

Clinical Pathology III

Only Study Guide for BMI3707

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Clinical Pathology III

WELCOME MESSAGE

Welcome to Clinical Pathology III. We hope this course will broaden your understanding of Clinical Pathology, and help you further your studies.

Welcome Note

Welcome to Clinical Pathology (BMI3707). Pathology is essentially the study of **disease**. This module is an introductory course, and will focus on human systems pathology. Although there are thousands of diseases that can affect humans, this course will focus on just a few in order to give you a general understanding of the disease process and its underlying mechanisms. This will enable you to recognise the medical clues that will help you identify the cause of a problem presented to you. As a student studying pathology, you will be required to think like a doctor or specialist pathologist.

Welcome to Clinical Pathology (BMI3707). Pathology is essentially the study of **disease**. This module is an introductory course, and will focus on general human pathology. Although there are thousands of diseases that can affect humans, this course will focus on just a few in order to give you a general understanding of the disease process and its underlying mechanisms. This will enable you to recognise the medical clues that will help you identify the cause of a problem presented to you. As a student studying pathology, you will be required to think like a doctor or specialist pathologist.

This module is a 12-credit course, which means that you will need to devote at least **120 study hours** to it. You will need to prepare a portfolio. The myUnisa website will be the main teaching medium for this module. Please visit this site frequently to interact with fellow students and to participate in discussions about certain topics that we will be covering. Try to be online at least once a week. I will say more about the structure of the course in the next sections.

Course Information

How this course is organised

Before you begin studying the first learning unit, I would like to give you some details about the module as a whole. This guide consists of seven units:

- Learning unit 1: Cardiovascular diseases
- Learning unit 2: Pulmonary diseases
- Learning unit 3: Gastrointestinal diseases
- Learning unit 4: Gynaecological diseases
- Learning unit 5: Central nervous system diseases
- Learning unit 6: Endocrine diseases
- Learning unit 7: Genitourinary diseases

Recommended textbook

The textbook for BMI3707, which you will be using in conjunction with the online material or study guide, is:

Finlayson, C. J. and Newell, B. A. 2009. Pathology at a glance. Chichester, UK, Wiley-Blackwell. ISBN: 978-1-4051-3650-1

The textbook is an introductory guide to pathology. This course will focus on general pathology, and provide you with a basic knowledge of pathology in humans. The online study material will guide you in terms of what you need to learn. You will need to study all the recommended reading sections and any other sections that may be mentioned in the study guide. If you find a topic particularly interesting, you are more than welcome to do further reading about it.

Please note that if you purchase the latest edition of the textbook, you may find that the pages in the study guide do not directly correlate to the pages in this latest edition of the textbook. However, I am sure that you will find it easy to locate the relevant section, rather than the specific pages, in the newer textbook.

In the study guide I will refer to the textbook as **Finlayson and Newell**.

This introductory course deals with the fundamentals of pathology. We will be applying and adapting the disciplines of biochemistry, microbiology, molecular biology, physiology, immunology and genetics as foundation studies to investigate changes in human cells, tissues or organs that affect various aspects of health and disease in humans. The purpose of this module is to enable you to identify and apply practices, processes and principles of pathology to solve problems relating to health and disease.

I hope that you will find this module interesting, and that it will give you an overview of some basic principles of pathology that are applicable to the biomedical sciences. What makes this subject matter even more exciting is that you will be able to apply it in other courses and in your daily lives. For example, you might be asked to identify and explain the principles governing the impact of infection by human immunodeficiency virus (HIV) on the human body. You would be able to respond and say that infection with HIV contributes to a defective immune system that, in turn, may allow unchecked changes in cell division and growth (i.e. the development of cancer cells) or allow microorganisms to damage human tissue.

Distance learning

Distance learning is very different from learning in a contact situation. Once you have received your study material, please plan how you will approach and complete this module. Draw up a reasonable study schedule for the whole module. Remember to include the assignment due dates as given in Tutorial Letter 101.

Independent study

A crucial element in understanding and learning the basics of pathology is the ability to express your ideas both orally and in writing. Only when you have tried this for yourself will you understand the full value of this exercise.

Assessment measures an aspect of your success. For this module there is both formative (ongoing) and summative (final) assessment in the form of assignments and examinations. These are mainly in the form of written work. Your reflections on your learning are therefore also an important part of your studies. Since the focus in this module is on understanding and applying the concepts of pathology, assessment will focus on the competencies you need to display. Work through your study guide, making use of the guidelines in the next section. Construct mind maps and make your own summaries of the objectives and content of chapters of the textbook. Restrict summaries to one page. Additional textbooks and articles give alternative views or provide more insight into issues under discussion, and are optional additional reading.

Be focused. Build up your own study and exam preparation **portfolio** (consisting of your assignments, activities, reflections, summaries, self-evaluations and notes) throughout your academic and/or experiential learning. **The lecturer will not assess this portfolio, but you will need to prepare it in order to be able to complete the assignments and ultimately pass the final examination.** It is also very important to use this portfolio, in combination with your assignments and subsequent feedback (tutorial letters), for your **exam preparation**. The advantage is that by doing this you take part actively in your learning, you set goals, you evaluate your own progress through reflective actions, and you evaluate your ability to realise the learning outcomes, thus becoming a more independent and self-directed learner.

What is a portfolio? A portfolio is a folder or file in which you gather and compile additional and/or summarised information during the year as you work through the study guide and textbook. This portfolio will help you to prepare for the examination by focusing on the most important facts and issues.

Your portfolio should comprise:

- answers to each activity in each learning unit
- a mind map/summary of each learning unit
- your marked assignments (or a copy you made prior to submitting your assignment)
- your reflections on each learning unit
- extra reading material taken from the internet, additional books, and medical and/or scientific journals
- a new vocabulary of words or glossary of new terms defined in your own words

To help you, in the next sections I provide some study skills guidelines you may find helpful.

Improved study skills

It is critical that you think independently and learn to look beyond the study guide and textbook. I have included a number of additional references in this study guide, and I really encourage you to consult them. In addition, as a more advanced distance-education student, you need to learn how to search for research/scientific articles via the internet.

How to search for research/scientific articles

Google has created an additional search engine under “Advanced search”, called Google Scholar. This has its own advanced search function. If you state your subject query in four to six words and press “Search enter”, a variety of websites relating to the query will appear. This has the advantage of allowing you to access most of the journal references from any internet site in addition to myUnisa. Some journals, however, such as Science Direct, can be accessed only through a tertiary academic institution such as Unisa. To access this journal:

1. Go to Unisa online at <http://www.unisa.ac.za/>
2. Click on Library at the top of the page.
3. In the maroon area on the top of the page, click on “Search for information resources”.
4. Follow the guidelines if you are a first-time user.
5. Click on the option “A–Z list of the names of all electronic resources” on the right-hand side of the page.
6. Various links for databases will now appear on your screen. Click on any database to do a search. For biotechnology I recommend Science Direct, Nature or Springer Link.
7. Once you have entered one of these databases, you can search for scientific articles by typing keywords in the “Search” box. Use specific keywords. If you type in just a single, general word, you will usually get too much information, and it won’t necessarily relate to the topic you are looking for.
8. You will need to do some independent searches yourself for your portfolio, assignments and exam preparation.

Contact the Unisa Library at +27 12 4293206 if you have any difficulties or if you need assistance, or consult the library website for the telephone number of your local branch library.

Skimming, scanning and study-reading strategy (SSS strategy)

The SSS strategy is one of a number of strategies you may find helpful. The three techniques in the SSS strategy are:

- skimming,
- scanning and
- study-reading.

Skimming

1. **Page through and explore.** First, read the section, chapter or unit quickly, forming a rough idea of the content. Concentrate on headings and subheadings, any words or phrases in bold or italics, text in boxes, tables and illustrations, and – in the case of a chapter or unit – introductions and summaries. The objectives set for a unit or chapter are important. (Think of how you would page through a magazine. When starting a new study unit, scan it and concentrate on the concepts that catch your eye.)
2. **Make a cursory survey.** As you read, ask yourself: What key terms occur in this section, unit or chapter? Stop when you identify a key term, read carefully what is said about it, and mark it so that you will be able to find it again easily later when you need to. Your key question at this point is: **Where?**

Scanning and reflecting

3. **Scan** the section, chapter or unit.
4. **Start a mind map** (either for the whole section, unit or chapter or for parts of it). You are looking for items and concepts while reading the information in the section, unit or chapter in a more evaluative way. Reflect on relationships between concepts. The question now is: **What?** What is the meaning and the purpose? Visualisation is important, and at this point you begin to write down key concepts.
5. **Deeper reflection.** As you work through the prescribed activities of the section, unit or chapter, keep returning to the mind map to fill in the detail. Reflect on the value and meaning of categories, concepts, motivations, variables and key terms.

Study-reading

6. **Study-read.** There is a close relationship between this stage and stages 2, 4 and 5. Read carefully, thoroughly and thoughtfully. During this stage you link the key terms and concepts you have already identified, and this is where the mind map and summaries are important. (Remember to put your detailed mind map in your portfolio.) Pause while reading, consolidate what you remember and consider how new information fits in with what you already have.
7. **Activity-based approach**
Whenever you get to an activity in your study guide, complete it in full on loose pages which you then insert in your portfolio, grouped together per section and study unit. Supplement this with your own notes. (You do not need to submit activities or the portfolio to the lecturer, but these are essential for exam preparation.)

8. Understanding what you read

Whenever you get to an activity in your study guide, complete it in full on loose pages which you then insert in your portfolio, grouped together per section and study unit. Supplement this with your own notes. (You do not need to submit activities or the portfolio to the lecturer, but these are essential for exam preparation.)

Managing your self-paced study time

If you are an average student, you need to devote at least **120** study hours to this module (however, this time may vary substantially). You should therefore plan to devote at least **8** study hours per week to the module, in which case you should complete it in **15** weeks. If you have registered for more than one module, you need to plan time for each module accordingly. I advise you to keep a study schedule or diary, so that you have a clear idea of the time you have available for study. This will help you to manage your studies within the time you have available, and balance study with work and family life. In Tutorial Letter 101 you will find a list of due dates for the assignments, so enter these in your diary. Divide the large assignments into a series of smaller tasks to complete one step at a time.

