogenesis and clinical features of myeloproliferative disorders other than CML, including polycythaemia vera, myelofibrosis and primary thrombocythaemia.
9. Describe the complications that may result from bone marrow failure and pancytopenia.
10. Describe the investigation of a patient with suspected leukaemia.

### ***Trial exam questions:***

1. Compare and contrast the pathophysiology of the acute and chronic leukaemias.
2. Write brief notes on the causes of pancytopenia.

### ***Case protocols associated with this topic – 29, 42***

## Lymphoma

The aim of this topic is to gain familiarity with the common neoplasms involving the lymphoid system and to correlate the clinical features of these diseases with the underlying pathology.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. Describe the normal anatomy of the lymphoid system, lymph nodes, spleen and thymus.
2. Outline the ontogeny of T and B cells, and the laboratory methods used to recognise them.
3. Describe the common causes of lymphadenopathy, and discuss clinical features that may provide information regarding the likely aetiology.
4. Describe the major differences between Hodgkin and non-Hodgkin lymphoma.
5. Outline the common classifications of Hodgkin and non-Hodgkin lymphomas.
6. Describe the staging of lymphomas, and the investigations required to determine the extent of organ involvement.
7. Describe a typical suite of medicines used to treat lymphoma and contrast their mechanisms of action.
8. Discuss the aetiological factors involved in the pathogenesis of lymphomas.
9. Indicate the appropriate investigation of a patient with lymphadenopathy.
10. Describe the pathogenesis of the common local and systemic complications of lymphomas.
11. Discuss the recommended treatment of oral candidiasis in immunocompromised patients.

### ***Trial exam questions:***

1. Discuss the prognostic factors in Hodgkin and non-Hodgkin lymphomas.
2. Outline an appropriate sequence of investigations to determine the cause of persistent cervical lymphadenopathy.

### ***Case protocol associated with this topic – 23***



## Multisystem disease and polyarthritis

The aim of this topic is to review the pathophysiology and treatment of the systemic autoimmune diseases, with particular reference to systemic lupus erythematosus. The pathophysiology and clinical features of common causes of polyarthritis will also be reviewed.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. List the systemic autoimmune diseases and their common systemic manifestations.
2. Classify systemic vasculitides according to the type of vessels affected.
3. Describe the immunological derangements associated with systemic lupus erythematosus and relate them to the clinical manifestations.
4. Outline the investigation of a patient with suspected systemic lupus erythematosus. What pharmacotherapies are available and what is the rationale for their use?
5. Define the term "rheumatoid factor" and list the clinical associations.
6. Describe the differing specificities of anti-nuclear antibodies and the respective clinical associations.
7. Outline the potentially fatal complications of systemic lupus erythematosus affecting the central nervous system, kidneys, lung and blood.
8. List the medications that can induce lupus erythematosus in susceptible patients.
9. Describe the different types of joints and describe the normal anatomy of a di-arthrodial joint
10. Classify polyarthritis based on the major disease processes.
11. Describe the pathophysiology of rheumatoid arthritis.
12. Outline the histopathological changes that occur within the joint in rheumatoid synovitis. Contrast the pharmacological actions of methotrexate and leflunomide.
13. Describe the extra-articular manifestations of rheumatoid arthritis.
14. Discuss the pathophysiology of seronegative arthropathies - ankylosing spondylitis, Reiter's syndrome, reactive arthritis, psoriatic arthritis.
15. Describe the changes found in the synovial fluid in the different types of arthropathies.
16. Outline the role of genetic factors in the pathogenesis of rheumatoid arthritis and the seronegative arthropathies.

### ***Trial exam questions:***

1. Discuss the following statement: "Systemic lupus erythematosus is a prime example of disease mediated exclusively by type III hypersensitivity."
2. Describe the clinical manifestations and complications of scleroderma.
3. Discuss the following statement: "The clinical effects of rheumatoid arthritis are due to a combination of type III and type IV hypersensitivity."

### ***Case protocols associated with this topic – 24, 30***

## Opportunistic infections and AIDS

The aim of this topic is to review common acquired immunodeficiency states and their associated opportunistic infections, with particular emphasis on AIDS.

### ***Learning objectives***

At the completion of this topic you should be able to:

1. List the common causes of acquired immunodeficiencies in approximate order of frequency.
2. Describe the types of opportunistic infections in patients with the following acquired immunodeficiency states: acquired neutropenia, malnutrition, leukaemia/lymphoproliferative disorders and high dose corticosteroid therapy.
3. Explain why patients with immunodeficiency are at increased risk of developing infections, neoplasms, allergies and autoimmune disease.
4. List groups at risk of developing HIV/AIDS as well as modes of transmission of HIV.
5. What are the common drug interactions between anti-retroviral drugs?
6. Outline the stages in the natural history of HIV infection and the clinical and laboratory features of each stage.
7. List the major opportunistic infections seen in AIDS and HIV-associated immunodeficiency and outline the recommended antibiotic therapy for each.
8. Describe the neoplasms most commonly found in patients infected with HIV.

### ***Trial exam questions:***

1. Discuss the common causes of death in patients with HIV infection.
2. Critically evaluate the statement that "HIV is the ultimate human pathogen".
3. Outline the common causes and effects of acquired immunodeficiency syndromes other than HIV/AIDS.

### ***Case protocol associated with this topic – 26***



## Scrotal masses

The aim of this topic is to review the pathophysiology of scrotal masses, with particular emphasis upon testicular tumours.

### ***Learning objectives:***

At the completion of this topic you should be able to:

1. List the common causes of scrotal masses, and where possible distinguish between these causes on clinical grounds.
2. Discuss the pathophysiology of disorders of the tunica vaginalis, undescended testis, indirect inguinal hernia, hydrocoele, haematocoele and spermatocoele.
3. Explain the pathogenesis and consequences of torsion of the testis.
4. Distinguish between the causes of acute and chronic epididymo-orchitis and relate these causes to the clinical manifestations.
5. List the factors that predispose to testicular neoplasms.
6. Compare and contrast the epidemiology, morphology, biological behaviour and prognosis of seminomas and non-seminomatous germ cell tumours of the testis.
7. Discuss the role of biochemical tumour markers in the diagnosis and management of testicular tumours.

### ***Trial exam questions:***

1. Write brief notes on testicular seminoma. In particular, indicate the predisposing factors and usual biological behaviour.
2. Discuss the utility of tumour markers in the diagnosis and management of testicular tumours.

### ***Case protocol associated with this topic – 33***

## Clinicopathological case protocols

The case protocols listed on the following pages are for use by students, either as part of a structured hospital-based teaching session or for independent study. Teaching sessions in which these protocols may be used have been indicated previously in the section of this Manual dealing with specific learning objectives for each topic.

## Examples of protocol answers

As a guide to the scope and depth of answer expected in the case protocols, some typical answers have been provided below for a case protocol relating to skin cancer. Use these answers as a guide in your approach to the other case protocols.

### Case protocol A (Pigmented lesion on the hand)

#### **Case History**

A 58-year-old farmer consulted his general practitioner because of a persistent skin lesion on his back. The lesion had been present for three months, was not itchy, but had bled on several occasions after minor trauma, and had increased in size over the last two weeks.

Examination revealed a fair skinned man with numerous scaly lesions on the back of both hands. There was an elevated and pigmented lesion in the middle of his back, 1.5 cm in diameter. The contour and margins of the lesion were irregular.

#### **Questions**

1. State your diagnosis and differential diagnosis.
2. What further information would you attempt to elicit from the history and physical examination?
3. If the patient had evidence of axillary lymphadenopathy how would this affect your differential diagnosis?
4. How would you substantiate your diagnosis?
5. A histopathological diagnosis of malignant melanoma was made. What histological features would have led to this diagnosis?
6. What is known of the aetiology of this disease?
7. What is the probable nature of the scaly lesions also present on this man's hands?
8. Name the main types of skin lesions that may be aetiologically related to chronic excessive solar exposure.
9. Indicate the main factors that determine the prognosis in patients with this disease.
10. Outline the more common modes of disease progression.

#### **Suggested answers**

1. The most important lesion to consider is melanoma, though there are a variety of other diagnostic possibilities, including squamous cell carcinoma, basal cell carcinoma, naevi, kerato-acanthoma, pyogenic granuloma and seborrhoeic keratoses.
2. Points to be considered in the history include factors associated with the development of skin tumours, such as solar and chemical exposure, previous history of skin malignancies, family history of such lesions and history of immunosuppression. It would be necessary to determine whether there was a pre-existing lesion at this site or elsewhere, and whether there had been a recent increase in the size of the lesion, or the development of satellite lesions. A thorough search for evidence of spread should be made, both by relevant questioning and by examination of the draining nodes and other organ systems.
3. The presence of axillary lymphadenopathy would make a diagnosis of melanoma more likely and would exclude most of the differential diagnoses outlined above, with the exception of squamous cell carcinoma. The possibility of lymphadenitis secondary to ulceration of the lesion should be considered.
4. Where there is a clinical suspicion of melanoma, the diagnosis should be established by complete excision of the lesion.

5. The lesion would be expected to show nests and clumps of melanocytes invading the superficial epidermis and extending down into the dermis. The melanocytes would show features of abnormal differentiation (high nucleus:cytoplasm ratio, angulated nuclei, prominent nucleoli). Histopathological sections through the lesion should be carefully examined to ensure that the lesion has been completely excised and that there is no evidence of lymphatic or vascular invasion.
6. The main aetiological factor is sunlight exposure, particularly intense exposure during childhood. There is an increased risk in patients with the autosomal dominantly inherited dysplastic naevus syndrome.
7. The lesions are likely to be solar (actinic) keratoses.
8. Basal cell carcinoma, squamous cell carcinoma, melanoma, solar elastosis, solar keratosis.
9. The major factor affecting the prognosis is the depth of invasion of the lesion. Lesions with a depth less than 0.75 mm are unlikely to metastasise. Lesions that have invaded more than 1.5 mm below the stratum granulosum of the epidermis are much more likely to metastasise. Males tend to have a worse outcome than females, perhaps due to later detection. Nodular and acral lentiginous melanomas have worse prognoses than lentigo maligna melanomas (Hutchinson melanotic freckle). Dermal lymphocytic infiltration in the primary tumour is a favourable prognostic indicator, while a high mitotic rate correlates with a worse outcome. The presence of vascular and/or lymphatic invasion is also important to ascertain, as is the completeness of the surgical excision.
10. The lesion arises from the melanocytes at the dermo-epidermal junction, and migration of the malignant cells occurs both down into the dermis, and throughout the epidermis. Spread along the epidermis is common in the superficial spreading form of this disease, and is known as the "radial growth phase". The commencement of vertical growth phase into the dermis indicates a heightened ability of the malignant cells to invade tissue, and it is at this stage that metastatic spread is likely to occur. This may occur via the lymphatics, resulting in enlargement of the regional lymph nodes, or it may occur through invasion of dermal blood vessels, causing widespread haematogenous dissemination. The lungs, brain and liver are favoured sites, though malignant cells may spread to most areas of the body.

## Case Protocol 1

### Case History

A 52-year-old woman was noted to have a large mass in the right fornix during a routine pelvic examination. She had been in good health and specific questioning regarding vaginal bleeding or abdominal symptoms was negative. There had been no change in her bowel habit and no weight loss or anorexia. The involuted uterus was anteverted, and the cervix was mobile.

### Questions

- What are the possible lesions that may result in a mass in the right fornix?



- An ultrasound examination of the pelvis demonstrated a cystic ovarian mass. What abnormalities may cause such an appearance?



- What further investigations would you consider appropriate?



4. At operation, fleshy nodules were spread widely throughout the peritoneal cavity. What may have caused such an appearance?



*A histopathological section of the tissue obtained at operation was reported as showing serous adenocarcinoma of the ovary.*

5. What types of ovarian malignancies can occur, and what factors predispose to the development of this disease?



*Following her diagnosis, the woman was commenced on chemotherapy.*

6. Which drugs are most effective in chemotherapy for ovarian cancer, and what are their mechanisms of action?



7. The woman remained well for some six months after her initial operation, but then developed recurrent episodes of abdominal pain, vomiting and constipation. What complication of this disease has occurred, and how would you confirm the diagnosis?



8. What other complications of this disease may occur?



9. The woman succumbed to her disease three months later. What was the likely mode of death?



## Case Protocol 2

### Case History

An obese 56-year-old woman with long-standing type 2 diabetes presented to her gynaecologist with bleeding per vagina, which alarmed her because she had been menopausal for six years. During that time, she had regular Pap smear screening, which had never shown any abnormalities. She had taken hormone replacement therapy (HRT) for several years but had ceased three years ago. There were no other symptoms, and no abnormalities were detected on physical examination. Specifically, the involuted uterus was of normal size, and the cervix was mobile.

### Questions

1. What is the definition of post-menopausal bleeding per vagina, and what are the likely causes in this woman? What risk factors does this woman have for endometrial carcinoma, and which other risk factors should you enquire about?



2. A transvaginal ultrasound examination demonstrated that the uterine endometrium was greater than 5 mm in thickness. What is the significance of this finding?



3. What further investigations would you consider appropriate? Can a cervical screening test (using liquid-based cytology) detect endometrial carcinoma?



4. A histopathological section of tissue obtained by endometrial biopsy was reported as showing a well-differentiated endometrial adenocarcinoma. What factors are likely to influence this woman's prognosis?



*A total abdominal hysterectomy, bilateral salpingo-oophorectomy, peritoneal cytology, and pelvic and para-aortic lymphadenectomy were performed. Histopathological and cytological assessment determined that the endometrial adenocarcinoma was confined to the wall of the uterine corpus (stage 1B).*

5. How might the cancer have progressed if not detected and treated at an early stage?



## Case protocol 3

### Case history

A 52-year-old woman suddenly developed breathlessness seven days after laparoscopic cholecystectomy. The patient, who was previously otherwise well, had a strong family history of ischaemic heart disease and smoked 20 cigarettes per day. Examination revealed an obese, distressed woman with obvious tachypnoea and a non-productive cough. Auscultation of her chest revealed decreased air entry at the right base.

### Questions

- What is your provisional diagnosis, and what is the differential diagnosis of acute respiratory distress in this woman?



- What factors predisposed her to this disease?



### Vital Signs

Heart Rate (b/min)	122
Blood Pressure (mm Hg)	100/60
Respiratory Rate (/min)	30
Temperature (°C)	37.8
Urinalysis	pH 6.5, Prot -ve, Blood -ve

3. What investigations would you perform to substantiate your diagnosis? Describe the ECG changes likely to be present in this case and explain why they occur.



A chest X-ray showed an area of opacification at the right base, together with a small right pleural effusion.

4. What pathological process may have produced this appearance?



5. Arterial blood gas analysis on room air is shown below. How would you interpret these results, and are they compatible with your diagnosis?



#### Arterial Blood Gases

pH	7.50	7.35-7.45
PaO <sub>2</sub> (mm Hg)	61	80-100
PaCO <sub>2</sub> (mm Hg)	30	35-45
Bicarbonate (mmol/L)	26	24-32
O <sub>2</sub> Saturation (%)	90	95-105
Base Excess	-1	-3<BE<3

6. What drug therapy would you think most likely is needed? What are the principles of establishing therapy with this drug? How would you monitor this therapy?



The patient was sent for a CT pulmonary angiogram, but during transport she developed central chest pain, increasing dyspnoea and cyanosis. Her blood pressure fell to 70/40 mm Hg and the JVP was elevated 7 cm. Despite attempted resuscitation, the patient died in the Intensive Care Unit four hours later.

7. Outline the sequence of events that occurred in this woman from the time of presentation until death, and suggest the likely cause of death.



8. Is a post-mortem examination mandatory in this case, and if so, why?



9. Outline the major pathological findings you would expect at autopsy.



10. If the patient had survived, what long-term complications might she have developed?



## Case protocol 4

### Case History

A 66-year-old woman was brought by ambulance to the Emergency Department in extremis. She had obvious upper airway obstruction, with tachypnoea, inspiratory and expiratory stridor, and bilateral rhonchi. She was tachycardic, hypotensive, pale, drowsy and incoherent. Her face, eyes and tongue were swollen and her skin showed widespread urticaria.

The patient was intubated and ventilated, treated with adrenaline, intravenous fluids, glucocorticoids and antihistamine. She was then admitted to the intensive care unit. Results of initial investigations are outlined below.

Vital Signs		Arterial Blood Gases	
Heart Rate (b/min)	140 regular	pH	7.24      7.35-7.45
Blood Pressure (mm Hg)	60/-	PaO <sub>2</sub> (mm Hg)	52      95-100
Respiratory Rate (/min)	30	PaCO <sub>2</sub> (mm Hg)	50      35-45
Temperature (°C)	36.8	Bicarbonate (mmol/L)	18      24-32
Urinalysis	pH 5.0, NAD	Base Excess	-6      -3<BE<3
		O <sub>2</sub> Saturation (%)	78      95-100

### Questions

Clinical Chemistry		
Sodium (mmol/L)	136	135-145
Potassium (mmol/L)	3.9	3.5-5.0
Chloride (mmol/L)	106	95-107
Bicarbonate (mmol/L)	18	24-32
Urea (mmol/L)	5.8	3.0-8.0
Creatinine (μmol/L)	90	60-110

1. What is your clinical diagnosis? What is the appropriate emergency management of this situation?



2. What further information is required to substantiate your diagnosis?



3. Why were adrenaline, glucocorticoids and antihistamine administered? Comment on their mechanisms of action.



**The patient's husband reported that his wife woke from sleep complaining of a swollen tongue and breathlessness. She had no past history of allergy and she was well apart from acute bronchitis, for which she had recently been commenced on amoxicillin.**

4. What is the likely cause of this woman's reaction? Outline the immunological reactions involved in the pathogenesis of this disease.



5. Explain the pathological basis of the clinical features seen in this case.



6. Explain the results of the investigations based on your understanding of the underlying pathophysiology.



7. What are the common allergic and non-allergic causes of this syndrome?



8. What laboratory investigations may be helpful in the determination of:

- the specific trigger of this patient's signs and symptoms?
- whether anaphylaxis is the cause of shock in this case?



9. What is meant by the term "shock", and what may cause it?





10. Explain the major features of the shock syndrome in terms of the underlying pathophysiology.



11. What are the main organs affected by shock, and are these changes always reversible?



12. Bacterial sepsis can also lead to shock. Outline the bacterial factors that play an important role in the aetiology of septic shock.



13. What microbiological specimens would you collect in a case of suspected septic shock of unknown source?



14. What empirical therapy would you recommend in a patient with suspected septic shock where there is no obvious source of infection?



## Case protocol 5

### Case History

An 81-year-old woman was brought to the Emergency Department after a fall while shopping. She had severe pain in her left hip and was unable to stand. Her left leg was shortened and externally rotated. Radiological examination confirmed the clinical diagnosis of a fractured neck of the femur, and appropriate orthopaedic management was instituted.

Two days after admission to the hospital, she developed a low-grade fever ( $38.2^{\circ}\text{C}$ ) and at this stage examination of the chest revealed bilateral basal crackles and occasional coarse wheezes. A day later she developed a cough productive of mucopurulent sputum and her temperature rose to  $39.4^{\circ}\text{C}$ . Appropriate investigations were ordered and presumptive treatment commenced. However, at 1.00 am the following morning she became acutely dyspnoeic, collapsed and could not be resuscitated. An autopsy was performed.

### Questions

1. What disease(s) is/are most likely to predispose to a fracture of the neck of the femur in a woman of this age?



2. What is the most common cause of fracture in this age group, and what radiological findings do you associate with this disease?



3. What other diseases would predispose to a fracture of the femur? What additional investigations would assist in the differential diagnosis?



4. What is known of the pathogenesis of osteoporosis? Could it possibly have been prevented by hormone replacement therapy (HRT), and what are the risks and benefits of HRT?



5. What other medications are available to treat osteoporosis and what is their mechanism of action?



6. Outline the biochemical abnormalities you would expect to find in this patient's serum and urine, and contrast these with those found in patients with osteomalacia, Paget's disease and renal osteodystrophy.



	Osteoporosis	Osteomalacia	Paget's disease	Renal Osteodystrophy
Calcium				
Phosphate				
Serum alkaline phosphatase				
Urinary hydroxyproline				
PTH				
Vitamin D				

7. What would a biopsy of osteoporosis reveal?



8. What other diseases may result secondarily in osteoporosis?



9. How do you explain the patient's pulmonary manifestations? What would the appropriate investigations have been?



10. Was the autopsy obligatory? What is the likely cause of death in this case?



## Case protocol 6

### Case History

A 13-year-old boy complained of pain and swelling above his left knee for the preceding three weeks. He remembered injuring the leg whilst playing football and had not paid much attention to the pain until it seemed to be getting worse. He had also noticed a persistent cough for the past week.

Examination revealed a hard swelling above the left knee. The remainder of the examination was normal.

### Questions

- What further information would you seek from the history and physical examination?



- What do you think is the most likely diagnosis? What else could cause pain and swelling of the leg?



- How could you explain this boy's cough based on your presumptive diagnosis?



4. What investigations would you order?



An X-ray of the boy's left femur revealed a region of elevated metaphyseal periosteum with underlying speckles of calcification and interruption of the cortical bone.

5. What further investigations would you perform to determine whether this lesion might be neoplastic? What other investigations would be relevant to the management of this patient?



6. Describe the histopathological appearance you would expect to find in a biopsy of the lesion.



7. A full blood count is shown below. What are the likely causes of this boy's neutrophil leucocytosis and raised CRP?



<b>Full Blood Count</b>			
Haemoglobin (g/L)	128	130-180	
Haematocrit (%)	39	40-54	
RCC ( $\times 10^{12}/L$ )	4.5	4.5-6.5	
MCV (fL)	84	80-100	
MCH (pg)	28	27-32	
MCHC (g/L)	305	300-350	
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>11.5</b>	<b>4-11</b>	
Neutrophils	9.2	2.5-7.5	
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>332</b>	<b>150-400</b>	
<b>Clinical Chemistry</b>			
CRP (mg/L)	63	< 5	

8. What is the natural history of this disease?



9. What is known about the pathogenesis of this disease?



## Case protocol 7

### Case History

A 36-year-old woman presented to her local doctor after noticing a lump in her breast. Her sister had recently had a benign breast lump removed. Examination revealed a 1 cm mass in the lower outer quadrant of the right breast. The lesion was firm and non-tender, without attachment to deeper structures. There was no axillary lymphadenopathy.

### Questions

1. State your provisional and differential diagnoses.



2. What features in the history and examination would arouse suspicion of carcinoma?



3. What is meant by "triple assessment"? What type of imaging is relevant in this case?



***A tissue sampling procedure was performed and reported as being consistent with adenocarcinoma of the breast.***

4. Compare and contrast fine-needle aspiration biopsy (FNA) and core biopsy. What types of information can be obtained by those methods?



5. What are the main histological types of breast carcinoma? Why is this classification important?



**The biopsy confirmed invasive ductal carcinoma which was ER/PR positive and HER2 negative. There were no lymph nodes detected on imaging. The patient elected to undertake breast conserving surgery rather than mastectomy.**

6. What is breast conserving surgery? What is the Van Nuys Prognostic indicator for DCIS?



7. What is the lymphatic drainage of different parts of the breast? What are the anatomical locations of the groups of axillary lymph nodes that are palpable during physical examination? How is the concept of "sentinel lymph node" useful in the management of breast neoplasm?



**Three axillary lymph nodes removed at operation revealed evidence of metastatic carcinoma. At a follow-up visit, the patient complained of swelling of her right arm.**

8. What are the possible causes of this swelling?



9. During post-operative outpatient visits, what clinical features would suggest recurrent disease?



10. What modalities other than surgery might be employed to treat this woman's breast cancer? What are their major side-effects?



***The patient was concerned that her daughter might be at risk of developing breast cancer, as she had been told that this disease might run in families.***

11. What information would you give her in relation to the genetic basis of breast cancer? What other factors might play a role in its pathogenesis?



## Case protocol 8

### Case History

An 18-year-old woman was brought by ambulance to the Emergency Department with uncontrolled haemorrhage following extraction of a wisdom tooth at a dentist's surgery. She had always "bruised easily" and often experienced "heavy periods", but there had been no previous operations.

On examination, she was pale and extremely anxious, with cool extremities. Vital signs were as shown opposite.

### Vital Signs

Heart Rate (b/min)	110
Blood Pressure (mm Hg)	90/60
Respiratory Rate (/min)	18
Temperature (°C)	36.2

### Questions

- What are the likely causes of her excessive bleeding?



- After instituting appropriate resuscitative measures and stabilising the patient's blood pressure, what further information would you seek from the patient?



**Direct pressure was applied to the bleeding point, and the following investigations were ordered:**

<b>Full Blood Count</b>			<b>Tests of Haemostasis</b>		
<b>Haemoglobin (g/L)</b>	<b>105</b>	<b>115-165</b>	<b>Activated Partial Thromboplastin Time (APTT) (seconds)</b>	<b>40</b>	<b>25-35</b>
Haematocrit (%)	35	37-47			
RCC ( $\times 10^{12}/L$ )	3.5	3.8-5.8			
MCV (fL)	74	80-100	<b>Prothrombin Time (seconds)</b>	<b>15</b>	<b>13-17</b>
MCH (pg)	31	27-32			
MCHC (g/L)	270	300-350	<b>Von Willebrand Factor Antigen (vWF:Ag) (% of normal)</b>	<b>15</b>	<b>40-160</b>
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>9.7</b>	<b>4-11</b>	<b>Ristocetin cofactor assay (% of normal)</b>	<b>10</b>	<b>50-200</b>
Neutrophils	6.8	2.0-7.5			
Lymphocytes	2.5	1.5-4.0			
Monocytes	0.3	0.2-0.8			
Eosinophils	0.1	0.04-0.4			
Basophils	0.0	<0.1			
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>425</b>	<b>150-400</b>			
<b>Film</b>	Microcytes	++			
	Hypochromasia	++			
	Poikilocytes	+			

3. How would you interpret the full blood count and tests of haemostasis shown above?



4. What is the likely cause of this woman's anaemia? What further investigations would you order, and what results would you expect?



***This patient has the most common inherited disorder of haemostasis - von Willebrand's disease. Her mother and maternal grandfather both had bleeding tendencies, but her father and two sisters are unaffected.***

5. Draw the family pedigree below. What is the mode of inheritance?



6. What do you think might be an effective treatment of her bleeding diathesis? How would the treatment help to minimise this woman's bleeding tendency?



7. Is this patient at risk of spontaneous bleeding into joints (haemarthroses)? Give your reasons. Which bleeding diatheses are associated with haemarthroses?



8. Consider the following results of investigations from six patients with disorders of haemostasis. Give a diagnosis or differential diagnosis for each patient.

<b>Tests of Haemostasis</b>						
Patient Number	1	2	3	4	5	6
APTT (25-35 secs)	78	45	37	52	49	28
Prothrombin Time (13-17 secs)	15	49	34	26	16	14
Platelets (150-400 x 10 <sup>9</sup> /L)	310	28	297	276	325	18

**Patient diagnoses:**



Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6

## Case protocol 9

### Case History

A 58-year-old man presented to his local GP with a two-hour history of severe chest pain. The pain had commenced while running, and was initially associated with nausea, vomiting and agitation. The patient had experienced similar, less severe chest pain while running over the previous three weeks. He had a 27-year history of type 1 diabetes mellitus.

### Vital Signs

Heart Rate (b/min)	114
Blood Pressure (mm Hg)	165/110
Respiratory Rate (/min)	22
Temperature (°C)	36.5

On examination the man was distressed, diaphoretic and mildly obese. Blood pressure was 165/105 mm Hg, pulse rate 114/min with frequent ventricular ectopic beats (VEBs) and there was an  $S_4$  heard on auscultation of the precordium. Basal crepitations were audible over both lungs.

### Questions

- What is your provisional diagnosis?



- What cardiovascular risk factors are present and what additional risk factors should be assessed?



- Outline the investigations you would perform, the costs, and the results that you would expect.



Investigations	Expected Result	Cost

The ECG was consistent with an acute anterior myocardial infarction.

4. What abnormalities would have been present on the ECG, and what is the pathological basis of these changes? What is the significance of the biochemical abnormalities shown opposite?



Clinical Chemistry			
Sodium (mmol/L)	137	135-145	
Potassium (mmol/L)	4.3	3.5-5.0	
Chloride (mmol/L)	101	95-107	
Bicarbonate (mmol/L)	28	24-32	
Urea (mmol/L)	8.9	3.0-8.0	
Creatinine (μmol/L)	140	60-110	
BSL (fasting)	12.9	3.0-6.0	
hs-Troponin T (ng/L)	112	<14	

5. Outline the likely sequence of events leading to this man's clinical presentation.



6. What are the important principles of the emergency management of this man's evolving myocardial infarction? What are the mechanisms of action of the drugs that would be administered?



7. Which arteries, and what areas of these, are likely to be diseased? Describe the sequential changes that occur in the myocardium following infarction.



8. What complications might develop in the first 48 hours after admission?



***On the 4th hospital day the patient developed severe chest pain lasting 60 minutes, requiring morphine for relief.***

9. What is the likely cause of this chest pain?



***The patient's pain persisted and examination revealed pallor and diaphoresis, blood pressure 80/40 mm Hg, heart rate 110/min with frequent ventricular ectopic beats, S3 and S4 gallop rhythm and oliguria.***

10. What is the most likely diagnosis? Explain the pathophysiological basis of this condition.



***Despite appropriate treatment the patient died on the fifth hospital day.***

11. What is the likely cause of death? Does this man require an autopsy under the Coroner's Act? Outline the pathological findings expected at autopsy.



## Case protocol 10

### Case History

An 81-year-old man was brought by ambulance to the Emergency Department with severe back pain. The pain had been intermittent for six days but had become increasingly severe in the past four hours. He had a history of myocardial infarction six years previously and a strong family history of ischaemic heart disease. He was also suffering from hypertension, hypercholesterolaemia and gout. There was no history of gastrointestinal, renal or hepato-biliary disease.

Examination revealed a distressed, pale old man with ankle oedema. There was an expansile, pulsating mass 6 cm in diameter, in the epigastrium. A systolic bruit was audible over the mass as well as over the femoral arteries. There was mild cardiomegaly, an S3 gallop rhythm and his chest was clear.

### Vital Signs

Heart Rate (b/min)	78
Blood Pressure (mm Hg)	170/105
Respiratory Rate (/min)	15
Urinalysis	pH 7.0, Prot + Blood -ve
Temperature (°C)	36.6

### Questions

- What is the most likely cause of this man's abdominal mass? How would you confirm your provisional diagnosis?



- What risk factors for the development of this disease are present in this case? What would have been appropriate pharmacological treatment options for his hypertension and hypercholesterolaemia?



3. Outline the mechanisms believed to be responsible for the development of this lesion.



4. What other diseases may be associated with this condition?



5. If the patient developed a painful, pale leg with absent peripheral pulses in that limb, what would be the most likely explanation? Describe the sequence of events resulting in this complication.



*Three hours after admission, he had an episode of severe abdominal pain that extended into the left loin and back. Within minutes, he developed significant hypotension and was greatly distressed.*

6. What had occurred to produce these symptoms and signs?



***Surgical intervention was attempted, but the patient died intra-operatively.***

7. Would a post-mortem examination be necessary prior to writing a death certificate?



## Case protocol 11

### Case History

A 62-year-old woman developed increasing dyspnoea over 5 years. She had suffered from a chronic cough for "many years", and had smoked 40 cigarettes/day. There was a past history of pneumonia 3 years previously and recurrent episodes of "bronchitis" over the past 20 years.

Examination revealed a thin woman, dyspnoeic at rest and using her accessory respiratory muscles. She was centrally cyanosed with bilateral expiratory rhonchi on auscultation. There was no evidence of clubbing of the fingers. Her cough was productive of copious mucopurulent sputum.

Vital Signs		Arterial Blood Gases	
Heart Rate (b/min)	106	pH	7.34      7.35-7.45
Blood Pressure (mm Hg)	140/70	PaO <sub>2</sub> (mm Hg)	52      80-100
Respiratory Rate (/min)	26	PaCO <sub>2</sub> (mm Hg)	50      35-45
Temperature (°C)	37.5	Bicarbonate (mmol/L)	34      24-32
		Base Excess	6      -3<BE<3
		O <sub>2</sub> Saturation (%)	80      95-100

### Questions

- What is the most likely cause of this woman's symptoms?