In order to manage your workload, study frequently and regularly. Establish a routine in an environment with low noise and good lighting. Reward yourself after a productive session.

Academic specialist guidance

If you need help, please contact the staff of the Department of Life and Consumer Sciences who are responsible for this module.

Plagiarism

Never try to pass off other people's work (and that includes Unisa study material) as your own. If you want to quote other people's words and ideas or Unisa study material in your own answers, you must use quotation marks and acknowledge your source. (Use the Harvard method.) If you are unsure about the correct way of acknowledging sources, contact Unisa's Library Information Desk.

Students who fail to acknowledge quotations or who draw on lecture notes and other sources without acknowledgment or who copy someone else's answers may be refused permission to write the examination, or may be penalised in the assignment.

Assessment

Assessment measures an aspect of your success. For this module there is both formative (ongoing) and summative (final) assessment in the form of assignments and examinations. In addition to learning a new subject (essentially a new language), it is important for you to reflect on the subject and also on your process of learning.

In conclusion

After reading this general introduction you should have a better understanding of what the module involves and how you should approach your studies in Clinical Pathology.

Getting started

To get to know your online environment and fellow students, I would like you to do an activity called an ice breaker.

This activity will help you to

- understand the technologies that will be used in the course
- get to know and connect with your fellow students

For this ice breaker, you need to create a blog entry.

Ice breaker: personal blog entry

Create your own blog entry and share your thoughts on the following: How do you think your life may have been affected if there were no pharmacotherapeutic agents (medicinal drugs)?

Go to the Blog tool by clicking on Blogs in the tool list on the left-hand side of your screen. You will find the instructions on how to use the blog in the FAQ section in the tool list on the left-hand side of your screen.

You can add links, bullets, lists and colour if you would like to, by using the editing buttons. You can also go back and edit your blogs. The next time I ask you to use the blog, you just click on "Add blog entry" again, and create a new blog, which will appear under your name.

CLINICAL PATHOLOGY III

SYSTEMS PATHOLOGY

Introduction

An organ system is a group of anatomical structures that work together to perform a specific task. Although we learn about each organ as a distinct entity, the functions of the body's organ systems overlap considerably, and the body could not function without the cooperation of all of its organ systems. In fact, the failure of even one organ could lead to severe disability or even death.

This module will provide students with information on the diagnosis of diseases based on laboratory analyses of histological changes in samples, using the tools of biochemistry, microbiology and physiology. The knowledge gained from this module will enable students to understand concepts related to diseases from a multi-dimensional perspective.

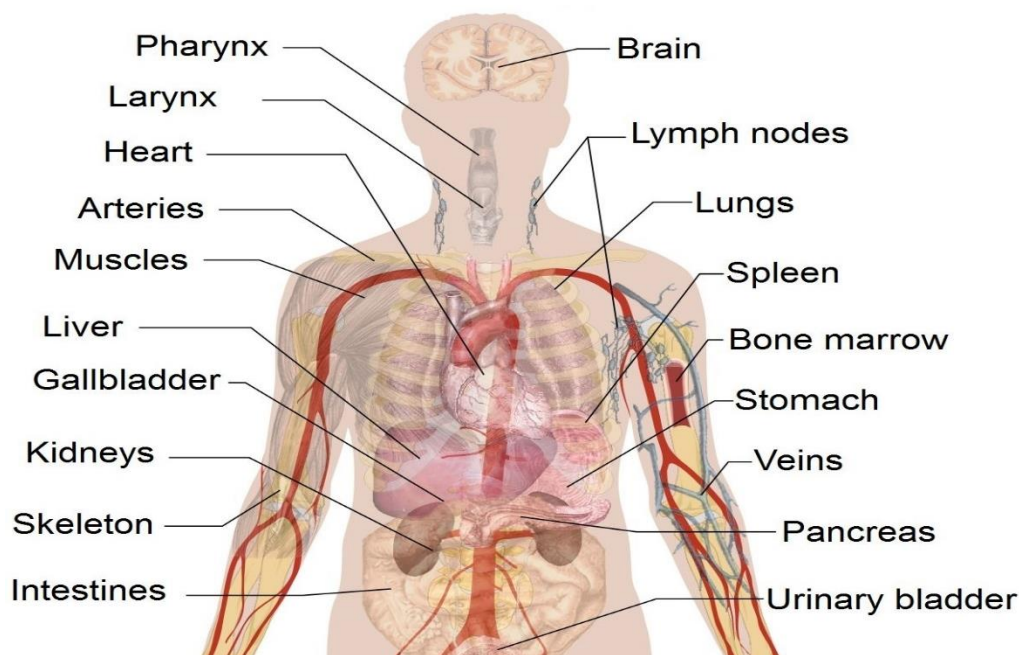


Figure 0.1: Human organ system

(<https://humananatomy-libs.com/wp-content/uploads/2017/06>)

Systems pathology is the study of structural, biochemical and functional changes – in cells, tissues and organs – that underlie disease, through the integration of clinical, morphological, quantitative and molecular parameters, using mathematical analytical frameworks. In practice,

systems pathology aims to personalise therapy and predictive outcomes for patients. It does so by seeking to integrate all levels of functional and morphological information into a coherent model that enables us to understand perturbed physiological systems and complex pathologies in their entirety (Saidi *et al.*, 2007).

Clinical systems pathology is an approach that deals with the specific problems of a particular patient, using the tools of complex science to arrive at a solution(s) to the clinical problem (Saidi *et al.*, 2007; Donovan *et al.*, 2009a; Faratian *et al.*, 2009). It answers case-specific diagnostic, prognostic and predictive questions, thus embodying personalised medicine. Eventually it is hoped that the predictive/prognostic power will be so enhanced that the disease course in a given patient can be modelled and projected into the future, thus providing a medical forecast that is specific for each patient, rather than based on the aggregate outcome data obtained from a cohort.

LEARNING UNIT 1: CARDIOVASCULAR DISEASES

1.1 Introduction

The cardiovascular system comprises the heart and blood vessels. Cardiovascular disease (CVD) is defined as any serious, abnormal condition of the heart or blood vessels (arteries and veins) that may result from a number of causes, including the build-up of plaque in the blood vessels and heart. As a result of the plaque, the blood vessel walls thicken, making it difficult for blood to reach various parts of the body. This damage can lead to heart attack, stroke or death.

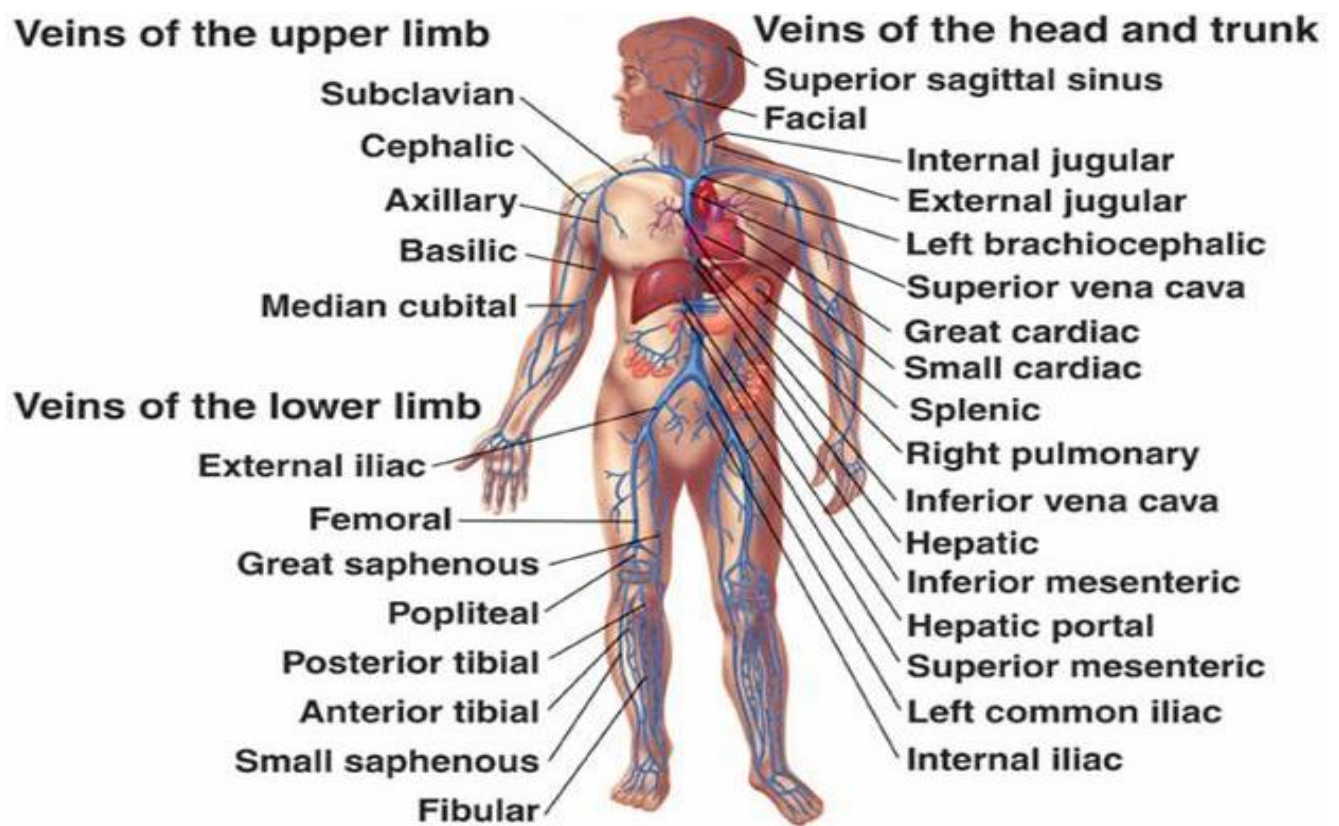


Figure 1.1: Human cardiovascular system

(<http://www.clubupton.com/wp-content/uploads/2017/03/body-veins-and-arteries-images-human-blood-circulatory-anatomy-diagram.jpg>)

To complete this learning unit, you will need to refer to chapters 32–40 in Finlayson and Newell (2009).