- How would you substantiate your provisional diagnosis? What differential diagnostic possibilities must you exclude?



*A chest x-ray showed hyperinflated lung fields with diaphragmatic flattening. There were no mass lesions or areas of consolidation.*



3. What information could be gained from examination of sputum and a full blood count?



4. Draw and label the normal components present in a part of the conducting component of the airways, such as the bronchi. How may the function of these components have been compromised in this patient?



5. What are the major microbial causes of acute bronchitis and acute exacerbations of chronic bronchitis? Outline the approach to antibiotic therapy in these two conditions.



6. Describe the macroscopic and histopathological changes that would be present in this woman's lungs. How would these morphological changes account for the patient's symptoms and investigative abnormalities?



7. What are the long-term cardiovascular effects of this lung disease?



8. Outline the pathogenesis of emphysema, emphasising the role of cigarette smoke in producing the structural changes seen in this disease.



9. The patient had a history of treatment with inhaled glucocorticosteroids, beta-2 adrenergic agonists, and anticholinergic inhaled medicines. What is the rationale for their use?



## Case protocol 12

### Case History

A 19-year-old female medical student presented to the Emergency Department with severe bloody diarrhoea. The diarrhoea had commenced three weeks earlier and had gradually worsened, so that each day she was passing 8-10 stools containing stringy mucus and blood. The diarrhoea was associated with crampy lower abdominal pain, urgency and tenesmus.

On examination, she was pale, thin, lethargic and dehydrated. There was tenderness in the left lower quadrant without guarding or rigidity, and the bowel sounds were increased. Rectal examination revealed no masses, but blood and mucus were evident on the glove.

### Vital Signs

Heart Rate (b/min)	114
Blood Pressure (mm Hg)	110/60
Respiratory Rate (/min)	20
Urinalysis	pH 6.2, Prot -ve, Blood -ve HCG -ve
Temperature (°C)	37.9

### Questions

- What is the probable diagnosis? What differential diagnoses would you consider, and what further aspects of the history and examination would be helpful?



- What investigations would you perform to support your provisional diagnosis, and what results would you expect?



3. A rectal biopsy was reported by the histopathologist as being consistent with ulcerative colitis. What histological features would have supported this diagnosis?



4. Apart from the colon, what other organs can be involved in this disease?



5. What is the mechanism of action of sulphasalazine, and what is its role in the management of this disease? What other medical therapy is available for her condition?



***On the sixth hospital day she complained of increased abdominal pain and became febrile, with a temperature of 39°C. The abdomen was now distended. Tenderness and guarding were prominent in the left lower quadrant and bowel sounds were diminished.***

6. How would you explain these clinical manifestations?



7. What is the relationship between this disease and carcinoma of the colon?



8. What other intestinal complications can occur as a result of this disease?



9. What is known regarding the aetiology and pathogenesis of inflammatory bowel disease?



## Case protocol 13

### Case History

A 35-year-old woman with a three-year history of scleroderma presented with five weeks of increasing dysphagia. This was initially for solids and dry food, but now almost any solid food or even thick soup would cause lower chest discomfort and an inability to swallow. The patient slept on three pillows with the head of the bed raised but still experienced significant reflux each night. Despite a "good" appetite she had lost 8 kg in weight over the last 2 months.

On examination the patient appeared thin with tight, thickened skin on her arms, face and upper trunk. Abdominal and rectal examination were normal.

### Vital Signs

Heart Rate (b/min)	78
Blood Pressure (mm Hg)	145/90
Respiratory Rate (/min)	23
Temperature (°C)	36.6
Urinalysis	pH 7.0, Prot -ve, Blood -ve

### Questions

- What is the likely cause of this woman's dysphagia?



- Outline the investigations you would perform, the costs, and the results that you would anticipate.



3. How would you interpret the FBC and CRP results shown below? What is the most likely cause of these abnormalities?



<b>Full Blood Count</b>			
Haemoglobin (g/L)	<b>102</b>	<b>115-165</b>	
Haematocrit (%)	36	37-47	
RCC ( $\times 10^{12}/L$ )	4.3	3.8-5.8	
MCV (fL)	110	80-100	
MCH (pg)	31	27-32	
MCHC (g/L)	305	300-350	
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>4.8</b>	<b>4-11</b>	
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>158</b>	<b>150-400</b>	
Film	Oval macrocytes ++ Target cells +		
<b>Clinical Chemistry</b>			
CRP (mg/L)	47	< 5	

***Endoscopy revealed evidence of severe reflux oesophagitis and an ulcer on the anterior aspect of the lower 3 cm of the oesophagus.***

4. What long-term complications may arise as a direct result of this disease process?



***Despite appropriate treatment for her reflux oesophagitis the patient continued to lose weight and developed diarrhoea with bulky offensive stools.***

5. What complication of scleroderma may explain this clinical situation?



6. What investigations would you perform to ascertain the cause of her diarrhoea and continued weight loss?



*Three years later the patient developed progressive dysphagia for solids. Endoscopy revealed reflux oesophagitis and a persistent ulcer in the lower oesophagus.*

7. What complication may develop as a result of this persistent ulceration?



8. What treatment would you recommend for this patient's gastro-oesophageal reflux?



## Case protocol 14

### Case History

A 65-year-old man presented to the Emergency Department with a six-hour history of interscapular pain, urinary retention and mild bilateral leg weakness. On further questioning, he revealed that he had felt unwell for six weeks and had lost 3 kg in the past month.

On examination he had a distended bladder, signs of corticospinal dysfunction in both legs, decreased sensation to the level of his rib cage and reduction in vibration sense below his iliac crest.

### Questions

1. State your diagnosis and differential diagnosis, and explain how each disease would produce the clinical features of this case.



2. What investigations would you perform to substantiate your diagnosis?



*A chest X-ray taken at the time of initial presentation showed multiple discrete sclerotic lesions in the ribs and spine. An MRI of the thoracic spine showed severe compression of the thecal sac by a mass occurring within the sixth thoracic vertebral body. A surgical procedure was performed on the second hospital day to relieve compression of the spinal cord. The patient regained urinary function and partial use of his legs. Histopathological assessment of the vertebral lesion revealed metastatic adenocarcinoma.*

3. What methods may the pathologist use to identify the primary source of the tissue in the biopsy?



4. What is the likely site of the primary tumour? Which further investigations may be helpful?



Serum Prostate Specific Antigen (PSA) was 55 U/L (reference interval 0-4). Per rectal examination revealed a craggy mass in the posterior lobe of the prostate. A diagnosis was made of carcinoma of the prostate (stage IVB, AJCC 8th ed.) Anti-androgen therapy was administered.

Three months later the man presented to his local doctor, on this occasion complaining of increasing difficulty with urination, lack of energy and malaise. Serum biochemistry is shown opposite.

Clinical Chemistry			
Sodium (mmol/L)	133	135-145	
Urea (mmol/L)	38	3.0-8.0	
Calcium (mmol/L)	2.4	2.1-2.55	
Phosphate (mmol/L)	1.9	0.7-1.5	
Potassium (mmol/L)	5.5	3.5-5.0	
Chloride (mmol/L)	93	95-107	
Bicarbonate (mmol/L)	18	24-32	
Creatinine (μmol/L)	550	60-110	

5. What problem has developed in this man and what is the most likely cause?



**An urgent abdominal ultrasound revealed a distended bladder and bilateral hydronephrosis. The diagnosis was urinary tract obstruction secondary to invasion of the base of the bladder by the prostatic carcinoma.**

6. What is the vascular pathway for the spread of prostatic carcinoma to the vertebral column? Apart from local infiltration and metastasis to bone, what other organs may be affected by this disease?



7. What are the likely causes of death for this patient?



8. Could this man's cancer have been detected at an earlier (curable) stage by population screening? Which groups would you target and what screening procedures would you use?



9. What pain management strategies would you recommend for this man?



## Case protocol 15

### Case History

A 51-year-old woman presented to the Emergency Department with an eight-hour history of severe upper abdominal pain which radiated around to her back and was associated with nausea and vomiting. On examination she was distressed by the pain, with tachycardia, fever, and tenderness in the right upper quadrant (RUQ). She had a past history of episodic epigastric pain, which on one occasion was accompanied by jaundice.

### Vital Signs

Heart Rate (b/min)	110
Blood Pressure (mmHg)	145/80
Respiratory Rate (/min)	18
Temperature (°C)	38.5
Urinalysis	pH 6.0, Prot -ve, Blood -ve

### Questions

1. What are your provisional and differential diagnoses, and what further information would you seek from the history and physical examination?



2. What is the anatomical and pathological basis of the previous episodes of abdominal pain and jaundice, and why has the pain worsened on this occasion?



3. Outline the investigations you would perform, the costs, and the results that you would expect.



Investigations	Expected Result	Cost

Urea (mmol/L)	12	3.0-8.0
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<b>Clinical Chemistry</b>		<b>Liver Function Tests</b>		
Sodium (mmol/L)	<b>140</b>	135-145	Bilirubin ( $\mu$ mol/L)	<b>25</b> 2-20
Potassium (mmol/L)	<b>3.8</b>	3.5-5.0	Alkaline Phosphatase (U/L)	<b>128</b> 38-126
Chloride (mmol/L)	<b>104</b>	95-107	Aspartate Transaminase (U/L)	<b>34</b> <45
Bicarbonate (mmol/L)	<b>23</b>	24-32	Alanine Transaminase (U/L)	<b>26</b> <45
Creatinine ( $\mu$ mol/L)	<b>60</b>	60-110	$\gamma$ -Glutamyltransferase (UL)	<b>38</b> <30
			Albumin (g/L)	<b>45</b> 33-48
			Globulin (g/L)	<b>28</b> 25-35
			Total Protein (g/L)	<b>73</b> 62-80

4. Biochemistry results are shown above. What abnormalities do they indicate?



*An upper abdominal ultrasound demonstrated the presence of gallstones in the gallbladder.*

5. Can this clinical presentation occur in the absence of such abnormalities?



6. What are the possible complications in this case?



***The patient was treated with antibiotics and analgesia, and recovered gradually over the next week. The gallbladder was removed at operation some five weeks later.***

7. Which antibiotics and analgesia would you prescribe? Why?



8. Describe the pathological changes likely to be present in the gallbladder, and discuss how they would differ from the appearance of the organ at the time of initial presentation.



***The gallstones removed at operation were given to the patient as a memento.***

9. What was their likely composition, and what other types of gallstones can occur?



10. Discuss the pathogenesis of gallstones. What conditions predispose to their development?



## Case protocol 16

### Case History

A 49-year-old male academic was admitted for investigation of vomiting and diarrhoea for the past 24 hours. In the last 3 hours he had noted that his motions had been of a black and tarry nature. He had a past history of intermittent epigastric pain. On examination the patient appeared pale and sweaty, with tenderness in the epigastrium. Rectal examination revealed black liquid faeces.

### Questions

- With which clinical syndrome did this man present, and what is your provisional diagnosis?



- How would you interpret the haematology results shown opposite?



### Vital Signs

<b>Heart Rate (b/min)</b>	120
<b>Blood Pressure (mm Hg)</b>	70/50
<b>Respiratory Rate (/min)</b>	20
<b>Temperature (°C)</b>	36.8
<b>Urinalysis</b>	pH 7.0, Prot -ve, Blood -ve

- After instituting appropriate resuscitative measures and stabilising the patient's blood pressure, what further information would you seek?



- Outline the common causes of haematemesis and melaena.



### Full Blood Count

<b>Haemoglobin (g/L)</b>	<b>123</b>	<b>130-180</b>
Haematocrit (%)	32	40-54
RCC ( $\times 10^{12}/L$ )	3.8	4.5-6.5
MCV (fL)	93	80-100
MCH (pg)	31	27-32
MCHC (g/L)	315	300-350
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>8.8</b>	<b>4-11</b>
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>470</b>	<b>150-400</b>
<b>Film</b>	Normochromic, normocytic	

5. What investigations would you perform to ascertain the cause of this man's bleeding?



***Gastroscopy showed antral gastritis and a sharply punched-out ulcer 3 cm in diameter in the pre-pyloric region of the stomach. A biopsy was reported as being consistent with a benign chronic gastric ulcer. Helicobacter pylori was detected in the inflamed gastric antrum.***

6. Which vessels are closely related to the duodenum and stomach and may be eroded to cause life-threatening haemorrhage? What other complications may occur in this clinical situation?



7. Is eradication of H. pylori important in this patient? If so, why, and what pharmacotherapy would you recommend? What other factors could predispose to peptic ulceration?



8. If the patient developed further rapid bleeding and remained severely hypotensive for 60 minutes, what complications may develop?



## Case protocol 17

### Case History

A 60-year-old man presented to his GP with right loin pain and macroscopic haematuria. He had been feeling unwell for six weeks, had lost 6 kg in weight and had felt feverish on several occasions. Examination revealed an obese, plethoric, elderly man who looked unwell.

### Questions

- What further information would you seek from the history and examination?



- What is the most likely cause for this man's haematuria, and what is the differential diagnosis?



- What abnormality is present on the full blood count (below), and what processes may cause it?



### Vital Signs

Heart Rate (b/min)	90
Blood Pressure (mm Hg)	140/90
Respiratory Rate (/min)	20
Temperature (°C)	37.9
Urinalysis	pH 7.0, Prot ++, Blood +++++

### Full Blood Count

Haemoglobin (g/L)	210	130-180
Haematocrit (%)	62	40-54
RCC ( $\times 10^{12}/L$ )	7.2	4.5-6.5
MCV (fL)	86	80-100
MCH (pg)	30	27-32
WBC ( $\times 10^9/L$ )	10.7	4-11
Platelets ( $\times 10^9/L$ )	470	150-400

### Clinical Chemistry

CRP (mg/L)	2	< 5
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4. What further investigations would you consider appropriate?



*An abdominal CT scan with intravenous contrast revealed a mass in the upper pole of the right kidney, consistent with a renal cell carcinoma.*

5. What is the likely course of this disease if not treated?



6. What other clinical manifestations, unrelated to the urinary tract, may be associated with this disease?



7. Describe the typical macroscopic and histopathological features of the lesion in the kidney.



## Case protocol 18

### Case History

A 45-year-old man complained of progressive lethargy and swelling of the ankles over the past three weeks. Examination revealed a pale and ill-looking man with pitting oedema of both ankles. The JVP was raised 3 cm, there was a fourth heart sound and crepitations were heard at both lung bases. Microscopy of fresh urinary sediment showed granular and red cell casts. Over the next 24 hours the total urine volume was 400 ml.

Vital Signs	
Heart Rate (b/min)	80
Blood Pressure (mm Hg)	150/110
Respiratory Rate (/min)	22
Temperature (°C)	36.3
Urinalysis	pH 7.0, Prot ++, Blood ++

Clinical Chemistry		
Sodium (mmol/L)	133	135-145
Potassium (mmol/L)	5.2	3.5-5.0
Chloride (mmol/L)	92	95-107
Bicarbonate (mmol/L)	18	24-32
Urea (mmol/L)	15	3.0-8.0
Creatinine (μmol/L)	210	60-110

### Questions

- What is the likely cause of this man's illness, and what further information would you seek from the history and examination?



- What is meant by the term "oliguria"?



3. What is the likely pathological basis of the haematuria, oliguria and cast formation?



4. Why is this man hypertensive, with an elevated JVP and peripheral oedema?



5. What further investigations would you perform?



***A renal biopsy was performed and was reported as consistent with acute proliferative glomerulonephritis.***

6. What are the basic features of this type of glomerulonephritis?



7. What types of glomerulonephritis are associated with the nephritic syndrome, and which of these are associated with acute kidney injury?



***Because of an elevated antistreptolysin-O titre and the findings on renal biopsy, a diagnosis of post-Streptococcal glomerulonephritis was made.***

8. What advice would you give this patient regarding the long-term outlook for his disease?



## Case protocol 19

### Case History

A 61-year-old woman presented to her GP with a three-week history of cough and chest pain. She had coughed up a small amount of blood-stained sputum. There was no history of fever or night sweats.

Examination revealed a thin woman with dyspnoea on mild exertion. There was decreased expansion of the left side of the chest and the percussion note at the left base was stony dull. Auscultation revealed expiratory rhonchi, and there was no friction rub.

### Questions

- What further information would you seek from the history and physical examination?



- What are your provisional and differential diagnoses?



<b>Full Blood Count</b>			
<b>Haemoglobin (g/L)</b>	<b>135</b>	<b>115-165</b>	
<b>Haematocrit (%)</b>	<b>39</b>	<b>37-47</b>	
<b>RCC (<math>\times 10^{12}/L</math>)</b>	<b>6.8</b>	<b>3.8-5.8</b>	
<b>MCV (fL)</b>	<b>87</b>	<b>80-100</b>	
<b>MCH (pg)</b>	<b>30</b>	<b>27-32</b>	
<b>MCHC (g/L)</b>	<b>330</b>	<b>300-350</b>	
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>7.2</b>	<b>4-11</b>	
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>350</b>	<b>150-400</b>	
<b>Film</b>		Red cell morphology normal	
<b>Clinical Chemistry</b>			
<b>CRP (mg/L)</b>	<b>72</b>	<b>&lt; 5</b>	

3. Outline the investigations you would perform, the costs, and the results that you would expect.



Investigations	Expected Result	Cost

***Further enquiry revealed that the patient had lost 6 kg in weight during the preceding 3 months. She had smoked 40-50 cigarettes a day since she was 18 years old. A chest x-ray revealed a left pleural effusion. Sputum culture was negative, as was microscopy and PCR testing for AFB's.***

4. What further investigations would you now consider?



***The patient was admitted to hospital for aspiration of the effusion. Cytological analysis of the aspirated pleural fluid revealed malignant cells. A subsequent chest x-ray revealed a 2cm coin lesion in the left lower lobe near the hilum. Bronchoscopy and biopsy were performed.***

5. Describe the histopathology of the most likely bronchial lesion.



6. What is the natural history and prognosis of this disease?



***Two weeks later she complained of further left-sided pleuritic chest pain and fever.***

7. What is the likely diagnosis? What other complications may develop?



***The patient's condition deteriorated over the following three months and she eventually died at home.***

8. What are the likely causes of death, and what would you expect to find at autopsy?



## Case protocol 20

### Case History

A 27-year-old soldier presented to the Emergency Department with a two-day history of fever, headache and rash. She had recently returned from an army camp where she and two of her companions had developed sore throats but had not received any treatment.

Examination revealed an ill-looking woman with haemorrhagic, papular lesions over the forearms and abdomen. Neck stiffness was present and Kernig sign was positive. Fundi were normal. Her vital signs are summarised in the table opposite.

### Questions

- State your provisional and differential diagnoses.



Vital Signs	
Heart Rate (b/min)	110
Blood Pressure (mm Hg)	90/60
Respiratory Rate (/min)	24
Temperature (°C)	39.4
Urinalysis	pH 5.5, Prot +ve Blood +ve

- Outline the sequence of events that occurred in this case. Indicate the route of infection. What is the significance of the patient's occupation and the illness in her companions?



- What, if any, empirical therapy would you recommend in this patient? If so, when should this be commenced?



- Outline the investigations you would perform, the costs, and the results that you would expect.



Investigations	Expected Result	Cost

5. How would you interpret the full blood count and CRP shown opposite?



<b>Full Blood Count</b>			
<b>Haemoglobin (g/L)</b>	<b>142</b>	<b>115-165</b>	
<b>WBC (x10<sup>9</sup>/L)</b>	<b>24.</b>	<b>4-11</b>	
Neutrophils	7	2.0-7.5	
Lymphocytes	20.3	1.5-4.0	
Monocytes	3.2	0.2-0.8	
Eosinophils	0.8	0.04-0.4	
Basophils	0.3	<0.1	
		0.1	
<b>Platelets (x10<sup>9</sup>/L)</b>	<b>78</b>	<b>150-400</b>	
<b>Film</b>		Toxic granulation of neutrophils	
		Band forms	
<b>Clinical Chemistry</b>			
<b>CRP (mg/L)</b>	<b>580</b>	<b>&lt; 5</b>	

Outline the results you would expect if a lumbar puncture was performed.



6. What factors may have predisposed to the development of this disease in this case?



7. What complications may develop if this disease is not recognised and treated?



8. Describe the abnormalities you would expect to find at autopsy if this patient died of overwhelming septicaemia.



9. What are the common causes of death in patients with suppurative meningitis?



10. What are the micro-organisms that most commonly cause meningitis in infants, children and adults?



11. What is the pathological basis of the rash in this case?



## Case protocol 21

### Case History

A 44-year-old female clerical worker was brought into the Emergency Department following a "grand mal" seizure of two minutes duration, witnessed by her partner. She had never had any fits before, and was in good health apart from headaches that had been present for several months, which she had attributed to the stress of her job. In fact, her employer had dismissed her only one week before, on the grounds that she had become forgetful and slow.

On examination, she was initially drowsy, with bilateral upgoing plantar responses, though these returned to normal after 4 hours. The remainder of the physical examination was normal.

### Questions

- What other features of the history and examination would you consider to be important? What are the red flags in her case?



- Do you think her employment difficulties might be relevant in this case? If so, how?



**A cerebral CT scan was performed the next day. A 4 cm discrete lesion was noted in the left parietal region. It was uniformly vascular.**

- What might be the pathological basis of this radiological abnormality?



The lesion was favoured to represent a meningioma.

- Can you diagnose a meningioma on CT scan?



5. What is the appropriate management in this patient?



***The meningioma was removed surgically and sent to Anatomical Pathology for histopathology. Grossly, the tumour was broadly attached to dura and appeared rounded and well circumscribed, with a vaguely whorled cut surface.***

6. What are the characteristic histological features of this lesion?



7. Where else do meningiomas occur?



8. What is the prognosis for meningiomas? Is the lesion likely to recur locally, and can it spread to other parts of the body if not completely removed?



9. What are the risk factors for meningioma?



## Case protocol 22

### Case History

A 63-year-old woman was referred to her local hospital for assessment of ankle oedema and weakness. She had been divorced for 23 years and lived alone. She had previously worked as a cook in the local RSL club but had been on sickness benefits for the past 15 years because of depression. She smoked 40 cigarettes a day and drank 5-6 glasses of sherry per day.

Examination revealed a woman who looked older than her stated age. Her gait was ataxic. Pitting oedema was present in both lower limbs. The abdomen was distended and tense, with shifting dullness. The liver was not palpable; however, the spleen was palpable 3 cm below the costal margin. Rectal examination revealed bleeding haemorrhoids.

<b>Full Blood Count</b>			
<b>Haemoglobin</b>	(g/L)	<b>112</b>	<b>115-165</b>
MCV (fL)		103	80-100
<b>WBC</b>	( $\times 10^9$ /L)	<b>4.4</b>	<b>4.5-11</b>
Neutrophils		2.8	2.0-7.5
Lymphocytes		1.2	1.5-4.0
Monocytes		0.3	0.2-0.8
Eosinophils		0.1	0.04-0.4
<b>Film</b>		Round macrocytes ++ Poikilocytes +	
<b>Platelets</b> ( $\times 10^9$ /L)		<b>98</b>	<b>150-400</b>

### Questions

- What is your provisional diagnosis, and what further information would you seek from the history and physical examination?



- What are the pathophysiological mechanisms underlying the distended abdomen and haemorrhoids, and where else in the body may abnormalities occur because of this mechanism?



**Liver Function Tests**

Albumin (g/L)	<b>28</b>	33-48
Globulin (g/L)	<b>38</b>	25-35
Total Protein (g/L)	<b>66</b>	62-80
Bilirubin ( $\mu$ mol/L)	<b>45</b>	2-20
Alkaline Phosphatase (U/L)	<b>145</b>	38-126
Aspartate Transaminase (U/L)	<b>25</b>	<45
Alanine Transaminase (U/L)	<b>21</b>	<45
$\gamma$ -Glutamyltransferase (UL)	<b>134</b>	<30

3. How would you interpret the full blood count and liver function tests shown above? What other investigations are likely to provide information on the state of hepatic function?



4. Is a liver biopsy indicated in this case? What are the contraindications to this procedure? Describe the histopathological changes you would expect to be present in the biopsy.



5. List the liver disorders that may result from long-term excessive alcohol use.



6. What are the common causes of cirrhosis?



7. What are the major complications of cirrhosis, and what events may precipitate these complications?



8. What other organs of the body are adversely affected by alcohol? What evidence is there for such involvement in this case?



9. What pharmacotherapy could be used to treat alcohol dependence, and what are the contraindications?



## Case protocol 23

### Case history

A 48-year-old man presented to his GP with a two-week history of sore throat, swollen lymph nodes in the neck and 7 kg weight loss. He had also noted drenching night sweats during the last week.

Examination revealed pharyngitis with white plaques on the soft palate and tonsillar area, and swelling of the lymphoid tissues of the oropharynx. Several lymph nodes of 2-3 cm diameter were readily palpable in the submandibular region, while nodes of a similar size were present in the left axilla and even larger nodes in the groin of up to 4cm.

### Vital Signs

Heart Rate (b/min)	80
Blood Pressure (mm Hg)	120/75
Respiratory Rate (/min)	12
Temperature (°C)	37.8
Urinalysis	pH 7.0, Prot -ve, Blood -ve

### Questions

- What diseases could produce this clinical picture?



- What further aspects of the history and examination are important in this case?



- Outline the investigations you would perform and the reasons for these tests.



**A full blood count, biochemistry and excision biopsy of an enlarged cervical lymph node were performed, among other tests.**

4. How would you interpret the full blood count and biochemical tests shown below? What clinical emergencies would you be concerned about?

FULL BLOOD COUNT		Range	Units
<b>Haemoglobin</b>	<b>125 L</b>	130-180	g/L
MCV	89	76-96	fL
MCH	30	27.0-32.0	pg
<b>Platelets</b>	<b>145 L</b>	150-400	$10^9/L$
WBC	4.5	4.0-11.0	$10^9/L$
Neutrophils	3.8	2.0-7.5	$10^9/L$
<b>Lymphocytes</b>	<b>0.5 L</b>	1.5-4.0	$10^9/L$
Film: Normochromic, normocytic			
BLOOD CHEMISTRY		Range	Units
Sodium	136	135-145	mmol/L
<b>Potassium</b>	<b>5.5 H</b>	3.5-5.2	mmol/L
Chloride	98	95-110	mmol/L
Bicarbonate	22	22-32	mmol/L
Urea	3.5	3.5-8.0	mmol/L
<b>Creatinine</b>	<b>125 H</b>	60-110	$\mu\text{mol}/\text{L}$
eGFR	55	>60	$\text{mL}/\text{min}/1.73\text{m}^2$
<b>Uric acid</b>	<b>0.60 H</b>	0.25-0.50	mmol/L
<b>Inorg. Phos.</b>	<b>1.65 H</b>	0.75-1.50	mmol/L
Magnesium	0.80	0.70-1.10	mmol/L
Calcium	2.60	2.10-2.60	mmol/L
<b>Ca alb corr</b>	<b>2.65 H</b>	2.10-2.60	mmol/L
<b>Albumin</b>	<b>30 L</b>	33-48	g/L
Tot. protein	70	60-80	g/L
Tot. bilirubin	20	0-20	$\mu\text{mol}/\text{L}$
ALT	35	0-40	U/L
AST	30	0-35	U/L
Alk. phos.	45	30-110	U/L
GGT	40	0-50	U/L
<b>LDH</b>	<b>400 H</b>	120-250	U/L
<b>CRP</b>	<b>50 H</b>	<5.0	mg/L
<b>ESR</b>	<b>40 H</b>	1-10	(mm/hour)



5. When requesting pathological examination of a lymph node biopsy, what clinical information should be provided as an aid to accurate diagnosis?



***The lymph node biopsy was reported as showing High-Grade B-cell non-Hodgkin Lymphoma with MYC and BCL2 rearrangement.***

6. Describe the features used by pathologists to classify lymphomas and indicate the relevance of histological classification to the treatment of this disease.



7. What is the staging system used to describe the extent of spread of this disease?



8. What factors may predispose to the development of this disease?



9. Why might oral candidiasis have occurred in this man? What is the recommended treatment?



10. What is the likely prognosis in this case?



## Case protocol 24

### Case History

A 27-year-old woman presented to her GP with a persistent facial rash and loss of scalp hair. She gave a history of Raynaud phenomena occurring during the previous three winters, and glomerulonephritis several years ago.

Examination revealed an erythematous rash over the malar region of her face and bridge of the nose. Her hands were pale and cold, with soft tissue swelling of the metacarpophalangeal joints of both hands.

### Vital Signs

Heart Rate (b/min)	76
Blood Pressure (mm Hg)	150/95
Respiratory Rate (/min)	14
Temperature (°C)	37.5
Urinalysis	pH 6.0, Prot ++, Blood ++

### Questions

- What are your provisional and differential diagnoses?



- What further information would you seek from the history and physical examination?



- What is your interpretation of the FBC, ESR and CRP results opposite?



### Full Blood Count

Haemoglobin (g/L)	90	115-165
Haematocrit (%)	30	37-47
RCC ( $\times 10^{12}/L$ )	3.2	3.8-5.8
MCV (fL)	89	80-100
MCH (pg)	31	27-32
MCHC (g/L)	320	300-350
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>3.1</b>	<b>4-11</b>
Neutrophils	1.9	2.0-7.5
Lymphocytes	0.7	1.5-4.0
Monocytes	0.3	0.2-0.8
Eosinophils	0.2	0.04-0.4
Basophils	0.0	<0.1
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>62</b>	<b>150-400</b>
Film		Normochromic, normocytic
<b>ESR (mm/hour)</b>	<b>88</b>	<b>3-12</b>
<b>CRP (mg/L)</b>	<b>62</b>	<b>&lt;5</b>

4. What further investigations would you perform to substantiate your diagnosis? For each of the major investigations you requested, give your reason for the test, the cost, and the results you would expect.



***Microscopy of urine revealed 100 erythrocytes/mL, with both red and white cell casts, as well as granular casts present in the urinary sediment.***

5. How would you interpret these results? What further relevant investigations would you request? What renal abnormalities are found in this disease?



Investigations	Expected Result	Cost

***The antinuclear antibody (ANA) test was positive at a titre of 1/2,560 with a homogeneous pattern.***

6. What does this indicate and what further tests would help to substantiate your diagnosis?



***Biopsies of the involved skin and of normal skin from the patient's buttock were performed.***

7. What histological findings do you predict would be present?



8. What other major organ systems may be involved in this disease?



9. What are the likely causes of this patient's pancytopenia?



10. What is known of the aetiology and pathogenesis of this disease?



## Case protocol 25

### Case History

A 65-year-old widow presented to her GP complaining of increasing tiredness and lethargy over the previous 6 months. She had a past history of pernicious anaemia treated with monthly injections of Vitamin B12.

On examination she was pale and apathetic. Her face was puffy and there were bilateral xanthelasmata. There was a small, non-tender goitre and evidence of peripheral neuropathy.

### Vital Signs

Heart Rate (b/min)	48
Blood Pressure (mm Hg)	85/65
Respiratory Rate (/min)	12
Temperature (°C)	35.0
Urinalysis	pH 6.5, Prot +, Blood -ve

### Questions

- What further questions would you consider necessary in the history?



- What is the most likely diagnosis, and what are the most common causes of this syndrome?



- Outline the investigations you would perform, the costs, and the results that you would anticipate.



Investigations	Expected Result	Cost

4. How would you interpret the thyroid function tests shown opposite?



Thyroid Function Tests		
Free T4 (pmol/L)	<b>4</b>	9.8-23.8
Free T3 (pmol/L)	<b>1.7</b>	2.3-7.1
TSH (mU/L)	<b>25</b>	0.4-5.0

***Thyroid autoantibodies were present in high titres. A diagnosis of Hashimoto's thyroiditis was made.***

5. What is the relationship between Hashimoto's thyroiditis and Graves' disease?



6. What are the histopathological features of the thyroid gland in Hashimoto's disease?



7. What is known of the pathogenesis of autoimmune thyroiditis?



8. What is the drug of choice for the treatment of hypothyroidism and what is its mechanism of action?



9. What is the relevance of the patient's history of pernicious anaemia? What other autoimmune conditions are associated with Hashimoto's thyroiditis?