1.2 Learning outcomes

Upon completion of this learning unit you should be able to

- define cardiovascular diseases.
- describe the aetiology, epidemiology, pathogenesis, prognosis and treatment of cardiovascular diseases.
- distinguish between normal endothelium, and the types and complications of aneurysms.
- discuss different cardiovascular diseases.
- describe the functions of stimulated and unstimulated endothelial cells.
- describe the subtypes of capillary endothelium.
- distinguish between cyanotic and acyanotic congenital heart diseases.
- discuss the control, causes and complications of systemic hypertension.
- distinguish between atherosclerosis and arteriosclerosis.
- describe angina pectoris and myocardial infarction.
- describe the pathologically significant locations of thrombus.
- distinguish between thromboses and emboli.
- describe disseminated intravascular coagulation.
- describe the causes of cardiac valvular disease.
- distinguish between hypertrophic, dilated and restrictive cardiomyopathy.
- describe myocarditis, pericarditis, constrictive pericarditis and cardiac tamponade.

1.3 Cardiovascular disease

Cardiovascular disease includes the following:

- a) Rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria
- b) Congenital heart disease – malformations of the heart structure, existing at birth
- c) Deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs
- d) Systemic hypertension
- e) Atherosclerosis
- f) Ischaemic heart disease
- g) Thrombosis
- h) Embolism and disseminated intravascular coagulation
- i) Cardiac valvular disease
- j) Myocardial and pericardial disease.

Each disorder has been characterised epidemiologically, but their incidence and prevalence rates may vary widely, both demographically and culturally. We will discuss each of the disease categories, their individual epidemiology, aetiology and risk indicators, as well as their primary prevention, diagnostic assessment prognosis and treatment. Although many cardiovascular diseases are preventable, they are still labelled the number one killer, accounting for over 30 per cent of mortalities worldwide each year: they account for 50 % of all deaths in many developed countries, and more than 50 % in Africa and Western and Southeast Asia. They are

also the major cause of death in adults. In addition, many cardiovascular incidents are not necessarily fatal, but may impair the individual's ability to lead a normal daily life, resulting in enormous healthcare costs (estimated at R 700–2 100 billion per year) to society.

1.4 Normal blood vessels and types of aneurysm

1.4.1 Endothelium

Endothelium is a type of epithelium tissue that lines the interior surface of blood vessels and lymphatic vessels, forming an interface between circulating blood or lymph in the lumen and the rest of the vessel wall. It is a thin layer of simple squamous cells called endothelial cells.

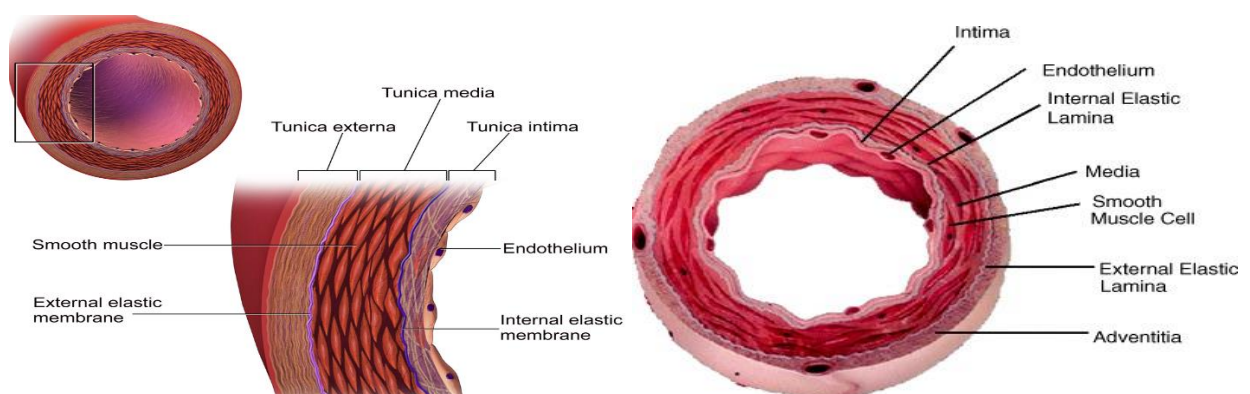


Figure 1.2: Normal arterial wall

(https://upload.wikimedia.org/wikipedia/commons/thumb/c/c8/Blausen_0055_ArteryWallStructure.png/1200px-Blausen_0055_ArteryWallStructure.png)

Endothelial cells (EC) are flattened cells that form the inside lining of the entire vascular tree, and they are amongst the most metabolically active cells. They develop from embryonic mesodermal cells, rather than from epithelial cells.

The properties of endothelial cells vary along the vascular tree.

For example:

- a) Larger vessels are more liable to endothelial damage by shearing forces and contain more Von Willebrand factor (vWF).
- b) At the capillary level, the endothelium is freely permeable to gases and also allows metabolites along concentration gradients (though less quickly and freely than gases).

Two of the most important of the many functions of unstimulated endothelium are

- maintenance of peripheral vascular resistance; and
- prevention of thrombosis (antithrombotic).

Many different agents can activate the endothelium. Activation induces new or increased gene expression of the following:

- a) Adhesion molecules
- b) Cytokines
- c) Growth factors
- d) Vasoactive mediators
- e) major histocompatibility complex (MHC) molecules (MHC I is constitutively expressed but increases with stimulation, while MHC II is occasionally induced).

Some changes in endothelial cells are rapid in onset (take minutes), for instance, reversible vasodilation and increased permeability are associated with histamine release or exposure to tissue factor (TF) on the cell surface. New protein synthesis or the alteration of gene expression, however, requires hours or days to complete. Damaged endothelium loses its antithrombotic properties and its surface becomes thrombogenic and abnormally adhesive to inflammatory cells. Increased numbers of MHC I molecules are displayed on the cell surface. This is important in initiating thrombosis and atherosclerosis. In addition, endothelial cells play a key role in angiogenesis and are important in healing and repair, as well as neoplasia.

1.4.2 Capillary endothelium

The structure of capillary endothelial cells varies with their anatomical location. The capillary endothelium is divided into three subtypes, depending on tissue type:

- a) **Continuous** – typical of skin, muscle, lungs and (most importantly) the nervous system, where the very tight cell–cell junction protects the brain from the blood-borne entry of damaging agents (the blood-brain barrier). The basement membrane layer is complete, sheathing the capillary and adding an extra layer of protection.
- b) **Fenestrated** – this is typical of renal glomeruli and intestinal villi; there are gaps between endothelial cells through which fluids and solutes can pass freely, though larger molecules (e.g., albumin, other plasma proteins) and blood cells are retained. The basement membrane is intact, and solutes and fluids must filter through the mesh.
- c) **Discontinuous** – this is typical of liver or splenic sinusoids. Large gaps exist between endothelial cells with corresponding basement membrane defects. Erythrocytes and plasma proteins pass freely through the gaps. The blood eventually drains back into the veins. Leucocytes can also pass through, while macrophages line the sinusoids and engulf bacteria and other particles, removing them from circulation (particularly in the spleen, where blood-borne pathogens can be presented to lymphoid tissue for an immune

response). Lymphatic endothelium is discontinuous in the bulb-like sacs in which the lymph vessels originate and becomes continuous as the blood vessel calibre increases; a muscle layer develops in the walls of medium-sized and larger lymphatics.

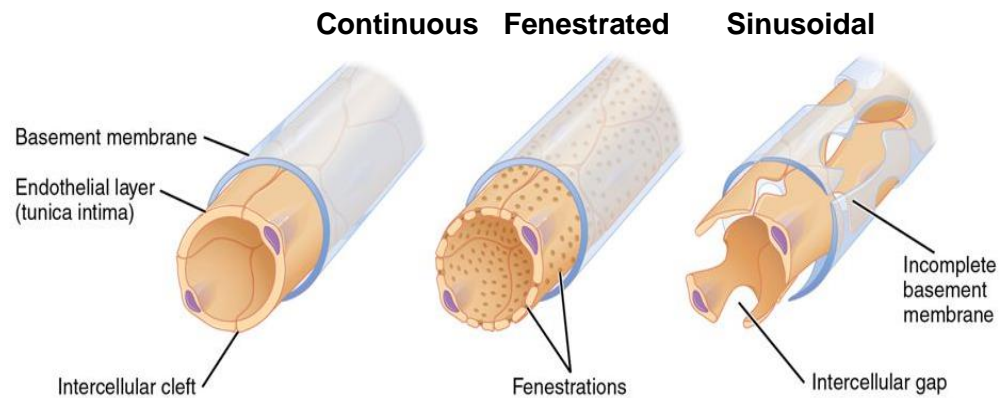


Figure 1.3: Types of capillary endothelium

(https://opentextbc.ca/anatomyandphysiology/wp-content/uploads/sites/142/2016/03/2104_Three_Major_Capillary_Types.jpg)

1.4.3 Normal endothelial cell function

Normal endothelial cell function primarily involves regulated mediator secretion or altered surface protein expression, which is vital for normal homeostasis. Functions include

- a) acting as an anti-thrombotic
- b) maintaining vascular tone through vasoconstrictor and/or vasodilator actions
- c) metabolising hormones and lipoproteins
- d) transferring gases and
- e) delivering solutes or hormones to, and removing toxic metabolites from, tissues.

1.4.4 Activated endothelial cell function

1) Endothelial activation describes the proinflammatory and procoagulant state of the endothelial cells lining the lumen of blood vessels. Activation of the endothelial cell function occurs through stimulation by

- a) cytokines and bacterial products
- b) Complement system
- c) haemodynamic stress
- d) lipid products
- e) advanced glycation end products
- f) hypoxia and
- g) viruses.