10. What are the likely causes for her peripheral neuropathy? What other complications may ensue if hypothyroidism is left untreated?



## Case protocol 26

### Case History

A 35-year-old man was seen in consultation because of progressive wasting, malaise and severe odynophagia for solids and liquids. He reported having unprotected sex with several male partners but had previously avoided screening for HIV.

Physical examination revealed a wasted appearance, mild dehydration and a fever of 38.2°C. There were white plaques on the tonsils, palate and tongue. The remainder of the physical examination was normal.

Investigations confirmed that he was HIV-positive. His CD4 count was  $0.1 \times 10^9/\text{L}$  (reference range  $0.5\text{-}1.4 \times 10^9/\text{L}$ ). A full blood count was also performed (see opposite).

<b>Full Blood Count</b>			
<b>Haemoglobin (g/L)</b>	<b>87</b>	<b>130-180</b>	
Haematocrit (%)	33	40-54	
RCC ( $\times 10^{12}/\text{L}$ )	3.9	4.5-6.5	
MCV (fL)	88	80-100	
MCH (pg)	29	27-32	
MCHC (g/L)	300	300-350	
<b>WBC (<math>\times 10^9/\text{L}</math>)</b>	<b>3.1</b>	<b>4-11</b>	
Neutrophils	2.5	2.0-7.5	
Lymphocytes	0.3	1.5-4.0	
Monocytes	0.2	0.2-0.8	
Eosinophils	0.1	0.04-0.4	
Basophils	0.1	<0.1	
<b>Platelets (<math>\times 10^9/\text{L}</math>)</b>	<b>55</b>	<b>150-400</b>	
Film	Normochromic normocytic		
<b>Clinical Chemistry</b>			
<b>CRP (mg/L)</b>	<b>88</b>	<b>&lt; 5</b>	

### Questions

- Explain the abnormalities present in the full blood count and CRP.



- How does HIV infection lead to a reduced CD4 count?



3. What is the most likely cause of this man's odynophagia? What investigation would you perform to confirm the cause?



4. What other investigations would be relevant in this case? What results would you expect from such investigations?



***The man made a full recovery from his odynophagia and was prescribed antiretroviral therapy.***

5. What are the principles underlying the typical recommendation made for the use of medicines from several different classes of anti-retroviral drugs? What are common adverse effects of antiretroviral drugs? What types of interactions might occur between these drugs?



6. What opportunistic infections commonly occur in patients with HIV/AIDS?



Organ or system	Clinical features	Protozoa	Viruses	Bacteria	Fungi
Lung					
CNS					
GIT					
Bones					

7. Which non-infectious causes of morbidity and mortality are more likely in patients with HIV/AIDS?



## Case protocol 27

### Case History

A 25-year-old woman presented with anorexia, lethargy and pallor. She had a long history of recurrent urinary tract infections, and had suffered from several episodes of acute pyelonephritis during her childhood, though none had occurred in the last five years. Over the past 12 months she had noticed increasing nocturia.

Vital Signs		
Heart Rate (b/min)	75	
Blood Pressure (mm Hg)	160/105	
Respiratory Rate (/min)	16	
Temperature (°C)	36.4	
Urinalysis	pH 7.0, Prot +++ Blood -ve Hyaline casts	
Clinical Chemistry		
Sodium (mmol/L)	141	135-145
Potassium (mmol/L)	4.3	3.5-5.0
Chloride (mmol/L)	114	95-107
Bicarbonate (mmol/L)	18	24-32
Urea (mmol/L)	18.8	3.0-8.0
Creatinine (μmol/L)	250	60-110
BSL - fasting (mmol/L)	3.7	3.0-6.0

### Questions

- What are your provisional and differential diagnoses?



- What further aspects of the history and examination are relevant to this case?



- What further investigations would you consider?



**A CT urogram was reported as being consistent with reflux nephropathy.**

4. What are the features visible on a CT urogram that are suggestive of kidney damage due to vesicoureteric reflux?



5. Would a voiding cystourethrogram (VCUG) be likely to demonstrate vesicoureteric reflux in this woman now? If not, at what stage in her life would vesicoureteric reflux have been evident?



6. What is the significance of nocturia in this case, and why are the serum bicarbonate reduced and the serum chloride elevated?



7. What is the likely pathological basis of the proteinuria (1.5 gm/24 hours) detected on subsequent investigations?



8. What is thought to be the basis of this woman's renal impairment, and is progression to chronic renal failure likely?



9. What would be the appearance of the kidneys in such a case, both macroscopically and microscopically?



10. Would you perform a renal biopsy to confirm your diagnosis?



## Case protocol 28

### Case History

A 54-year-old woman was referred to a specialist physician by her local doctor. She had a five-month history of malaise, lethargy, glossitis, paraesthesia and numbness of the extremities, easy bruising, and over the past two weeks had noticed increasing breathlessness on mild exertion.

Physical examination revealed a pale, grey haired, blue eyed woman with a sallow complexion. Her tongue was beefy-red and tender. There was reduced pain and touch sensation in a "glove and stocking" distribution, together with reduced vibration sense and proprioception in the lower limbs. There were bilateral upgoing plantar responses.

### Vital Signs

Heart Rate (b/min)	100
Blood Pressure (mm Hg)	110/80
Respiratory Rate (/min)	18
Temperature (°C)	37.2

### Questions

- What are your provisional and differential diagnoses?



- What further information would you seek in the history and examination?



- Outline the investigations you would perform, the costs, and the results that you would expect.



Investigations	Expected Result	Cost

4. How would you explain the abnormalities shown on the FBC and CRP below? What other conditions are associated with macrocytosis?



<b>Full Blood Count</b>			
Haemoglobin (g/L)	95	115-165	
Haematocrit (%)	29	37-47	
RCC ( $\times 10^{12}/L$ )	2.8	3.8-5.8	
MCV (fL)	107	80-100	
MCHC (pg)	38	27-32	
WBC ( $\times 10^9/L$ )	2.7	4-11	
Platelets ( $\times 10^9/L$ )	90	150-400	
Film	Oval macrocytes ++ Poikilocytes ++ Hypersegmented neutrophils		
<b>Clinical Chemistry</b>			
CRP (mg/L)	22	< 5	

5. What is the cause of this disease and what are the predisposing factors?



6. What is the reason for this woman's neurological abnormalities?



7. What other complications may result from this woman's primary disease?



8. List the autoimmune conditions associated with this disease.



9. What are the treatment options for this patient? Describe the mechanism of action.



## Case protocol 29

### Case history

A 45-year-old woman presented to her local doctor with a three-week history of easy bruising and menorrhagia, associated with increasing fatigue and intermittent fever. Physical examination revealed a pale, thin person with prominent ecchymoses on her arms, legs and abdomen. The spleen was "tippable" beneath the costal margin and there was slight bony tenderness over the sternum.

### Vital Signs

Heart Rate (b/min)	100
Blood Pressure (mm Hg)	100/60
Respiratory Rate (/min)	18
Temperature (°C)	38.5
Urinalysis	pH 7.0, Prot -ve, Blood +ve

### Questions

- What differential diagnoses should be considered in this case?



- What further history and physical findings would you seek to assist in making a diagnosis?



- What investigations would you perform?



**A full blood count was ordered, and the results are shown below.**

4. State your diagnosis and explain the pathological basis of the changes in the blood count and film.



5. What abnormalities are likely to be present in a bone marrow examination in this case?



<b>Full Blood Count</b>			
<b>Haemoglobin</b>	(g/L)	<b>82</b>	<b>115-165</b>
<b>Haematocrit</b>	(%)	<b>31</b>	<b>37-47</b>
<b>RCC</b>	( $\times 10^{12}/L$ )	<b>3.3</b>	<b>3.8-5.8</b>
<b>MCV</b>	(fL)	<b>88</b>	<b>80-100</b>
<b>MCH</b>	(pg)	<b>31</b>	<b>27-32</b>
<b>MCHC (g/L)</b>		<b>320</b>	<b>300-350</b>
<b>WBC</b>	( $\times 10^9/L$ )	<b>30</b>	<b>4-11</b>
Neutrophils		0.8	2.0-7.5
Lymphocytes		0.5	1.5-4.0
Monocytes		0.1	0.2-0.8
Eosinophils		0.0	0.04-0.4
Basophils		0.0	<0.1
<b>Platelets (<math>\times 10^9/L</math>)</b>		<b>15</b>	<b>150-400</b>
<b>Film</b>		Blasts +++ and myeloid precursors (70% of WBC total)	
<b>Clinical Chemistry</b>			
<b>CRP (mg/L)</b>		<b>100</b>	<b>&lt;5</b>

6. What factors predispose to this disease and what is known of its pathogenesis?



7. What are the major complications of this disease?



8. What is the prognosis in this disease?



## Case protocol 30

### Case History

A 24-year-old woman was referred to the rheumatology clinic for investigation of her arthritis. She was previously well until she developed symmetrical painful swelling of the proximal interphalangeal, metacarpophalangeal, wrist, and ankle joints. Examination revealed a thin, pale, ill-looking woman with warm, symmetrical swelling of all involved joints.

### Vital Signs

Heart Rate (b/min)	80
Blood Pressure (mm Hg)	110/70
Respiratory Rate (/min)	16
Temperature (°C)	37.8
Urinalysis	pH 6.2, Prot +ve, Blood-ve

### Questions

- What is your provisional diagnosis, and what other diseases may cause polyarthritis?



- What further information would you seek from the history and physical examination?



- What abnormalities of the full blood count and CRP are demonstrated below, and what other investigations would you perform to substantiate your diagnosis?



4. What are the characteristic features of rheumatoid arthritis you would expect to see on an X-ray of this woman's hands, and what is their pathological basis?



<b>Full Blood Count</b>			
Haemoglobin	(g/L)	92	115-165
Haematocrit	(%)	33	37-47
RCC	( $\times 10^{12}/L$ )	3.1	3.8-5.8
MCV	(fL)	90	80-100
MCH (pg)		27	27-32
MCHC (g/L)		310	300-350
<b>WBC</b>	( $\times 10^9/L$ )	<b>11.5</b>	<b>4-11</b>
Neutrophils		5.0	2.0-7.5
Lymphocytes		5.8	1.5-4.0
Monocytes		0.2	0.2-0.8
Eosinophils		0.1	0.04-0.4
Basophils		0.1	<0.1
<b>Platelets (<math>\times 10^9/L</math>)</b>		<b>287</b>	<b>150-400</b>
<b>ESR (mm/hour)</b>		<b>54</b>	<b>3-12</b>
<b>Clinical Chemistry</b>			
CRP (mg/L)		64	<5

5. Outline the investigations you would perform on a synovial fluid sample if it were available for analysis, and indicate the results you would expect.



6. What local complications may develop as a result of persistent synovitis?



***The patient subsequently underwent arthroscopy of her left ankle, and a synovial biopsy was performed.***

7. Describe the likely histological appearances of this tissue.



8. What are the general principles of pharmacotherapy for this disease? Outline the mechanisms of action of the commonly recommended medicines.



***The patient subsequently developed ulcerated nodular lesions over both elbows.***

9. One of these lesions was biopsied. What would it have revealed?



***At follow-up visits, the patient was noted to have dryness of her eyes, nose, mouth and skin, as well as an enlarged spleen, which was palpable five centimetres below the costal margin, and generalised lymphadenopathy.***

10. What is the likely cause of these changes? Does the patient require further investigations to ascertain the cause of her splenomegaly?



11. What other systemic complications are associated with this disease, and what is their pathological basis?



## Case protocol 31

### Case History

A 13-year-old girl was seen at home by her local doctor. She had been unwell for the past week, with increasing weakness and lethargy, and had also complained of thirst and vague abdominal pains. Her mother noted that the patient had not been eating, and had vomited repeatedly over the past two days.

Examination revealed a pale, thin, drowsy girl with dry mucosae and ketotic foetor. She was admitted to hospital.

### Vital Signs

Heart Rate (b/min)	118
Blood Pressure (mm Hg)	85/50
Respiratory Rate (/min)	18
Temperature (°C)	37.5
Urinalysis	pH 7.0, Prot + Glu +++ Ketones +++ Blood -ve

### Questions

- How would you interpret the history and physical findings?



- What investigations would you perform to quickly substantiate your provisional diagnosis?



3. How would you interpret the clinical chemistry and arterial blood gas results shown below?



Arterial Blood Gases		
pH	7.1	7.35-7.45
PaO <sub>2</sub> (mm Hg)	98	80-100
PaCO <sub>2</sub> (mm Hg)	23	35-45
Bicarbonate (mmol/L)	10	24-32
Base Excess	-15	-3<BE < 3
O <sub>2</sub> Saturation (%)	100	95-100

Clinical Chemistry		
Sodium (mmol/L)	125	135-145
Potassium (mmol/L)	6.1	3.5-5.0
Chloride (mmol/L)	89	95-107
Bicarbonate (mmol/L)	9	24-32
Urea (mmol/L)	16	3.0-8.0
Creatinine (μmol/L)	160	60-110
Glucose (mmol/L)	32	3.0-6.0
Osmolality (mmol/kg)	320	280-300

4. Outline the likely clinical course if this girl did not receive appropriate treatment.



5. What is the cause of this girl's ketoacidosis? Outline the pathophysiology of this condition.



***The patient was treated appropriately and made a satisfactory recovery.***

6. What is known of the aetiology of her underlying disease?



7. What would optimal long-term pharmacotherapy of her condition have entailed?



***Unfortunately, her disease was poorly controlled over subsequent years. Ten years after the initial diagnosis of her condition, she was noted to have developed nocturia and ankle oedema. Urinalysis demonstrated glucose +, ketones -ve, protein ++++.***

8. What complication of her primary disease has probably developed, and what microscopic features are likely to be present on renal biopsy?



9. What other long-term complications are likely to develop?



10. How can the metabolic control of hyperglycaemia be assessed?



## Case protocol 32

### Case History

A 47-year-old woman was seen in the outpatient clinic complaining of swelling of the feet and ankles. She had a thirteen-year history of severe seropositive rheumatoid arthritis treated with gold and NSAIDs. There was bilateral pitting ankle oedema and symmetrical polyarthritis, with typical rheumatoid deformities of her hands and feet. Apart from mild hypertension, the remainder of the physical examination was normal.

<b>Vital Signs</b>	
Heart Rate (b/min)	90
Blood Pressure (mm Hg)	140/95
Respiratory Rate (/min)	16
Temperature (°C)	36.7
Urinalysis	pH 7.0, Prot +++, Blood -ve

<b>Clinical Chemistry</b>		
Sodium (mmol/L)	132	135-145
Potassium (mmol/L)	3.9	3.5-5.0
Chloride (mmol/L)	100	95-107
Bicarbonate (mmol/L)	26	24-32
Urea (mmol/L)	7.9	3.0-8.0
Creatinine (μmol/L)	110	60-110

### Questions

1. Is this woman suffering from the nephrotic syndrome? If so, how could this be substantiated?



2. What is the relationship between the patient's proteinuria and ankle oedema?



*Further investigation revealed that the patient was excreting 6.5 g of protein per 24 hours in her urine.*

3. How did this protein reach the urine and what are the main types of protein likely to be present?



4. What are the possible lesions underlying the proteinuria in this case?



5. What further investigations would you perform and what do you predict they would reveal?



6. Could the patient's drug treatment be relevant in this case? In what way?



7. What clinical problems may develop as a result of this degree of proteinuria?



***A renal biopsy was performed and reported to be compatible with a diagnosis of membranous glomerulonephritis.***

8. What features would you expect to be present under light microscopy, and what secondary causes of this disease do you know?



## Case protocol 33

### Case History

A 36-year-old businessman sought medical advice because of a painless swelling in the left side of his scrotum, which had been present for three weeks. He was otherwise well apart from a history of surgical treatment for an undescended left testis as a child. Examination revealed a 5 x 3 cm, non-tender, firm mass at the upper pole of the left testis. It was possible to get above the lesion and it did not transilluminate.

### Questions

1. What further information would you seek from the history and physical examination?



2. What are the common causes of a scrotal mass lesion, and what do you think is the most likely diagnosis in this case?



3. Outline the investigations you would perform and give reasons for each of the tests.



***Histopathological assessment of an excisional biopsy of the left testis via the inguinal route confirmed that the mass was a seminoma of the testis.***

4. By what route(s) do testicular tumours metastasise?



5. What hormonal effects might be produced by testicular tumours?



6. What are the main types of testicular tumours and how do they differ in terms of prognosis?



7. Why is percutaneous biopsy of suspected testicular tumours usually contraindicated?



8. Outline the factors incriminated in the pathogenesis of testicular neoplasms. Which factors might be relevant in this case?



9. Compare and contrast the histological features of seminomas and teratomas.



## Case protocol 34

### Case history

A 65-year-old female, who had a 10-year history of hypertension and a myocardial infarction three years previously, presented to the Emergency Department with sudden onset of weakness in the left arm and leg. On examination, her pulse was rapid and irregularly irregular. She had a left VII cranial nerve palsy of the upper motor neuron type and left spastic hemiparesis, with an ipsilateral upgoing plantar response.

### Vital Signs

Heart Rate (b/min)	105
Blood Pressure (mm Hg)	145/100
Respiratory Rate (/min)	20
Temperature (°C)	36.7
Urinalysis	pH 6.0, Prot ++, Blood -ve

### Questions

- What further information would you seek from the history and physical examination?



- Where is the lesion that caused this neurological deficit, and what pathological process is likely to have occurred?



- Describe in chronological order the likely sequence of events that led up to this incident.



- What factors might have predisposed to this devastating illness?



- What investigations would you order and why?



The patient became increasingly drowsy over the next twelve hours and lapsed into a coma.

6. Why do you think the patient lost consciousness?



Two days later the patient was noted to be febrile and tachypnoeic with a respiratory rate of 40/min.

7. What are the possible causes of this change in her condition?



8. What investigations would you order, and why?



9. The patient died ten days after admission. Describe the abnormalities that you would expect to find at autopsy.



## Case protocol 35

### Case History

A 71-year-old woman was found lying on her kitchen floor in severe pain and unable to stand. She was taken to hospital, where examination revealed a thin, distressed woman with shortening and external rotation of her right leg. An X-ray confirmed a fracture of the neck of the femur.

<b>Clinical Chemistry</b>		
Sodium (mmol/L)	<b>130</b>	135-145
Potassium (mmol/L)	<b>3.9</b>	3.5-5.0
Chloride (mmol/L)	<b>90</b>	95-107
Bicarbonate (mmol/L)	<b>21</b>	24-32
Urea (mmol/L)	<b>17</b>	3.0-8.0
Creatinine (μmol/L)	<b>130</b>	60-110
Calcium (mmol/L)	<b>3.0</b>	2.1-2.55
Phosphate (mmol/L)	<b>1.2</b>	0.7-1.5

<b>Full Blood Count</b>			
<b>Haemoglobin (g/L)</b>	<b>85</b>	<b>115-165</b>	
Haematocrit (%)	27	37-47	
RCC ( $\times 10^{12}/L$ )	3.1	3.8-5.8	
MCV (fL)	95	80-100	
MCH (pg)	30	27-32	
MCHC (g/L)	310	300-350	
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>3.9</b>	<b>4-11</b>	
Neutrophils	2.1	2.0-7.5	
Lymphocytes	1.3	1.5-4.0	
Monocytes	0.1	0.2-0.8	
Eosinophils	0.1	0.04-0.4	
Basophils	0.1	<0.1	
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>140</b>	<b>150-400</b>	
Film	Nucleated RBC ++ Metamyelocytes + Rouleaux ++		
<b>ESR (mm/hour)</b>	<b>110</b>	<b>5-20</b>	

### Questions

- What pre-existing conditions could have predisposed to the fracture of the femoral neck?



A full blood count performed prior to hip surgery is shown above, and a pre-operative chest X-ray was reported to show multiple lytic lesions in the clavicles and ribs.

- How would you interpret these results?



3. What further investigations would be appropriate at this stage?



***A sample of urine was found to contain "Bence-Jones protein".***

4. What is Bence-Jones protein, and what is the basis for its occurrence in urine?



***An electrophoretogram of the patient's serum revealed a spike in the gamma region.***

5. What is a monoclonal band? What is immunofixation, and what further information is provided by this investigation?



6. A bone marrow biopsy was found to contain 30% plasma cells. Does this allow a definitive diagnosis to be made?



7. What is the pathological basis of the skeletal lesions seen in patients with this disease?



8. How would you assess this woman's pain? What analgesics can be used to relieve bone pain?



9. Why are patients with this disease particularly predisposed to develop pneumonia?



10. What might have caused the elevated urea and creatinine in this case?



11. What is meant by the term "monoclonal gammopathy of undetermined significance" (MGUS), and what features distinguish a benign paraproteinaemia from a malignant one?



## Case protocol 36

### Case History

A 24-year-old single man presented to his GP with a two-week history of lethargy, anorexia, nausea and arthralgia. Over the past two days he had noticed darkening of his urine. On examination he was found to have scleral icterus, an enlarged tender liver (16 cm liver span) and splenomegaly.

### Questions

- What is the likely cause of this man's illness?



- Which viruses commonly cause this clinical picture, and what further information would you seek in the history and physical examination?



- Are the liver function tests shown opposite consistent with your diagnosis? Explain the mechanism of each of the abnormalities.



### Vital Signs

Heart Rate (b/min)	85
Blood Pressure (mm Hg)	120/80
Respiratory Rate (/min)	14
Temperature (°C)	37.7
Urinalysis	pH 6.5, Prot + Blood -ve, Bili +++

### Liver Function Tests

Bilirubin ( $\mu$ mol/L)	120	2-20
Alkaline Phosphatase (U/L)	148	38-126
Aspartate Transaminase (U/L)	642	<45
Alanine Transaminase (U/L)	768	<45
$\gamma$ -Glutamyltransferase (UL)	88	<50
Albumin (g/L)	42	33-48
Globulin (g/L)	32	25-35
Total Protein (g/L)	74	62-80

4. Explain the pathological basis for the presence of bilirubin in the urine.



5. What serological investigations would be appropriate to make a specific diagnosis in this case?



6. Compare and contrast hepatitis A, B, C and E infections in terms of their epidemiology and sequelae.



	HAV	HBV	HCV	HEV
<b>Incubation (days)</b>				
<b>Transmission:</b> Blood Faeces Vertical				
<b>Fulminant necrosis</b>				
<b>Chronic hepatitis</b>				
<b>Carrier state</b>				
<b>Hepatocellular carcinoma</b>				

7. What is the role of the immune response in producing the characteristic features of HBV infection?



***Five days after admission to hospital, the patient became confused and tremulous.***

8. What pathological changes in the liver are likely to be the basis for this clinical deterioration, and what further complications may develop in other organ systems?



9. What treatments are available to manage chronic HBV infection, and what are their mechanisms of action?



## Case protocol 37

### Case History

A 36-year-old man presented to the Emergency Department with severe right loin pain. The pain had been present "on and off" for the past six hours, with each attack of pain lasting approximately 30 minutes. The patient recalled a similar episode of pain six months previously that had resolved spontaneously. Examination revealed a distressed man, pale and tachycardic. The abdomen was soft and non-tender, and no other abnormalities were detected on physical examination.

### Vital Signs

Heart Rate (b/min)	110
Blood Pressure (mm Hg)	170/105
Respiratory Rate (/min)	15
Temperature (°C)	36.6
Urinalysis	pH 7.0, Prot +, Blood ++

### Questions

- What are your provisional and differential diagnoses?



- What investigations would you perform while the patient is in the Emergency Department to confirm your diagnosis?



An abdominal helical CT scan showed a 5 mm radiodense lesion 2 cm lateral to the body of the fifth lumbar vertebra.

- What might produce such an appearance?



**The patient's pain settled with analgesia and he was discharged four hours later. Biochemistry results are shown below.**

4. What is the significance of these results? What further information do you require to interpret them correctly?



Clinical Chemistry			
Sodium (mmol/L)	<b>133</b>	135-145	
Potassium (mmol/L)	<b>4.1</b>	3.5-5.0	
Chloride (mmol/L)	<b>98</b>	95-107	
Bicarbonate (mmol/L)	<b>28</b>	24-32	
Urea (mmol/L)	<b>12</b>	3.0-8.0	
Creatinine (μmol/L)	<b>130</b>	60-110	
Calcium (mmol/L)	<b>2.9</b>	2.1-2.55	
Phosphate (mmol/L)	<b>1.4</b>	0.7-1.5	
Urate (mmol/L)	<b>0.6</b>	0.2-0.45	

***The next day the patient passed a stone 5 mm in diameter with an irregular, "mulberry" shape.***

5. What would you expect chemical analysis of the stone to reveal? What are the main types of renal calculi?



6. What complications of nephrolithiasis are present in this patient, and what other complications may occur?



7. What are the major factors implicated in the pathogenesis of renal calculi?



## Case protocol 38

### Case History

You are an "on-call" surgical resident asked to see a 73-year-old man who died in his sleep 12 hrs after undergoing surgery to bypass an occluded right popliteal artery. You have not seen him previously. His wife, who is very keen for you to sign the death certificate, tells you that he was known to have suffered from intermittent claudication in the right leg for the previous six months, with recent onset of nocturnal pain in the right calf. He had received treatment for systemic hypertension for the past 18 years, and had a history of angina for the past 2 years.

### Questions

1. Is a coronial autopsy necessary in this case, and if so, why? What legal obligations must be satisfied before performing an autopsy under these circumstances?



2. What is the likely pathological basis of his intermittent calf pain, and what may have occurred to precipitate the nocturnal calf pain present in the days before his death?



3. Describe the abnormalities you would expect to find at autopsy in the blood vessels of the abdomen and legs.



4. How might the finding of atherosclerosis involving the origin of the right renal artery explain the development of hypertension at the age of 55?



5. What factors predispose to atherosclerotic peripheral vascular disease?



6. Which organs are likely to undergo pathological changes as a result of long-standing hypertension, and what is the nature of the changes in each of those organs?



7. What do you consider to be the most likely cause(s) of death in this case?



8. What factors may have increased the risk of myocardial infarction in the peri-operative period?



## Case Protocol 39

### Case history

A 35-year-old woman was seen by her local doctor because of increasing dyspnoea over the previous 12 hours. She had suffered from asthma since childhood, requiring numerous hospital admissions, and consequently was reluctant to consult doctors or to go to hospital. Her only medication was a salbutamol puffer, used as required. She had been suffering from an upper respiratory tract infection for the past three days and had a cough productive of yellow sputum.

On examination, the woman was dyspnoeic at rest, having difficulty in carrying out a conversation. She was pale but not cyanosed, the chest was hyperinflated with prominent tracheal tug, and she was using accessory muscles of respiration. Bilateral inspiratory and expiratory wheezes were heard on auscultation. She was commenced on antibiotics, nebulised salbutamol and prednisone tablets, but refused admission to hospital.

### Vital Signs

Heart Rate (b/min)	120
Blood Pressure (mm Hg)	140/70
Respiratory Rate (/min)	26
Temperature (°C)	37.0
Urinalysis	pH 6.0, Prot -ve, Blood -ve

### Questions

1. What is your provisional diagnosis and what factors may have resulted in an exacerbation of this woman's disease? What would you consider to be optimal pharmacotherapeutic treatment for her? How should her treatment be monitored?



- Asthma exacerbation due to poor control previously

use SAMA > LAMA in COPD

- controller + reliever (GINA guidelines + stepwise approach)

@ Step 4,5

steroids : less likely to become hyperinflated if baseline inflam ↓

2. What features did this woman exhibit that indicated the severity of her airway obstruction?



dyspnoea @ rest

tracheal tug

hyperinflated lungs

accessory muscles.

but at least wheeze in and out can be heard - silent chest is a very bad sign.

3. What investigations would have been of value in assessing the nature and severity of her disease?



ABG. CXR. spirometry when she is well enough

Bloods (FBC. EVC. etc)

*Twelve hours after her initial consultation she was admitted to hospital following a respiratory arrest at home. Examination in the Emergency Department revealed a drowsy, cyanosed woman in severe distress and unable to talk. Respiratory effort was poor, the pulse rate was 180 beats per minute, the blood pressure 140/60 mm Hg with 30 mm Hg of paradox, and the chest was silent.*

4. What further information would you seek and what investigation would you perform?



CXR - concerned about a pneumothorax  
haemodynamic compromise - if HR is around / above systolic... BAD

5. How would you interpret the arterial blood gas results shown opposite?



Respiratory acidosis w/o metabolic compensation  
- hypercapnoea  
- hypoxia

consistent with type II respiratory failure

Arterial Blood Gases		
pH	7.28	7.35-7.45
PaO <sub>2</sub> (mm Hg)	53	80-100
PaCO <sub>2</sub> (mm Hg)	52	35-45
Bicarbonate (mmol/L)	30	24-32
O <sub>2</sub> Saturation (%)	82	95-105
Base Excess	1	-2<BE<2

due to retention of CO<sub>2</sub> from hypoventilation



6. What is known of the aetiology and pathophysiology of this disease?



atopic asthma : disease of the bronchioles. must be sensitised before to develop  
occupational asthma  
drug-induced : NSAIDs most common

type I hypersensitivity  
(driven by mast cells, IgE)  
and eosinophils.

*Despite all attempts at resuscitation, the patient's condition continued to deteriorate, and six hours later she had a cardiac arrest and died.*

7. Outline the findings you would anticipate at autopsy.



chronic remodelling - mucous plugging, inflammatory infiltrate in alveoli  
- thickened BM, SM  
- eosinophilic infiltrate (charcot baudouin crystals)  
- goblet cell hyperplasia Curshmann's spirals)

## Case protocol 40

### Case History

A 47-year-old woman was hurrying for a bus when she experienced a sudden violent headache and collapsed. She was assisted by a friend, who noted that the patient was conscious but confused and in pain.

Examination in the Emergency Department revealed a thin female, disoriented in time and place, with prominent nuchal rigidity. The remainder of the examination was normal apart from a sub-hyaloid haemorrhage in the right optic fundus.

### Vital Signs

Heart Rate (b/min)	70
Blood Pressure (mm Hg)	160/110
Respiratory Rate (/min)	18
Temperature (°C)	36.4
Urinalysis	pH 7.0, Prot -ve, Blood -ve

### Questions

1. State your diagnosis and differential diagnosis.



2. What investigations would you perform and why?



3. Outline the likely pathophysiological sequence of events in this case.



**A cerebral CT scan demonstrated blood in the subarachnoid space. Subsequent carotid angiography showed an aneurysm at the junction of the right anterior cerebral and anterior communicating arteries.**

4. What potentially fatal complications may develop in this disease?



5. What are the common anatomical sites for the primary lesion in this disease?



6. What other conditions may be associated with this disease?



7. What is the prognosis in this disease?



## Case protocol 41

### Case history

A 42-year-old woman was referred to the Endocrinology Clinic with suspected acromegaly. The patient had noticed gradually worsening bifrontal headache for the past six months. There were no visual disturbances. The patient had also noticed changes in her physical appearance especially enlargement of her hands and feet. There was a history of arthralgia in the knees, a feeling of increasing lethargy and tiredness, and of nocturia.

Physical examination revealed a woman with coarse facial features, enlargement of her jaw and tongue and a small goitre. Her hands were large and spade-like, blood pressure was 140/100. There was cardiomegaly and evidence of median nerve compression in the right hand. Crepitus was present in both knees. There was proximal muscle weakness in the upper and lower limbs. The remainder of the neurological examination was normal. The ocular fundus revealed no evidence of papilloedema, and visual fields examination was normal.

### Questions

1. What additional clinical information could have been elicited on further questioning?



2. What investigations would you perform to substantiate the diagnosis of acromegaly?



3. For each of the following symptoms or signs of acromegaly, outline the pathophysiological mechanisms involved in their production: acral enlargement; headaches; joint pains; cardiomegaly; proximal myopathy; carpal tunnel syndrome; hypertension.