- 2) It participates in inflammatory and coagulatory responses.
- 3) It upregulates leucocytes adhesion molecule expression on surfaces.
- 4) EC contracts in response to chemical mediation, increasing the gap between EC and increasing vascular permeability.
- 5) Secretes platelet-derived growth factor (PDGF) to stimulate fibrogenesis, secretes other growth factors to stimulate repair, and vascular endothelium growth factor (VEGF) to stimulate the growth of new vessels (neovascularisation).

1.4.5 Injured endothelial cell function

Damaged endothelial cells have several functions:

- 1) When injured they become pro-thrombotic through the upregulation of TF, vWF and endothelin-1 (ET-1).
- 2) TF, synthesised and expressed on the surface, initiates coagulation cascades.
- 3) Factor VIII (F VIII) moves from storage granules to surface bind platelets and participate in coagulation cascades.
- 4) ET-1 is a potent vasoconstrictor in health, but in disease it also stimulates cell migration, proliferation and fibrogenesis.
- 5) In injured state: stimulation of smooth muscle cell (SMC) migration, proliferation and secretion of collagen, elastin and proteoglycans through PDGF, ET-1 (inhibition by NO).
- 6) ECs stimulate vascular growth and repair (either for blood vessel repair) or provide new vessels, e.g. healing.
- 7) VEGF secretion and expression of VEGF 1 and 2 receptors (pro- and anti-vascular growth).

More information on endothelial cells can be found on the following websites:

(<https://www.ncbi.nlm.nih.gov/pubmed/2191579>)

(www.sciencedirect.com/science/article/pii/S0002870305801905)

ACTIVITY 1.1

Complete the following activities, which serve as part of your summary in preparing for the examination.

- (a) Define cardiovascular diseases.
- (b) What are endothelial cells and from which embryonic layer do they develop?
- (c) What are the functions of normal endothelial cells?

- (d) List the factors that activate the endothelial cells.
- (e) Compare the characteristics of stimulated and unstimulated endothelial cells.
- (f) Discuss the properties of endothelial cells found in capillaries and in larger vessels.
- (g) Which substances are expressed by activated endothelial cells?
- (h) Describe the subtypes of capillary endothelium.

FEEDBACK ON ACTIVITY 1.1

- (a) Did you mention abnormal conditions of the heart and blood vessels?
- (b) Endothelial cells are not a type of epithelium, but develop from the mesoderm.
- (c–e) Read section 1.2.3. and pages 76–77 in the textbook by Finlayson and Newell.
- (f) Distinguish between capillaries and larger vessels.
- (g) Think of the tissue restoration process.
- (h) Study section 1.4.2 and page 77 in the textbook by Finlayson and Newell.

1.5 Vascular smooth muscle cells (SMCs)

Smooth muscle cells can contract or relax in response to stimuli, either from endothelial catecholamines released by the sympathetic nervous system or from angiotensin II. They can migrate to and proliferate in the intima after injury. SMCs also have fibroblast-like functions (synthesis of collagen, elastin and proteoglycans, growth factors and cytokines). This is important in the generation of a fibrous cap which stabilises atheromatous plaque.

1.6 Aneurysms

An aneurysm, which is a bulge in the wall of a blood vessel, occurs when there is severe erosion of the media. Aneurysms occasionally occur in arteries, in the left ventricle (post-myocardial infarction) but very rarely in veins. Aneurysms occur at a point of weakness, with causes including high blood pressure and atherosclerosis, trauma, heredity, abnormal blood flow at the junction where arteries come together, inflammatory damage, connective tissue abnormalities (e.g. Marfan syndrome) and following trauma (e.g., partial medial tear, often due to traffic accidents).

Four types of aneurysm have been identified:

- a) **Fusiform** – most aneurysms are fusiform (spindle shaped), which is typical of atheroma.
- b) **Saccular** – these occur after focal vessel damage, e.g. trauma or infection. Bacteria from the bloodstream may lodge in the atheromatous plaque, which can be seen following an operation on bacterial-rich sites such as the bowel. A transient bacteraemia is often present. The roughened wall over an atheromatous plaque, often with overlying thrombus, provides a nidus for infection.
- c) **Berry** – a berry aneurysm (congenital weakness in the media at the branching point of cerebral vessels) is not related to atheroma.
- d) **Aortic** (previously called dissecting aneurysm) – this is only of partial thickness and is not a true aneurysm, but it is usually considered with aneurysms. Dissection is typical of Marfan syndrome, but may occur in the elderly, in whom media degeneration is not uncommon. A tear in the intima allows blood to track along a congenitally weak media. This may rupture back into the aorta (double-barrelled aorta) or rupture through the adventitia, causing death by cardiac tamponade or exsanguination. It is unusual for aortic dissection to complicate atheroma.

Complications of aneurysms include the following:

- a) **Rupture** – there may be pain depending on the location of the rupture, low blood pressure, a rapid heart rate and light-headedness.
- b) **Thrombosis** – depending on where the clot has travelled to, thromboembolism can cause pain in the extremities or the abdomen. If a clot travels to the brain, it can cause a stroke.
- c) **Thromboembolism.**
- d) **Re-bleeding** – an aneurysm that has ruptured or leaked is at risk of bleeding again.
- e) **Vasospasm** – after a brain aneurysm ruptures, blood vessels in the brain may narrow erratically.
- f) **Hydrocephalus**– a condition in which fluid accumulates in the brain, typically in young children, enlarging the head and sometimes causing brain damage.
- g) **Hyponatremia**– is a condition that occurs when the level of sodium in the blood is abnormally low.

1.7 Congenital heart disease

1.7.1 Aetiology

The major development of the heart occurs during weeks 3-12 of pregnancy, by week four the primitive heart has begun to beat. Thus, the developing heart is particularly susceptible to teratogenic influences such as maternal rubella infection during the period of gestation. Congenital cardiac defects can also be sporadic or associated with underlying disease such as Down syndrome or Edwards' syndrome.

The primitive heart is a single tubular structure. This tube must fold and partition itself into a left and right side, with each side being subdivided into an atrium, ventricles and outflow tract artery. All four chambers must also be appropriately connected to the relevant blood vessels and equipped with valves. In this regard, many congenital heart defects reflect a disruption of the processes of folding and partitioning.

The endothelial cushions are particularly important structures in the development of the heart. They form the valve rings, the valves, the interatrial septum and the upper (membranous) part of the interventricular septum. If their behaviour is aberrant, defects result in these compartments of the heart. A congenital heart defect (CHD) (also known as a congenital heart anomaly or congenital heart disease) is a problem in the structure of the heart that is present at birth. Symptoms can vary from none to life-threatening, and may include rapid breathing, bluish skin, poor weight gain and fatigue. CHD does not cause chest pain. Most congenital heart problems do not occur with other diseases. Complications that can result from heart defects include heart failure.

Congenital heart disease is divided into acyanotic and cyanotic forms.

Cyanosis is defined as the bluish discoloration of the skin due to poor circulation or inadequate oxygenation of the blood.

- a) **Acyanotic condition** – the blood in the systemic circulation is adequately oxygenated.
- b) **Cyanotic condition** – the defects disrupt the flow of blood to the extent that the systemic blood is inadequately oxygenated and cyanosis results. Cyanotic diseases usually present a more serious and immediate problem for the neonate than acyanotic disease.

1.7.2 Acyanotic congenital heart disease

There are four common acyanotic congenital heart defects:

a) **Ventricular septal defects (VSDs)** – the most frequent types of congenital malformations affect the heart. It is estimated that approximately eight in 1 000 new-borns have CHD. A VSD is the most frequent of the various types of CHD (25–30% of all CHDs). Approximately one infant in 500 will be born with a VSD. With the exception of the bicuspid aortic valve, it is the most common congenital heart defect, affecting approximately 40 per cent of patients. The defect is located on the membranous part of the interventricular septum. It permits a left-to-right shunt of a proportion of the oxygenated blood in the left ventricle into the right ventricle.

b) **Atrial septum defects** – the atrial counterpart of VSD, it accounts for around ten per cent of CHDs. Three common atrial septum defects have been identified:

- The defect arises most commonly in the ostium secundum and is located in the region of the fossa ovalis.
- Ostium primum defects are situated near the atrioventricular valves and are associated with Down's syndrome.
- Sinus venosus defects develop near the entry of the superior vena cava. The changes to cardiac blood flow are similar to those of a left-to-right shunt. Many patients are asymptomatic and do not present until adulthood.

c) **Patent ductus arteriosus** – the ductus arteriosus connects the pulmonary artery to the aortic arch. It functions *in utero* to shunt blood away from the lungs, to maintain systemic circulation. This is important because non-aerated lungs have a relatively high vascular resistance against which the right heart needs to be protected. Shortly after birth, the ductus arteriosus closes and normal circulation is established. In some individuals it remains open, however, allowing oxygenated blood from the aorta to re-enter the pulmonary circulation. Thus, the left ventricle pumps a fraction of its output back to itself. The pulmonary circulation is also exposed to the systemic pressures generated by the left ventricle, and pulmonary hypertension results.

d) **Coarctation of the aorta** – this is a narrowing of the aorta that accounts for seven per cent of CHDs. The coarctation usually occurs near the ductus arteriosus distal to the left subclavian artery. The increased peripheral resistance induces left ventricular hypertrophy and collateral vessels can develop to try to bypass the obstructed aorta.

1.7.3 Cyanotic congenital heart disease

Two cyanotic congenital heart diseases have been distinguished:

a) **Tetralogy of Fallot** – this is the most common cyanotic defect, accounting for 5–10 per cent of all CHDs. Associated with Down syndrome, it is an endocardial cushion defect. The four compartments of the Tetralogy of Fallot are

- a ventricular septum defect (VSD)
- a malplaced aorta that overrides the septal defect
- a stenotic pulmonary outflow tract and
- a hypertrophied right ventricle.

The overriding aorta, in combination with a VSD and hypertrophied right ventricle, allows deoxygenated blood to enter the systemic circulation to produce cyanosis.

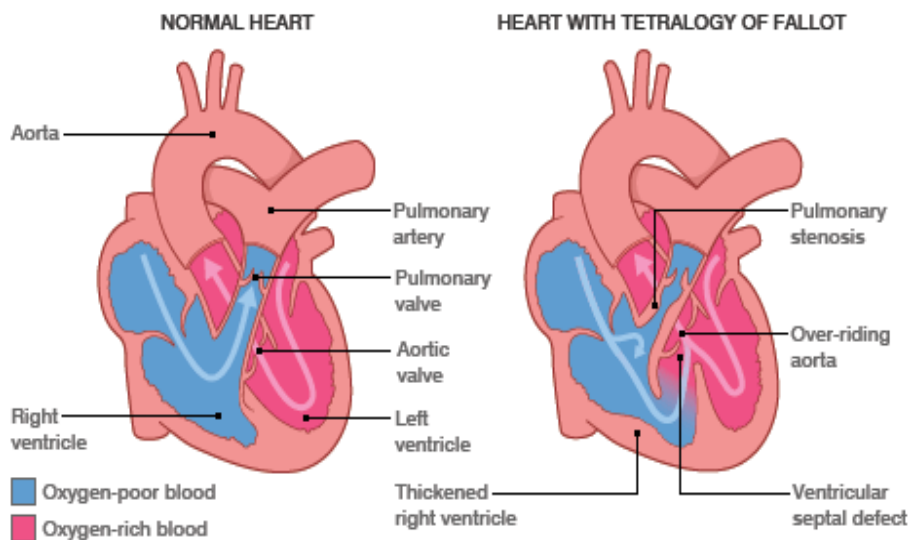


Figure 1.4: Tetralogy of Fallot

(http://newsimg.bbc.co.uk/media/images/45000000/gif/_45000556_tetralogy_heart466x250.gif)

b) **Transposition of the great vessels** – this contributes to 5-10 per cent of CHDs and occurs when the septum that partitioned the original single outflow tract of the primitive cardiac tube fails to follow the proper spiral pathway. This causes the aorta to arise from the right ventricle and the pulmonary artery from the left ventricle. As the vena cavae and pulmonary vein are appropriately sited, two independent circulations develop, with the blood in the systemic arteries continuously circling around a system that does not incorporate the lungs, thereby

causing cyanosis. This condition is fatal post-delivery, unless the ductus arteriosus and/or foramen ovale remain patent and provide some form of connection between the two circulations. Even then, marked cyanosis persists and surgical correction is essential.

ACTIVITY 1.2

- (a) Discuss the properties of smooth muscle cells.
- (b) Name the types and complications of aneurysms.
- (c) What are congenital heart diseases?
- (d) Describe the aetiology of congenital heart diseases.
- (e) What is cyanosis?
- (f) Distinguish between acyanotic and cyanotic heart diseases.
- (g) List four common acyanotic congenital heart diseases.
- (h) Describe two types of cyanotic heart disease.

FEEDBACK ON ACTIVITY 1.2

- (a) Did you mention contraction and relaxation, endothelin, catecholamines or angiotensin II, fibroblast-like function, i.e. collagen, elastin and proteoglycans, growth factors and cytokines?
- (b) The types of aneurysm are listed in section 1.6.
- (c) Did you mention malformations of the heart structure existing at birth?
- (d) Aetiology is the study of the causes of a disease, see section 1.7.1.
- (e) Cyanosis, did you mention bluish discoloration of the skin due to poor circulation or inadequate oxygenation of the blood?
- (f) Study section 1.7.1.
- (g) In answering this question, refer to section 1.7.2.
- (h) Did you mention the Tetralogy of Fallot and the transposition of the great vessels?

1.8 Systemic hypertension

Systemic hypertension is defined in terms of either systolic or diastolic blood pressure, and is considered to be present if there is a sustained systolic pressure of over 140 mmHg and/or a sustained diastolic pressure greater than 90 mmHg. These figures reflect the levels of blood pressure at which treatment becomes prudent, to prevent complications.

1.8.1 Control of blood pressure (BP)

Blood pressure is the product of cardiac output and peripheral arterial resistance. Cardiac output is dependent on the heart rate, stroke volume and the available circulating volume. Central to the regulation of cardiac contractility and peripheral vascular resistance is the sympathetic nervous system. Increased sympathetic activity produces positive inotropic and chronotropic effects in the heart, thereby increasing stroke volume. At the systemic level, increased sympathetic tone causes vasoconstriction, thereby raising peripheral vascular resistance. Baroreceptors within the aortic arc and carotid bodies sense blood pressure and relay this information back to the brain stem, where it is integrated with other parameters to modify autonomic tone. While the sympathetic nervous system is the main effector arm in controlling blood pressure, the parasympathetic nervous system can play a role in reducing blood pressure by slowing down the heart rate.

Hormones operate alongside the sympathetic nervous system by increasing the circulating volume. The kidney is integral to the body's regulation of sodium and water balance, therefore many of these hormones act through the kidney or are generated by it. The kidney releases renin through a complex response at the juxtaglomerular apparatus that detects decreased renal blood flow. This triggers the renin-angiotensin system which stimulates the endothelium cells to release angiotensin II, a vasoconstrictor that also stimulates the release of aldosterone, leading to increased water and sodium retention by the kidney and thereby increasing the volume of fluid in circulation. Operating in conjunction with renin-angiotensin-aldosterone is the antidiuretic hormone, which stimulates thirst or the need to drink liquids.

1.8.2 Causes of high blood pressure

Over 95 % of cases of hypertension are primary and have no cause. However, there are three secondary causes of hypertension:

- 1) **Renal** – Renal artery stenosis; Glomerulonephritis; Polycystic kidney; Renin-producing tumour and Scleroderma;
- 2) **Endocrine** – Cushing's syndrome; Acromegaly; Pheochromocytoma; Hyperaldosteronism;
- 3) **Miscellaneous** – Aortic coarctation; pregnancy.

1.8.3 Complications of hypertension

a) **Atherosclerosis** (also known as arteriosclerotic vascular disease or ASVD) – this is a specific form of arteriosclerosis in which an artery wall thickens as a result of the invasion and accumulation of white blood cells (foam cells) and the proliferation of intimal-smooth-muscle cells creating an atheromatous (fibrofatty) plaque. Arteries are blood vessels that carry blood from the heart throughout the body. They are lined with a thin layer of endothelial cells. The endothelium works to keep the inside of the arteries toned and smooth which, in turn, keeps blood flowing.

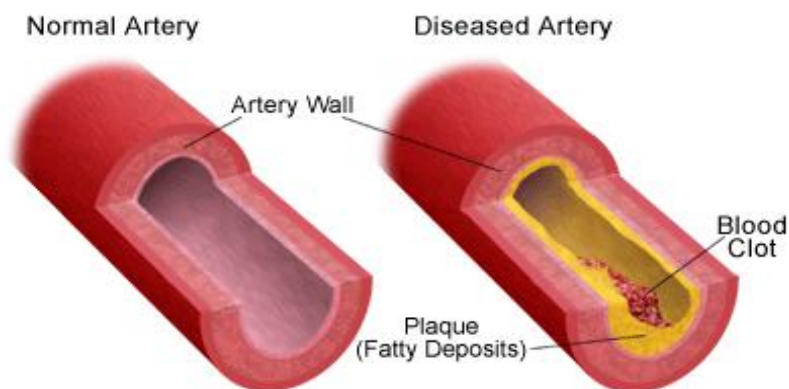


Figure 1.5: Normal healthy artery and an atheromatous diseased artery
(http://civtmd.columbia.edu/images/em_1807_000.gif)

Atherosclerosis begins with damage to the endothelium. It is caused by high blood pressure, smoking or high cholesterol. That damage leads to the formation of plaque or fatty deposits. When “bad” cholesterol or low-density lipoprotein (LDL) crosses the damaged endothelium, the cholesterol enters the wall of the artery, which causes white blood cells to stream in to digest the LDL. Over years, cholesterol and cells become plaque in the wall of the artery. Plaque creates a bump on the artery wall. As atherosclerosis progresses the bump grows bigger, to the point of potentially creating a blockage.

b) **Arteriosclerosis** – this is the thickening, hardening and loss of elasticity of the arterial walls. The endothelium of smaller arteries is damaged by pressure and this permits the leakage of proteins into the vessel wall, hence thickening and narrowing them, leading to downstream ischaemia. This process gradually restricts the blood flow to organs and tissues, which can lead to severe health risks brought on by atherosclerosis, a specific form of arteriosclerosis caused by the build-up of fatty plaque, cholesterol and other substances in and on the artery walls.

c) **Left ventricular hypertrophy (LVH)** – this is a condition in which the muscle wall of the left ventricle becomes thickened (hypertrophy). Other conditions, such as heart attack, valve disease and dilated cardiomyopathy can cause the heart (or the heart cavity) to grow bigger. The elevated afterload placed on the ventricle by systemic pressure induces hypertrophy of the left ventricle.

d) **Aortic dilatation** – hypertension also increases the load on the aortic arc, leading to enlargement or dilatation which can distort the aortic root. This leads to aortic regurgitation or culminates in a dissecting aneurysm.

e) **Haemorrhagic stroke** – hypertension can lead to haemorrhagic cerebrovascular accidents as a result of a weakened blood vessel rupturing or aneurysms (i.e. a pre-existing condition). The two types of haemorrhagic stroke are intracerebral (within the brain) and subarachnoid haemorrhage.

f) **Retinopathy** – hypertension can induce changes in, and damage to, the retinal blood vessels. This can result in patches and limit retinal function, and exert pressure on the optic nerve which results in vision impairment.

g) **Nephropathy** – hyaline arteriosclerosis in the kidney can disrupt blood supply in the glomeruli, causing ischaemic atrophy and necrosis.

h) **Accelerated hypertension** – this is defined as a recent significant increase over baseline BP that is associated with target organ damage. Also known as malignant hypertension, this is a serious, life-threatening condition in which there is severe, uncontrolled hypertension associated with headache, confusion and high risk of end organ damage, such as haemorrhagic cardiovascular arrest (CVA), renal haemorrhage and renal failure.