4. What is the most likely cause of this woman's nocturia?



5. How should this be further investigated?



6. What is the cause of hyperglycaemia in patients with acromegaly?



7. What is the significance of the patient's thyroid enlargement? Does this require investigation?



***The patient was subsequently found to have a pituitary tumour and this was removed surgically via the trans-sphenoidal approach.***

8. What are the short-term and long-term complications of trans-sphenoidal hypophysectomy?



9. What additional pathological effects can pituitary tumours cause other than those observed in this patient?



## Case protocol 42

### Case History

A 56-year-old man was seen in the Haematology Clinic for review. He was diagnosed with polycythaemia vera six years ago, and had been treated with regular venesections. Over the past few months he had noticed increasing tiredness, early satiety, some weight loss and "discomfort" in the left upper quadrant of his abdomen.

Examination revealed a cachectic man with conjunctival pallor. The splenic edge was palpable 10 cm below the costal margin in the mid-clavicular line. The remainder of his examination was normal.

### Vital Signs

Heart Rate (b/min)	90
Blood Pressure (mm Hg)	130/90
Respiratory Rate (/min)	16
Temperature (°C)	36.2
Urinalysis	Normal

### Questions

1. What complication(s) of his polycythaemia may account for the changes in his condition?



2. How would you interpret the FBC and CRP shown opposite? What other investigations would you perform, and why?



### Full Blood Count

Haemoglobin (g/L)	90	130-180
Haematocrit (%)	31	40-54
RCC ( $\times 10^{12}/L$ )	3.5	4.5-6.5
MCV (fL)	85	80-100
MCH (pg)	29	27-32
MCHC (g/L)	330	300-350
<b>WBC (<math>\times 10^9/L</math>)</b>	<b>14.6</b>	<b>4-11</b>
Neutrophils	11.0	2.0-7.5
Lymphocytes	1.5	1.5-4.0
Monocytes	1.4	0.2-0.8
Eosinophils	0.2	0.04-0.4
Basophils	0.5	<0.1
<b>Platelets (<math>\times 10^9/L</math>)</b>	<b>450</b>	<b>150-400</b>

Film	Leucoerythroblastic Nucleated RBC ++ Metamyelocytes ++ Tear drops + Blasts +
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### Clinical Chemistry

CRP (mg/L)	18	< 5
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3. What is meant by the term “leucoerythroblastic film”, and is it applicable in this case?



4. What are the main factors contributing to the anaemia in this case?



5. What abnormalities would you expect to find on bone marrow aspiration and trephine? How is the diagnosis confirmed?



***The patient had complained of an episode of painful swelling of his big toe two weeks earlier.***

6. What is the likely cause of this episode? What other risks or complications are associated with this disease?



7. What is the natural history of this disease, and what are the common modes of death?



8. What are the standard therapeutic options in this disease and what is the associated prognosis?



## Case protocol 43

### Case History

A 61-year-old woman presented to the Emergency Department complaining of abdominal pain. The pain was of gradual onset over the previous four hours, and was now severe and confined to the epigastrium.

On examination there was epigastric tenderness with guarding and rigidity. Bowel sounds were absent, and there was no evidence of hepatosplenomegaly or lymphadenopathy.

### Vital Signs

Heart Rate (b/min)	105
Blood Pressure (mm Hg)	90/55
Respiratory Rate (/min)	23
Temperature (°C)	37.4
Urinalysis	pH 5.6, Prot -ve, Blood -ve

### Questions

- State your differential diagnosis.



- What further information would you seek from the history and examination?



- Outline the investigations you would perform, the costs, and the results that you would expect.



Investigations	Expected Result	Cost

*Over the next two hours the patient became hypotensive, with pale cold extremities. The serum biochemistry was as shown:*

4. What is the diagnosis, and what other investigations would you perform?



Clinical Chemistry		
Sodium (mmol/L)	133	135-145
Potassium (mmol/L)	3.8	3.5-5.0
Chloride (mmol/L)	93	95-107
Bicarbonate (mmol/L)	20	24-32
Urea (mmol/L)	8.8	3.0-8.0
Creatinine (μmol/L)	110	60-110
BSL (mmol/L)	9.6	3.0-6.0
Calcium (mmol/L)	1.95	2.10-2.55
Lipase (U/L)	425	7-60

5. What causative factor(s) are recognised in this disease, and what is known of its pathogenesis?



6. What is the pathophysiological basis for the hypotension in this case?



7. How would you manage this patient's condition? How could the severity of the condition be evaluated?



8. What complications of the patient's disease may occur in the short-term and long-term?



*Whilst the woman made a gradual recovery and was discharged after two weeks, she unfortunately experienced repeated episodes of pain over the next few years. An abdominal X-ray taken four years from the time of initial presentation was reported as showing calcification in the pancreas.*

9. How would this radiological appearance develop?



## Case protocol 44

### Case History

A 32-year-old single mother with 2 children under the age 5 comes to see you, her GP, complaining about having headaches and lack of energy. She is unemployed and divorced 6 months ago. On further questioning, she reveals that she has had little appetite and has lost 5 kg in the last two months. She struggles to fall asleep, often wakes up in the middle of night and finds it hard to get back to sleep. She has lost interest in doing things that she used to enjoy, like walking and gardening, as well as worrying about her parenting. She finds herself losing her temper easily and yells at her children, leading her to believe that she is a bad mother. She often feels like crying for no apparent reason.

On discussing the situation with this woman, you believe that she is suffering from major depression. You discuss options for therapy, including CBT and pharmacotherapy. She does not feel she can commit to CBT at the present time.

### Questions

1. What classes of anti-depressant drugs are available, and which would you prescribe in this case? Justify your answer.



2. What information would you give this woman regarding the time of onset of drug action?



3. What information would you give this woman regarding potential drug-drug interactions?



4. List the potential adverse effects of the drug class you have selected.



## Case protocol 45

### Case History

A 23-year-old man with a 15-month history of paranoid-type schizophrenia presents for review by his GP. He is currently prescribed 25mg of clozapine daily. He has been compliant with his medication for over 4 months and has remained stable in the community. Before clozapine, he had previously been prescribed quetiapine for over 5 months and more recently risperidone for 6 months, but both of those drugs failed to improve his positive psychotic symptoms.

Results of a routine non-fasting blood test revealed that he had normal neutrophil levels, clozapine was in therapeutic range, liver and kidney function was normal. However, the non-fasting blood glucose level was high at 10.2 mmol/L. On examination, blood pressure and heart rate were within the normal range. He had previously maintained a stable weight of 80 kg, but has gained 15 kg in the past 4 months. He generally feels well, but is concerned by his increase in weight.

### Questions

1. What further test(s) would you order to investigate this man's high non-fasting blood glucose level?



2. How might this man's treatment affect his blood glucose level?



3. Why was clozapine commenced more than 1 year after his initial diagnosis of schizophrenia?



4. Name two medications that may help reduce this man's blood glucose level, and describe their mode of action.



## Appendix A: Glossary of terms

**Abscess:** a localised collection of pus in an organ or tissue

**Acquired:** a lesion occurring due to an event after birth (cf. congenital)

**Acquired immunodeficiency syndrome (AIDS):** a disease caused by the human immunodeficiency virus (HIV), resulting in progressive depletion of T-cells necessary for cell-mediated immunity, leading to susceptibility to opportunistic infections and tumours

**Adenoma:** a benign neoplasm derived from glandular (secretory) epithelial cells

**Acute respiratory distress syndrome (ARDS):** respiratory failure caused by diffuse damage to type 1 pneumocytes and alveolar capillaries, often secondary to shock (hence the term "shock lung")

**Aetiology:** cause of a disease

**Agenesis:** congenital absence of an organ or structure

**Allele:** one of two alternative genes at a locus that controls a particular characteristic

**Allergen:** antigen which gives rise to allergic reactions, usually mediated by IgE antibody

**Allograft:** a tissue graft between two individuals of the same species (synonymous with homograft)

**Amyloidosis:** extracellular deposition of an insoluble protein complex, usually derived from serum proteins, with a fibrillar structure and a characteristic conformation (twisted beta-pleated sheet); deposits stain homogeneously pink with H & E, and brick-red with a Congo red stain

**Anaemia:** a significant reduction in the level of circulating haemoglobin below the normal range

**Anaphylaxis:** an acute hypersensitivity reaction, characterised by bronchospasm, peripheral vasodilatation, hypotension (shock) and oedema (especially laryngeal oedema)

**Anaplasia:** less than normal differentiation of cells; an important feature of malignant neoplasms

**Anergy:** the inability to react to a number of common skin test antigens; usually denotes depressed cell-mediated immunity (CMI)

**Aneurysm:** a localised abnormal dilatation of a vessel due to weakness of its wall

**Anorexia:** loss of appetite

**Antibody:** immunoglobulin specifically reactive with a particular antigen

**Antigen:** a substance which can induce a detectable immune response

**Aplasia:** congenital disturbance leading to failure of development of a part (synonymous with agenesis)

**Apoptosis:** a form of individual cell death, particularly observed in physiological turnover, in which the morphological changes consist of nuclear condensation and fragmentation (cf. necrosis)

**Arteriosclerosis:** refers to a group of processes in which there is thickening and loss of elasticity ("hardening") of arterial walls; it includes atherosclerosis, Mönckeberg medial calcific sclerosis, and arteriolosclerosis

**Arthralgia:** pain (of any cause) in a joint or joints

**Arthritis:** inflammation of a joint or joints; usually signified by pain (arthralgia), erythema and swelling

**Ascites:** abnormal accumulation of fluid in the peritoneal cavity

**Atelectasis:** failure of normal degree of expansion of lung or segments of lung tissue

**Atheroma:** deposition of lipid in the intimal lining of systemic arteries accompanied by reactive changes in the vessel wall

**Atherosclerosis:** the commonest disease of arteries, characterised by focal or eccentric thickening of the intima by inflammatory and fibrotic lesions associated with the deposition of lipids; a circumscribed elevated lesion is referred to as an atheromatous plaque

**Atrophy:** diminution in size of an organ or tissue which had previously reached mature size, due to a decrease in size and/or number of its constituent specialised cells (cf. agenesis, aplasia and hypoplasia)

**Autoimmunity:** a disease caused by failure of normal immunological tolerance, such that the immune system identifies "self" antigens as foreign

**Autolysis:** post-mortem digestion of tissue by its own intracellular enzymes

**Bacteraemia:** the presence of bacteria in the blood (cf. pyaemia and septicaemia)

**Benign:** in reference to neoplasms, the term indicates strict localisation, growth by expansion, and frequent encapsulation (synonymous with innocent)

**Biopsy:** sampling of tissue for diagnosis, includes excisional, incisional and needle procedures, and also subsumes many cytological procedures

**Boil:** a small abscess of the skin, usually originating in a hair follicle or sweat gland (synonymous with furuncle)

**Bronchiectasis:** abnormal permanent dilatation of the bronchi, which may be localised or diffuse, congenital or acquired; associated with a chronic productive cough and recurrent pulmonary infections

**Bulla:** a large abnormal thin-walled cavity filled with liquid or gas

**Cachexia:** extreme wasting of the body, accompanied by weakness, anorexia and anaemia; most commonly seen in the terminal phase of malignancy

**Calculus:** a stone formed in a hollow tube or viscus, e.g. gallbladder, renal pelvis

**Cancer:** often used synonymously with carcinoma (see below); also a general term for all malignant neoplasms

**Carbuncle:** a multilocular abscess resulting from extension of a boil into the subcutaneous tissues

**Carcinogen:** an agent which can cause a cell to undergo neoplastic transformation, or which may initiate such a process by permanently altering cellular DNA

**Carcinoma:** a malignant neoplasm derived from epithelium

**Carcinoma in situ:** a malignant epithelial neoplasm which has not yet invaded through the basement membrane

**Catarrh:** inflammation of a mucosal surface associated with a mucoid exudate, e.g. nasal catarrh

**Cell-mediated immunity (CMI):** immune response in which T-cells and macrophages predominate

**Cellular differentiation:** process of development of phenotypic characteristics of a mature tissue by selective gene expression

**Cellular swelling:** a mild degenerative change of cells in which the affected tissues appear somewhat pale and swollen, resulting from failure of the 'sodium pump', permitting the entry of sodium and water into the cell

**Cellulitis:** a diffuse inflammation of subcutaneous tissue extending along connective tissue planes

**Chemokines:** peptide molecules that induce chemically-directed migration of inflammatory cells – "chemoattractant cytokines"

**Chemotaxis:** chemically-directed cellular migration

**Chronic inflammation:** an inflammatory response evoked by a persistent stimulus and characterised by aggregation of inflammatory cells and tissue proliferation rather than exudation

**Circumscribed:** well defined or demarcated, e.g. circumscribed lesion

**Complement:** a series of plasma proteins involved in many aspects of the inflammatory response, including opsonisation, chemotaxis and cytotoxicity

**Congenital:** literally, "born with" a disease; a condition attributable to events prior to birth

**Cirrhosis:** a chronic diffuse condition of the liver in which necrosis of hepatocytes is accompanied by fibrosis and regeneration, resulting in destruction of liver architecture and ultimate conversion of the parenchyma into numerous nodules separated by fibrous septa

**Clone:** a group of cells, all of which are the progeny of a single cell

**Clot:** a semi-solid mass formed from constituents of the blood after death (post-mortem clot), following haemorrhage, or in vitro (cf. thrombus)

**Congestion:** an excess of blood in the vessels, resulting from too much blood being delivered by the arteries (active congestion; synonymous with hyperaemia), or too little being drained by the veins (passive congestion, as in congestive cardiac failure)

**Consolidation:** becoming firm or solid: usually applied to the lung in which the alveolar spaces are filled to varying degrees with inflammatory exudate, retained secretions, neoplastic tissue or scar tissue

**Cyst:** a sac with a distinct wall lined by flattened cells enclosing fluid or other material

**Cytokines:** protein or peptide molecules mediating pathologically significant cellular reactions

**Degeneration:** a change in structure and function caused by injury to cells; the change is often reversible

**Delayed hypersensitivity (DTH):** cell-mediated immune response elicited by the subcutaneous injection of an antigen, with subsequent oedema and inflammation which are maximal between 24 and 48 hours (cf. immediate hypersensitivity)

**Desmoplasia:** induction of connective tissue growth, usually refers to the stroma of tumours (synonymous with fibroplasia)

**Disseminated intravascular coagulation (DIC):** widespread thrombosis in the microvasculature arising secondary to another illness, resulting in consumption of platelets and clotting factors (often leading to severe haemorrhage), traumatic damage to red cells and ischaemia to vital organs; common causes include septicaemia, obstetric emergencies and malignancy

**Diverticulum:** a pouch or sac arising from a hollow organ or structure

**Dysentery:** an inflammation of the colon characterised by pain, rectal tenesmus, profuse diarrhoea, with mucus and blood in the faeces (stool)

**Dysplasia:** atypical cellular differentiation; may be observed histopathologically within neoplasms or pre-neoplastic lesions

**Dystrophic calcification:** the localised deposition of calcium salts in dead or degenerate tissue (in the presence of normal plasma levels of calcium and phosphorus)

**Dysuria:** pain or difficulty with urination

**Ecchymosis:** a large area of discolouration of skin caused by extravasation of blood into subcutaneous tissues (synonymous with bruise)