ACTIVITY 1.3

- (a) Define systemic hypertension.
- (b) Describe how blood pressure is controlled in the body.
- (c) Describe the three major causes of hypertension.
- (d) Describe the complications of hypertension.

- (e) Distinguish between atherosclerosis and arteriosclerosis.
- (f) What is accelerated hypertension?

FEEDBACK ON ACTIVITY 1.3

- (a) Did you mention systolic and diastolic pressure values?
- (b) Do include cardiac output, heart rate, stroke volume and the available circulating blood volume. Did you mention baroreceptors, the sympathetic nervous system, hormones, kidneys, the renin-angiotensin system, aldosterone and antidiuretic hormones?
- (c) See section 1.8.2 above.
- (d) In your discussion, did you include atherosclerosis, arteriosclerosis and accelerated hypertension?
- (e) Discuss aneurysms (section 1.6 above) and see pages 76–77 in the textbook by Finlayson and Newell.
- (f) In accelerated hypertension, did you mention baseline blood pressure?

1.9 Ischaemic heart disease

The coronary arteries supply blood to the heart muscle. No alternative blood supply exists, so a blockage in the coronary arteries reduces the supply of blood to the heart muscle. Most ischaemic heart disease is caused by atherosclerosis, usually present even when the artery lumens appear normal when subjected to angiography.

Ischemic heart disease, also known as coronary artery disease, is a condition that affects the supply of blood to the heart muscles. The blood vessels are narrowed or blocked due to the deposition of cholesterol on their walls. This reduces the supply of oxygen and nutrients to the heart muscles, which is essential for the proper functioning of the heart. Eventually it may lead to a portion of the heart suddenly being deprived of its blood supply, leading to the death of that area of heart tissue, resulting in a heart attack. As the heart is the pump that supplies oxygenated blood to the various organs, any defect in the heart immediately affects the supply of oxygen to vital organs like the brain, kidneys, liver, etc. The effect is the death of tissue within these organs, and their eventual failure. Ischemic heart disease is the most common cause of death.

Six common causes of ischaemic heart disease are:

- smoking
- diabetes mellitus
- hypercholesterolemia
- hypertension
- genetic and hereditary factors and
- stress (risk factor).

1.10 Angina pectoris

Angina pectoris is an acute pain in the chest resulting from myocardial ischaemia (decreased blood supply to the heart muscle). The condition is also called cardiac pain of effort and emotion, because the pain is brought on by physical activity or emotional stress that places an added burden on the heart and increases the need for blood to be supplied to the myocardium. Angina pectoris occurs more frequently in men and in older persons. It can also result from stenosis of the aorta, pulmonary stenosis and ventricular hypertrophy, or connective tissue disorders such as systemic lupus erythematosus and periarteritis nodosa that affect the smaller coronary arteries.

The symptoms are the following:

- 1) The chief symptom is chest pain, usually unmistakably distinguished by the patient as different from other types of pain, such as that caused by indigestion. It is generally described as a feeling of tightness, strangling, heaviness or suffocation, and is usually concentrated on the left side, beginning just below the sternum; it sometimes radiates to the neck, throat and lower jaw, and down the left arm, and occasionally to the stomach, back or across to the right side of the chest. The pain seldom lasts more than 15 minutes and is usually relieved by rest and relaxation, or by administering nitrates.
- 2) Acute chest pain (which can be associated with acute coronary syndrome, unstable angina or myocardial infarction).
- 3) Heart failure and difficulty breathing, or swelling (oedema) of the extremities due to weakness of the heart muscle.

If blood flow becomes impaired due to coronary artery disease, the results include

- extreme fatigue
- shortness of breath
- dizziness, light-headedness or fainting
- chest pain and pressure, known as angina
- heart palpitations
- swelling in the legs and feet, known as oedema and
- swelling in the abdomen.

1.11 Myocardial infarction

Myocardial infarction (MI) can be defined as the irreversible death (necrosis) of myocardial muscle fibre caused by prolonged ischaemia, resulting from a sustained imbalance of perfusion, supply and demand. MI, commonly known as a heart attack, occurs when blood flow stops to a part of the heart, causing damage to the heart muscle. The most common symptom is chest pain or discomfort which may travel to the shoulder, arm, back, neck or jaw.

Often it is in the center or left side of the chest, and lasts for more than a few minutes. The discomfort may occasionally feel like heartburn. Other symptoms may include shortness of breath, nausea, feeling faint, a cold sweat or fatigue. About 30 per cent of people (more so women than men) have atypical symptoms. Among those over 75 years of age, about five per cent have had an MI with little or no history of symptoms. An MI may cause heart failure, irregular heartbeat, cardiogenic shock or cardiac arrest.

1.11.1 Aetiology and risk factors

Although there are many risk factors, atherosclerosis is by far the major underlying cause of ischaemic heart disease and MI. Genetic predisposition, age, male gender, cigarette smoking, obesity, lack of exercise, mental stress and high-risk diets (containing high cholesterol or saturated fats) are known risk factors. A personal history of diabetes mellitus, hypertension, hyperlipidaemia and elevated plasma homocysteine levels has also been reported to increase the risk.

Myocardial infarctions can be classified temporally from clinical and other features, as well as according to the pathological appearance, as evolving (<6 h), acute (6 h–7 days), healing (7–28 days) and healed (29 days and beyond).

Myocardial infarction can be classified as either acute, healing or healed.

a) **Evolving** MI in the inferior part of the heart is identified by ST segment elevation in the inferior leads II, III, and aVF. The ST segment elevation in lead II is less than 1 millimeter, but its shape is abnormal and suggests acute ischemia.

b) **Acute** – acute MI is characterised by the presence of polymorphonuclear leukocytes. If the time interval between the onset of the infarction and death is quite brief, e.g. six hours, minimal or no polymorphonuclear leukocytes may be seen.

c) **Healing** – the presence of mononuclear cells and fibroblasts, and the absence of polymorphonuclear leukocytes characterise healing infarction.

d) **Healed** – a healed infarction manifests as scar tissue without cellular infiltration. The entire process leading to a healed infarction usually takes at least 5–6 weeks. Reperfusion may alter the macroscopic and microscopic appearance of the necrotic zone by producing myocytes with contraction bands and large quantities of extravasated erythrocytes.

ACTIVITY 1.4

- (a) Define ischaemic heart disease.
- (b) What are coronary arteries?
- (c) Discuss the causes of ischaemic heart disease.
- (d) What is angina pectoris and what are its symptoms?
- (e) Explain the characteristics of impaired blood flow to the coronary arteries.
- (f) What is myocardial infarction?
- (g) Discuss the aetiology and risk factors of myocardial infarctions.
- (h) Discuss acute, healing and healed myocardial infarction.

FEEDBACK ON ACTIVITY 1.4

- (a) Consider heart and blood vessels.
- (b) Heart's own blood supply.
- (c) Consider the major causes of ischaemic heart disease, lifestyle and genetic factors.
- (d) Pain in the chest.
- (e) Consider symptoms of heart failure.
- (f) Blood supply and demand.
- (g) Risk factors, consider the causes of atherosclerosis.
- (h) Study section 1.10 above and pages 85-90 in the textbook by Finlayson and Newell (2009).

1.12 Thrombosis

Thrombosis is the formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system. When a blood vessel is injured, the body uses platelets (thrombocytes) and fibrin to form a blood clot to prevent blood loss. Even when a blood vessel is not injured, blood clots may form in the body under certain conditions. A clot (or a piece of the clot) that breaks free and begins to travel around the body is known as an embolus.

Thrombosis may occur in veins (venous thrombosis) or in arteries (arterial thrombosis). Venous thrombosis leads to congestion of the affected part of the body, while arterial thrombosis (and

rarely severe venous thrombosis) affects the blood supply and leads to damage of the tissue supplied by that artery (ischemia and necrosis).

A piece of either an arterial or a venous thrombus can break off as an embolus which can travel through the circulatory system and lodge somewhere else as an embolism. This type is known as a thromboembolism. Complications can arise when a venous thromboembolism (commonly called a VTE) lodges in the lung as a pulmonary embolism. An arterial embolus may travel further down the affected blood vessel where it can lodge as an embolism.

a) **Normal haemostasis** – the function of normal haemostasis is to activate the clotting system where it is needed and to target its action to the breach. This is achieved by the complex interaction between endothelial cells, platelets and clotting cascades. The endothelium, at its resting state, has an antithrombotic stance due to the secretion of the vasodilator nitric oxide (NO) and the antiplatelet aggregation agent prostacyclin. Once activated, the endothelium secretes the vasoconstrictor endothelin-1 (ET-1), expresses tissue factor (TF) on its surface and secretes platelet-activating factor (PAF). Endothelial damage leads to the expression of Von Willebrand factor (vWF) on the endothelial surface. If endothelial cells are so damaged that they tear away from the surface, the underlying basement membrane and collagen are exposed to the blood stream and trigger haemostasis. Tissue factor (also called platelet tissue factor, factor III, thromboplastin or CD142) is a protein encoded by the F3 gene present in subendothelial tissue and leukocytes necessary for the initiation of thrombin formation from the zymogen prothrombin.

Endothelins perform a number of physiological functions, including

- 1) neural crest cell development and neurotransmission in the vascular system. Endothelin – via the activation of endothelin receptor type A (ETA) receptors – has a basal vasoconstricting role and contributes to the development of vascular disease in hypertension and atherosclerosis.
- 2) contributing to myocardial contractility, chronotropy and arrhythmogenesis, as well as myocardial remodelling following post-infarct congestive heart failure.
- 3) in the lung, regulating the bronchial tone (Uchida *et al.*, 1988) and the proliferation of pulmonary airways blood vessels, and promoting the development of pulmonary hypertension.

- 4) controlling water and sodium excretion and acid-base balance in the kidney under physiological conditions, and promoting the development of glomerulosclerosis.
- 5) in the brain, modulating (as a system) cardio-respiratory centres and the release of hormones, and contributing to the growth guidance of developing sympathetic neurons.
- 6) affecting the physiology and pathophysiology of the immune system, in the liver, muscle, bones, skin, prostate, adipose tissue and reproductive tract, and being involved in glucose homeostasis.

b) **Platelets** – platelets normally circulate in an inactive state, but when activated they adhere to each other and to damaged endothelium, exposed basement membrane and fibrin, in order to form a plug. Platelets are activated by thrombin, contact with basement membrane and PAF. Activated platelets display surface receptors that allow them to bind to vWF, to collagen or to TF/VIIa on endothelial cells, thereby causing them to anchor to the site of damage, each other and the fibrin framework of a clot. The activation of platelets also precipitates the release of their granules. Thromboxane A₂ is a potent vasoconstrictor that slows blood flow and platelet aggregation. Activated platelets absorb clotting factors onto their phospholipid surfaces, which brings them into close apposition, thereby facilitating the cascades. Small breaches on the endothelium occur all the time and platelet plugs seal them, while the endothelium regenerates.

c) **Coagulation cascades** – the role of clotting cascades is to generate an insoluble mesh of cross-linked fibrin in which platelets, erythrocytes and leucocytes become trapped to yield a clot. The components of the cascades are the clotting factors, most of which are proteins made by the liver. They activate in sequence, thereby amplifying a small initial signal into the generation of a large quantity of fibrin. The main precipitant for the cascade is the activation of factor VII by tissue factor. Tissue factor is expressed on all cells except undamaged endothelium, and the blood cells will readily be exposed if the endothelium is disrupted. The cascades then spiral down until prothrombin is converted to thrombin which, in turn, triggers the conversion of fibrinogen to fibrin. The factor VII-mediated sequence is known as the extrinsic pathway. There is, however, also an intrinsic pathway that is initiated by the activation of factor XI by thrombin or by activated factor IX/factor VIII complexes on platelets. The intrinsic pathway allows the platelets to feed onto the cascades, and also for the cascades to amplify themselves. Deficiencies in factors VIII and IX cause severe bleeding problems (haemophilia

and Christmas disease), deficiencies in factor VII cause severe bleeding problems in embryonal life, and deficient tissue factor is incompatible with life.

1.12.1 Pathological significant locations of thrombus

a) **Arterial thrombosis** – this is the formation of a thrombus within an artery. In most cases, arterial thrombosis follows a rupture of the atheroma (a fat-rich deposit in the blood vessel wall), and is therefore referred to as atherothrombosis. An arterial embolism occurs when clots migrate downstream, and this can affect any organ. Alternatively, arterial occlusion occurs as a consequence of the embolism of blood clots originating from the heart (cardiogenic emboli). The most common cause is atrial fibrillation, which causes a blood stasis within the atria with easy thrombus formation, but blood clots can develop inside the heart for other reasons too.

b) **Cardiac (coronary) thrombosis** – this is the formation of a blood clot inside a blood vessel of the heart which interrupts blood flow to the heart. The blood clot restricts blood flow within the heart. It is associated with the narrowing of blood vessels subsequent to clotting, usually as a consequence of atherosclerosis, and is characterised by intense pain. If left untreated, it can lead to a myocardial infarction or even a heart attack.

c) **Venous thrombosis** – a venous thrombus is a blood clot (thrombus) that forms in a vein. A common type of venous thrombosis is deep vein thrombosis (DVT), which is a blood clot in the deep veins. If the thrombus breaks off (embolises) and flows towards the lungs, it can become a pulmonary embolism (PE), a blood clot in the lungs. An inflammatory reaction is frequently present, mainly in the superficial veins and, for this reason, the pathology is usually called thrombophlebitis. The inflammatory reaction and the white blood cells play a role in the resolution of venous clots. The initial treatment for venous thromboembolism is typically with either low molecular weight heparin (LMWH) or unfractionated heparin. LMWH appears to have lower rates of side effects, however both result in similar rates of survival.

1.13 Thrombolysis

Thrombolysis, also known as thrombolytic therapy, is a treatment to dissolve dangerous clots in blood vessels, improve blood flow, and prevent damage to tissues and organs. Once the thrombus has been generated, a process needs to occur that can remove the thrombus when

the damage to the vessel has been repaired. The thrombolytic system functions to break down thrombi and remove them. It also opposes the initiation of clotting in the first place and ensures that haemostasis only occurs when the precipitating signal is of appropriate magnitude to warrant this activation.

Sequelae following thrombosis

- 1) **Embolisation** – all or part of the thrombus detaches and is carried to another site by blood flow. Effects vary according to the site of origin of the embolus.
- 2) **Resolution** – the thrombus is cleared by the normal antithrombotic mechanism or by therapeutic drugs such as streptokinase.
- 3) **Re-canalisation** – small endothelial-lined channels develop to bypass the thrombosed segment.
- 4) **Repair** – as much thrombus as possible is removed by thrombolytic activity, then the remainder is organised and re-endothelialised to restore the integrity of the blood vessel. This causes a degree of laminal stenosis.
- 5) **Fibrous obliteration** – the organisation and fibrosis of the thrombosed segment causes fibrous obliteration of the lumen of the vessel.

1.14 Embolism and disseminated intravascular coagulation

1. Embolism – an embolus is a substance carried in the blood that lodges in and obstructs vessels distant to the point of origin of the thrombus.

An embolism involves the lodging of an embolus, a blockage-causing piece of material, inside a blood vessel. The embolus may be a blood clot (thrombus), a fat globule, a bubble of air or other gas (gas embolism) or foreign material. An embolism can cause partial or total blockage of blood flow in the affected vessel. Such a blockage (a vascular occlusion) may affect a part of the body distant from where the embolus originated. An embolism in which the embolus is a piece of thrombus is called a thromboembolism.

Causes of embolus

- 1) **Ninety-nine per cent** of emboli are formed from thrombi (thromboemboli) which can originate on either the arterial or the venous side of the circulation. Portal vein thrombus seldom embolises, in part due to low pressure within the system.

- 2) **Fat globules or chunks of bone marrow** may embolise if mobilised in circulation, e.g. fracture of the long bones due to trauma. Large pieces are seen in the lungs, but showers of fat globules may cause microcirculatory damage, particularly in the brain.
- 3) **Accidental introduction of air** into the venous system may occur through faulty intravenous cannulation equipment.
- 4) **Amniotic fluid** may accidentally enter the maternal circulation, e.g. through unskilled instrumentation during a back-street abortion.
- 5) **Nitrogen** may come out of solution and cause bubbles that obstruct the microvasculature of the brain, joints and other organs in divers who ascend to the surface too quickly (“the bends”).

The effects of thromboembolism are dictated by the direction of flow and the site of the originating thrombus. Four types of thromboembolism are distinguished:

a) **Arterial thromboembolism** – blood flows from the aorta to the tissues, passing from larger to smaller arteries. Arterial emboli usually arise from an atheroma-associated thrombus on the walls of larger vessels, or from a thrombus in the heart. Emboli from these sources cause distant infarction when they become impacted in a smaller artery (e.g. infarction of toes, segments of the bowel, kidney). Sometimes cholesterol crystals can be seen upon microscopic examination. Arterial infarcts tend to be wedge shaped.

b) **Cardiac thromboembolism** – a cardiac mural thrombus can develop in atrial fibrillation during an acute myocardial infarction or a ventricular aneurysm. Emboli can be anywhere in the systemic arterial tree, but are particularly likely to cause cerebrovascular complications, such as a transient ischaemic attack or an ischaemic stroke.

c) **Systemic venous thromboembolism** – venous blood drains towards the heart from the tissues, and so the first site of impaction is the pulmonary circulation, resulting in pulmonary embolism.

d) **Portal vein thrombosis** – portal vein thrombosis is a blockage or narrowing of the portal vein (the blood vessel that brings blood to the liver from the intestines) by a blood clot. Most people have no symptoms, but in some, fluid accumulates in the abdomen, the spleen enlarges and/or severe bleeding occurs in the oesophagus. Doppler ultrasonography usually confirms

the diagnosis. The cause is treated, if possible related problems are treated, and drugs may be used to dissolve the clot or prevent the clot from enlarging or recurring.

Because the portal vein is narrowed or blocked, pressure in it increases. This increased pressure (called portal hypertension) causes the spleen to enlarge (splenomegaly). It also results in dilated, twisted (varicose) veins in the oesophagus (called oesophageal varices) and often in the stomach (called gastric varices). These veins can bleed profusely.

Fluid accumulation in the abdomen (called ascites) is not common. It may, however, develop when people also have liver congestion (backup of blood in the liver) or liver damage, such as severe liver scarring (cirrhosis), or when large quantities of fluids are given intravenously to treat massive bleeding from ruptured varicose veins in the oesophagus or stomach. If portal vein thrombosis develops in people with cirrhosis, their condition deteriorates. About 25 per cent of adults with cirrhosis have portal vein thrombosis, usually because blood flow through the severely scarred liver is slow. When blood flow is slow, blood is more likely to clot. Any condition that makes blood more likely to clot can cause portal vein thrombosis.

2. Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a pathological process characterised by the widespread activation of the clotting cascades that result in the intravascular formation of fibrin, and ultimately the thrombotic occlusion of small and midsize vessels.

Intravascular coagulation can also lead to compromised tissue blood flow and can ultimately lead to multiple organ damage. In addition, as the coagulation process consumes clotting factors and platelets, normal clotting is disrupted and severe bleeding can occur from various sites.

Complications of DIC include the following:

- acute kidney injury
- change in mental status
- respiratory dysfunction
- hepatic dysfunction
- life-threatening thrombosis and haemorrhage
- cardiac tamponade
- haemothorax
- intracerebral haematoma
- gangrene and loss of digits and
- shock.

1.15 Cardiac valvular disease

Cardiac valvular disease is characterised by damage to, or a defect in, one of the four heart valves: the mitral, aortic, tricuspid or pulmonary. The mitral and tricuspid valves control the flow of blood between the atria and the ventricles (the upper and lower chambers of the heart).