**Effusion:** abnormal collection of fluid in a body cavity

- Embolism:** the transportation by the blood of abnormal material and its impaction in a vessel at a point remote from its entry into the circulation
- Empyema:** the presence of pus in a cavity or hollow organ, e.g., empyema of gall bladder
- Epidemiology:** the study of the incidence, distribution, and determinants of disease in a population, and its application to the control of health problems
- Epistaxis:** bleeding from the nose
- Erythema:** redness of the skin resulting from vasodilatation
- Exudate:** proteinaceous fluid resulting from the selective extravasation of intravascular plasma in response to an inflammatory stimulus; exudate usually has a specific gravity exceeding 1.020 due to its relatively high content of protein and cellular debris (cf. transudate)
- Fatty change:** the abnormal accumulation of lipid within parenchymal cells
- Fibrinoid:** a descriptive term for a variety of microscopic changes that occur in various tissues under dissimilar circumstances, in which the affected tissues stain brightly with eosin
- Fibrinous:** the adjetival form of fibrin - the protein formed by interaction of thrombin and fibrinogen
- Fibrous:** literally, containing fibres; but often used in Pathology to refer to collagenous connective tissue
- Fine needle aspiration (FNA):** a form of biopsy in which a fine needle (usually 25 gauge) is inserted into an area of tissue and a number of cells are collected, then expelled onto a slide and stained for cytological examination
- Fistula:** an abnormal communication between two body surfaces (cf. sinus)
- Fracture:** a break in the continuity of bone
- Free radicals:** highly reactive molecular forms capable of causing injury
- Gangrene:** necrosis with putrefaction of macroscopic portions of tissue
- Goitre:** an enlarged thyroid gland
- Grade:** degree of malignancy of a neoplasm, judged from histological features
- Graft versus host disease:** the rejection of host tissues that are recognised as foreign by transplanted immunocompetent cells which are capable of replication - usually a complication of bone marrow transplantation; typical manifestations include skin rash, jaundice, vomiting and diarrhoea
- Granulation tissue:** consists of newly formed blood vessels, fibroblasts and their products, and inflammatory cells: the tissue of repair
- Granulomatous inflammation:** a form of chronic inflammation; characterised by focal aggregations of chronic inflammatory cells, principally activated macrophages (epithelioid cells) and their derivatives; these focal lesions are known as granulomas, and may exhibit central necrosis
- Hamartoma:** a developmental malformation consisting of an overgrowth of tissue(s) proper to the part, sometimes resembling a neoplasm (cf. haematoma)
- Haemangioma:** a developmental malformation of blood vessels (i.e. an example of a hamartoma)
- Haematemesis:** vomiting of blood
- Haematoma:** localised collection of blood or clot in solid tissues
- Haematuria:** blood in the urine
- Haemoptysis:** coughing up of blood-stained sputum or gross blood
- Healing:** the process by which the body replaces damaged tissue with living tissue; healing includes both regeneration and repair
- Hernia:** the abnormal protrusion of the whole or part of a viscus or other internal structure through an opening
- HLA (Human Leucocyte Antigen):** the major histocompatibility (MHC) genetic region in man; important in control of immune responses and graft rejection
- Humoral immunity:** immune response in which the predominant effector mechanism involves antibodies
- Hyaline:** a descriptive term for homogeneous, somewhat glassy or refractile microscopic appearance exhibited by various extracellular tissue elements or by the cytoplasm of cells
- Hydronephrosis:** Abnormal dilatation of the renal pelvis and calyces, often associated with renal cortical atrophy
- Hyperaemia:** an increased volume of blood within actively dilated vessels in an organ or part of the body (cf. congestion)
- Hyperplasia:** an increase in size of an organ or tissue due predominantly to an increase in the number of its constituent specialised cells
- Hypertrophy:** an increase in size of an organ or tissue due predominantly to increase in size of its constituent specialised cells
- Hypoplasia:** the failure of development of an organ to a full, mature size (cf. aplasia)
- Iatrogenic:** implies 'caused by doctors', incorrectly derived from Greek root
- Immediate hypersensitivity:** immune response elicited within a few minutes after exposure to an antigen (allergen) due to the presence of preformed IgE antibodies; demonstrable after intradermal injection as a wheal with surrounding vasodilatation

**Immunity:** a state of reactivity following exposure to an antigen

**Infarct:** circumscribed ischaemic necrosis of tissue resulting from interference to blood flow, usually arterial

**Infection:** the invasion of the body by pathogenic micro-organisms

**Inflammation:** the process by means of which exudate and cells accumulate in irritated tissues and usually tend to protect them from further injury; may be acute or chronic –when unqualified, the term "inflammation" usually refers to acute inflammation

**Inspissated:** thickened, e.g. inspissated mucus obstructing an airway

**Interleukins:** a subset of cytokines originally construed to mediate leucocyte interactions

**Ischaemia:** a state of inadequate blood supply to a tissue or organ - potentially reversible

**Karyolysis:** loss of basophilic staining of the nucleus due to the action of DNase, often seen in necrotic cells (cf. pyknosis, karyorrhexis)

**Karyorrhexis:** fragmentation of the nucleus of a necrotic cell (cf. pyknosis, karyolysis)

**Keloid:** hypertrophic cutaneous scar, in excess of that necessary to heal the original defect

**Lesion:** an alteration of structure or of functional capacity due to injury or disease

**Leucocytosis:** an elevated number of circulating white blood cells

**Leucopenia:** a decreased number of circulating white blood cells

**Leucoplakia:** a lesion characterised by whitish thickening of mucosal epithelium

**Lithiasis:** formation of stones (calculi), e.g., nephrolithiasis, cholelithiasis

**Lymphokines:** soluble products of lymphocytes (especially T-cells) involved in cell-mediated immune responses (cf. cytokines)

**Malignant:** literally means virulent or life-threatening; in reference to neoplasms, the term indicates rapid growth, invasion of neighbouring tissues, potential for spread by metastasis, and frequently a fatal outcome; the single most important histopathological criterion of malignancy is tissue invasion

**Melaena:** tarry black coloured faeces due to altered blood from haemorrhage into the bowel, usually from the stomach or duodenum

**Metaplasia:** an adaptive substitution of one type of differentiated cell(s) by another type of differentiated cells

**Metastasis:** in reference to malignant neoplasms, the term refers to the development of secondary growths which arise from, but are discontinuous with, the primary lesion; such is termed a metastasis or metastatic lesion (synonymous with secondary)

**Metastatic calcification:** precipitation of calcium salts in apparently normal tissue as a result of disturbed calcium-phosphorus metabolism (e.g., hypercalcaemia) (cf. dystrophic calcification)

**Monoclonal:** attributable to a single clone of cells, and so more characteristic of a neoplastic than a reactive process (polyclonal)

**Morphology:** the structure of tissues and organs

**Mutagen:** an agent capable of damaging the DNA structure of cells; initiators of neoplastic transformation are mutagenic

**Necrosis:** death of cells in a restricted portion of tissue, recognisable by the autolytic changes undergone after the cells have died

**Neoplasm:** an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissues, and persists in the same excessive manner after cessation of the stimuli which evoked the change

**Occult:** hidden, concealed, not evident; as 'occult blood in faeces' requiring special techniques for detection

**Oedema:** excessive accumulation of fluid causing swelling of tissues

**Oliguria:** abnormally low urine output (< 400 mL/day)

**Organisation:** a part of the healing process, occurring after an injury that has destroyed tissue which is unable to regenerate; involves the ingrowth of granulation tissue

**Paraneoplastic:** effects of a neoplasm not related to either the primary tumour mass or metastatic tumour deposits, e.g. abnormal hormone production, cachexia, etc.

**Paraprotein:** an abnormal band on serum protein electrophoresis, due to a monoclonal immunoglobulin and often associated with B cell neoplasia

**Pathognomonic:** characteristic/diagnostic of a particular disease

**Pathogenesis:** mechanism(s) by which the cause (aetiology) of a disease produces the clinical manifestations

**Pathology:** the scientific study of diseases

**Peptic ulcer:** an ulcer occurring in a portion of the alimentary tract exposed to the effect of gastric acid and pepsin

**Petechiae:** minute rounded spots of haemorrhage on skin, mucous membrane or cut surface of an organ; singular = petechia

**Phagocytosis:** ingestion of foreign or particulate matter by cells

**Phlebothrombosis:** formation of a thrombus in a vein

**Polymerase chain reaction (PCR):** a molecular diagnostic technique based on amplification by DNA polymerase of a known sequence of genomic DNA isolated from cells, or of DNA reverse-transcribed from mRNA or viral RNA; permits rapid, sensitive and specific detection of e.g. genetic mutations

**Polyp:** a projecting mass of tissue arising from an epithelial surface; may be composed of neoplastic, inflammatory or other tissues, found especially on mucous membranes

**Prognosis:** forecast of the outcome of an illness, based on the natural history of the disease and the likely response to treatment

**Promoter:** an agent, not acting as a mutagen, which causes an initiated cell or cell population to complete the process of neoplastic transformation

**Proto-oncogene:** a gene present in the normal cell (e.g. *RAS*, *MYC*); when one allele is inappropriately activated may cause or accompany the onset of cellular neoplastic transformation

**Purpura:** bleeding into the skin and/or mucous membranes, e.g. petechiae (pinpoint), ecchymoses (bruises)

**Pus:** typically a semi-fluid of creamy colour, pus is composed of necrotic and living neutrophils, together with necrotic tissue cells and exudate

**Putrefaction:** decomposition of organic matter by micro-organisms, accompanied by the development of disagreeable odour

**Pyaemia:** the presence of pus-inducing micro-organisms in the circulation with resultant formation of abscesses at sites of their lodgement (cf. bacteraemia and septicaemia)

**Pyknosis:** shrinkage and increased basophilic staining of the nucleus in a necrotic or apoptotic cell, caused by reduced pH (cf. karyolysis, karyorrhexis)

**Regeneration:** replacement of parenchymal cells by multiplication of similar surviving cells

**Repair:** replacement of lost tissue by connective tissue elements and parenchymal cells in varying proportions; when replaced completely by granulation tissue, which later matures to fibrous tissue, the result is referred to as a scar

**Resolution:** the return of a diseased tissue or organ to normal without residual scarring

**Sarcoma:** a malignant neoplasm arising from mesenchymal tissue

**Sclerosis:** hardening of tissue, especially from overgrowth of fibrous tissue

**Septicaemia:** severe infection with marked systemic clinical features; septicaemia is usually the expression of rapid and continuous invasion of the blood stream by microorganisms from the tissues, or multiplication in blood stream (cf. bacteraemia and pyaemia)

**Shock:** a clinical state in which there is widespread inadequate perfusion of tissues

**Sign:** a clinical feature identified by observation or examination of the patient (cf. symptom)

**Sinus:** in Pathology, this relates to an abnormal communication between a lesion (e.g., an abscess) in an organ, and an overlying surface (e.g., skin) (cf. fistula)

**Staging:** assessment of the size and extent of spread of a malignant neoplasm, important in determining the treatment and prognosis

**Stem cell:** a primitive cell from which differentiated cells arise during development, renewal and maintenance

**Suppuration:** the formation or discharge of pus

**Symptom:** a manifestation of disease which the patient may be aware of, or describe

**Syndrome:** a group of symptoms and signs which, when considered together, characterise a disease or lesion

**Telangiectasis:** a cluster of dilated malformed blood vessels (usually capillaries) producing a small red focal lesion, most common in skin or mucous membranes

**Teratogen:** an environmental agent which acts in utero to cause abnormal development, resulting in malformation of the fetus; teratogens include infective agents, radiation, drugs and chemicals

**Teratoma:** a true neoplasm arising from totipotential cells and therefore composed of numerous tissues which may not be indigenous to the part in which it occurs

**Thrombophlebitis:** inflammation of a vein (phlebitis) with associated thrombosis

**Thrombus:** a solid or semi-solid mass formed from the constituents of blood within the intact vascular system during life (cf. clot)

**Tolerance:** a state of non-responsiveness of cells of the immune system to a particular antigen

**Toxaemia:** the presence in the blood of toxic products produced by bacteria or formed in body cells

**Transudate:** fluid accumulated in tissue planes or spaces which is low in protein and which has leaked into the tissues from the micro-circulation; it occurs in non-inflammatory disorders such as congestive cardiac failure and venous obstruction (cf. exudate)

**Tumour:** a lump or swelling; however, the term is frequently used as a synonym for neoplasm

**Tumour suppressor gene:** a gene present in normal cells, which acts to suppress cellular proliferation (e.g. *TP53*, *RB*); when both alleles are inactivated, may cause or accompany the onset of neoplastic transformation

**Ulcer:** a lesion resulting from a circumscribed loss of surface epithelium of variable depth, often accompanied by inflammation of the adjacent tissue

**Vesicle:** a small blister

**Western blotting (immunoblotting):** a molecular diagnostic technique involving separation of proteins by gel electrophoresis, transferring them to a solid membrane via a blotting procedure, incubating with specific antibodies and applying a sensitive technique for detection of bound antibody; often used to detect specific proteins (e.g. viral) present in the serum

**Zoonosis:** a disease "accidentally" transmitted to humans from an animal host

## Appendix B: Appropriate specimens and laboratory investigations to document in the Clinical Skills Acquisition Logbook

### Anatomical Pathology:

- processing, embedding, sectioning and staining of tissues for histopathological examination (this is a separate activity from the cut-up session attended)
- fine needle aspiration biopsy (FNAB)
- frozen section
- immunofluorescence
- electron microscopy

### Haematology:

- FBC, peripheral blood film
- ESR
- bone marrow aspiration and biopsy
- cytogenetics and flow cytometry

### Clinical Biochemistry:

- liver function tests, renal function tests, CRP
- ABG
- Lipid studies
- BSL and HbA1C
- Troponins
- Joint fluid analysis
- CSF analysis

### Clinical Pharmacology (usually part of Clinical Biochemistry Laboratory)

- Clinical data required to interpret a plasma drug concentration result
- Interpreting a plasma drug concentration result
- Appropriate dose selection based on drug concentration result

### Microbiology:

- Specimens: blood culture, urine, sputum, joint fluid, CSF, deep wound swab, tissue.
- Microscopy, culture and sensitivity (MCS) testing, including Gram staining
- Serology (HIV, Hepatitis, syphilis)
- PCR/nucleic acid amplification, Multiplex PCR
- Antigen tests

### Immunology:

- Autoantibodies (ANA, RF, ACPA)
- Allow cytometric analysis of lymphocyte subsets
- HIV infection/exposure
- Allergy tests
- Serum immunoglobulins, protein electrophoresis and immunofixation

### Molecular Genetics:

- antenatal screening
- screening for genetic predisposition to specific cancers
- molecular profiling of cancers
- tests may include FISH, karyotype, CGH array, SNP array, MLPA, Sanger sequencing, next-generation sequencing (including whole exome sequencing WES, and whole genome sequencing WGS), RNA sequencing, methylation arrays, etc.

## Appendix C: Online Tutorials linked from Moodle

Online Clinical Pharmacology modules via the National Prescribing Service (NPS), which students must satisfactorily complete by the end of Phase 3.

### Online tutorials on:

- Antibody abnormalities
- Fluid Balance – Clinical Assessment and Management
- Liver Function Tests
- Thyroid Function Tests
- Tests for Thrombophilia
- Pain Management Adaptive Tutorial
- Bone Marrow Biopsies

### Online tutorials covering Diagnostic Imaging:

- Introduction to CT imaging
- CT Scan Formative Feedback Quiz
- Introduction to Molecular Imaging
- Introduction to Magnetic Resonance Imaging (MRI)
- Introduction to Head CT Part 1
- Introduction to Head CT Part 2
- Head CT Test Cases
- Introduction to Chest CT Part 1
- Introduction to Chest CT Part 2
- Chest CT Test Cases
- Introduction to Common Fractures on X-ray Part 1
- Introduction to Common Fractures on X-ray Part 2
- Common Fractures on X-ray Test Cases
- Introduction to Ultrasound Imaging
- Introduction to Basic Targeted Ultrasound Part 1
- Introduction to Basic Targeted Ultrasound Part 2
- Ultrasound Test Cases

### Online tutorials on coagulation studies and interpretation of blood films:

- Simple Coagulation Studies
- Blood Film Interpretation - Red Cells
- Blood Film Interpretation 2 - White Cells
- Blood Film Interpretation 3 - Platelets
- Blood grouping, Crossmatch and Transfusion
- Immunoglobulins in Health and Disease

### Online adaptive tutorials covering clinical Anatomy:

- A lump on the testis
- A medley of upper limb nerve damage
- A problem with reflux
- Abdominal pain in a young adult
- Central chest pain
- Cough and blood-stained sputum
- Fracture clinic: Lower limb
- Fracture clinic: Upper limb
- Gnawing pain in the upper abdomen and weight loss
- Haematuria for three months
- Heavy periods and colicky menstrual pain
- Loin to groin pain
- Obstructed delivery
- Per rectal bleeding
- Problems passing urine
- Right upper quadrant pain and fat intolerance
- Throat pain and voice changes
- Upper abdominal pain and haematemesis
- What organ is that?

10 eLearning modules by the Royal Australian and New Zealand College of Radiologists (RANZCR).