There are two functional abnormalities of cardiac valvular disease:

- Stenosis and
- Regurgitation.

1.15.1 Stenosis

Valvular stenosis is a narrowing or stricture of any of the heart valves. The condition may result from a congenital defect or may be caused by disease.

- a) **Aortic valve stenosis** is a narrowing of the aortic valve. The aortic valve allows blood to flow from the heart's lower left chamber (ventricle) into the aorta and to the body. Stenosis prevents the valve from opening properly, forcing the heart to work harder to pump blood through the valve.
- b) **Tricuspid valve stenosis** is a narrowing of the tricuspid valve opening. Tricuspid stenosis restricts blood flow between the upper and lower part of the right side of the heart, or from the right atrium to the right ventricle.
- c) **Mitral stenosis** is characterised by an obstruction to the left ventricular inflow at the level of the mitral valve, due to a structural abnormality of the mitral valve apparatus. The most common cause of mitral stenosis is rheumatic fever. Lutembacher syndrome is the association of an atrial septal defect with rheumatic MS.
- d) **Pulmonary stenosis** is a condition characterised by obstruction that prevents blood flow from the right ventricle to the pulmonary artery. Most commonly found with pulmonary valvar stenosis is a thickening of pulmonary valve leaflets and their fusion along their separation lines (commissures).

1.15.2 Regurgitation

Valvular insufficiency (or regurgitation, incompetence or "leaky valve") occurs when the leaflets do not close completely, letting blood leak backward across the valve. This backward flow is referred to as "regurgitant flow".

- a) **Aortic valve regurgitation** or aortic regurgitation is a condition that occurs when the heart's aortic valve does not close tightly. Aortic valve regurgitation allows some of the blood that was just pumped out of the heart's main pumping chamber (left ventricle) to leak back into

it. The leakage may prevent the heart from efficiently pumping blood to the rest of the body. As a result, the person may feel fatigued and short of breath.

b) **Tricuspid regurgitation** is a disorder in which the heart's tricuspid valve does not close properly, causing blood to flow backward (leak) into the right upper heart chamber (atrium) when the right lower heart chamber (ventricle) contracts.

c) **Mitral valve regurgitation** (also called mitral regurgitation, mitral insufficiency or mitral incompetence) is a condition in which the heart's mitral valve fails to close tightly, allowing blood to flow backward into the heart. Atrial fibrillation is a common symptom that only occurs with mitral valve regurgitation.

d) **Pulmonic regurgitation** refers to retrograde flow from the pulmonary artery into the right ventricle during diastole. Physiologic (trace-to-mild) pulmonic regurgitation is present in nearly all individuals, particularly in those of advanced age. However, pathological conditions that produce excessive and clinically significant regurgitation can result in impairment of the right ventricular function, and eventual clinical manifestations of right-sided volume overload and heart failure.

Causes of cardiac valvular disease include:

- 1) **Infective endocarditis** – endocarditis is an inflammation of the inner lining or tissues of the heart (endocardium). It generally occurs when infectious agents or pathogens (largely bacteria or other germs from another part of the body, such as the mouth) spread through the bloodstream and attach to damaged areas in the heart. Left untreated, endocarditis can damage or destroy the heart valves and can lead to life-threatening complications. Treatments for endocarditis include antibiotics and, in certain cases, surgery.
- 2) **Rheumatic fever (RF)** – this is an inflammatory disease that can involve the heart, joints, skin and brain. The disease typically develops two to four weeks after a streptococcal throat or scarlet fever infection.

1.16 Myocardial diseases

Myocardial diseases affect the heart muscles and are characterised by reduced blood flow into the muscle cells, usually as a result of a partial or complete blockage of the heart's arteries (coronary arteries).

Myocardial diseases can be subdivided into two types, namely primary and secondary myocardial diseases.

Primary myocardial diseases most commonly have a genetic cause, while **secondary myocardial diseases** are mostly acquired, but may be precipitated by a genetic background.

Primary myocardial diseases include:

- Hypertrophic cardiomyopathy (HCM)
- Dilated cardiomyopathy (DCM)
- Restrictive cardiomyopathy (RCM)
- Arrhythmic cardiomyopathy (ACM)
- Unclassified cardiomyopathy (UCM)

1) **Hypertrophic cardiomyopathy** is an autosomal dominant disease of the myocardium. It is characterised by left ventricular hypertrophy without chamber dilatation, in the absence of either a systemic or other cardiac disease, an increase in left ventricular wall thickness that is not solely explained by abnormal loading conditions. This disorder, which is caused by a mutation in the cardiac sarcomere protein genes, is most frequently transmitted as an autosomal dominant trait. HCM has a variable presentation.

2) **Dilated cardiomyopathy** is characterised by a poorly contracting dilated left ventricular chamber and systolic dysfunction, with normal left ventricular wall thickness. Right ventricular dilatation and dysfunction may be present, but are not necessary for the diagnosis.

3) **Restrictive cardiomyopathy** is a rare form of heart muscle disease that is characterised by restrictive filling of the ventricles. In this disease the contractile function (squeeze) of the heart and wall thickness are usually normal, but the relaxation or filling phase of the heart is abnormal.

4) **Arrhythmic cardiomyopathy** or arrhythmogenic right ventricular dysplasia/ cardiomyopathy (ARVD/ARVC) is an inherited cardiomyopathy characterised by structural and functional abnormalities in the right ventricle (RV), resulting in ventricular arrhythmias. It is an important cause of sudden cardiac death (SCD) in young adults, accounting for 11 per cent of all cases and 22 per cent of cases among athletes.

5) **Unclassified cardiomyopathy**

a) **Myocarditis**

Myocarditis is defined as inflammatory changes in the myocardium (the middle layer of the heart wall) and is characterised by myocyte necrosis and degeneration. It can affect both the heart's muscle cells and its electrical system, leading to a reduction in the heart's pumping function and to irregular heart rhythms. Myocarditis is a collection of diseases of infectious, toxic or autoimmune origin.

b) **Pericarditis**

Pericarditis is an inflammation of the lining surrounding the heart (the pericardial sac). Pericardial effusion is a collection of fluid in the pericardial sac. This fluid may be produced by inflammation. The cause of pericarditis in most individuals is unknown, but is likely due to viral infection. Pericarditis often occurs after a respiratory infection. Bacterial, fungal and other infections also can cause pericarditis. Most cases of chronic or recurring pericarditis are thought to be the result of autoimmune disorders. Examples of such disorders include lupus, scleroderma and rheumatoid arthritis.

Several different types of pericarditis exist:

- Serous – e.g., rheumatic fever, SLE, scleroderma, tumours and uraemia
- Fibrinous – this is the most common and often occurs during myocardial infarction, Dressler's syndrome occurs several weeks after MI
- Purulent/suppurative – infective in aetiology
- Haemorrhagic – may be seen in metastatic tumours
- Tuberculous
- Chronic – small adhesions are seen in post-mortems.

c) **Constrictive pericarditis**

Constrictive pericarditis is a potentially curable condition caused by a variety of situations which result in an inflamed, scarred, thickened or calcified pericardium.

When the abnormal pericardium limits diastolic filling, there are a series of haemodynamic consequences which manifest as fatigue, dyspnoea, abdominal bloating, peripheral oedema or right heart failure. These clinical manifestations of constrictive pericarditis are similar to those attributed to cardiomyopathy. Since their haemodynamic and clinical features are similar, it is often challenging to distinguish constrictive pericarditis from a myocardial disease.

d) **Cardiac tamponade**

Cardiac tamponade is a serious medical condition which usually results from a penetration of the pericardium – the thin, double-walled sac that surrounds the heart. The cavity around the heart can fill with enough blood or other bodily fluids to compress the heart. As the fluid presses on the heart, less and less blood can enter. Less oxygen-rich blood is pumped to the rest of the body as a result. Insufficient blood reaching the heart and the rest of the body can eventually cause shock, organ failure and cardiac arrest. Tamponade is an extreme form of a pericardial effusion in which the volume of fluid that has accumulated is sufficient to compress the atria and their inflow vein and prevent the filling of the heart. This produces severe cardiac failure or arrest, with pulseless electrical activity. The cause is usually myocardial rupture, aortic dissection, trauma or severe acute pericarditis.

ACTIVITY 1.5

- (a) Define thrombosis.
- (b) Distinguish between a thrombus and an embolus.
- (c) What is a thromboembolism?
- (d) Describe venous and arterial thrombosis.
- (e) Define haemostasis.
- (f) What are the functions of normal haemostasis?
- (g) Write down the antithrombotic secretions of the endothelium.
- (h) Discuss the physiological functions of:
 - 1) Endothelin-1; 2) Tissue factor; 3) Platelet activating factor; 4) Von Willebrand factor and 5) Thromboxane A₂.
- (i) Describe the mechanism of coagulation cascades.
- (j) Distinguish between haemophilia and Christmas disease.

- (k) Discuss the three pathologically significant locations of a thrombus.
- (l) Define thrombolysis.
- (m) Discuss the sequelae following thrombosis.
- (n) Describe the five causes of embolus.
- (o) Distinguish between the four types of thromboembolism.
- (p) What is meant by disseminated intravascular coagulation?
- (q) Write down the complications of disseminated intravascular coagulation.
- (r) Define cardiac valvular disease and write down two functional abnormalities.
- (s) Discuss valvular stenosis and valvular regurgitation.
- (t) What are the major causes of cardiac valvular disease?
- (u) What are myocardial diseases?
- (v) Name and discuss the five primary myocardial diseases.
- (w) Distinguish between myocarditis, pericarditis and endocarditis.
- (x) Name the different types of pericarditis.
- (y) What is cardiac tamponade?

FEEDBACK ON ACTIVITY 1.5

- (a–q) Refer to section 1.12 of the study guide and pages 88–94 of the textbook.
- (r–t) Study section 1.15 of study guide and pages 94–95 of the textbook.
- (u–y) Read pages 96–97 of the textbook and section 1.16 (a–d).

LEARNING UNIT 2: PULMONARY DISORDERS

2.1 Introduction

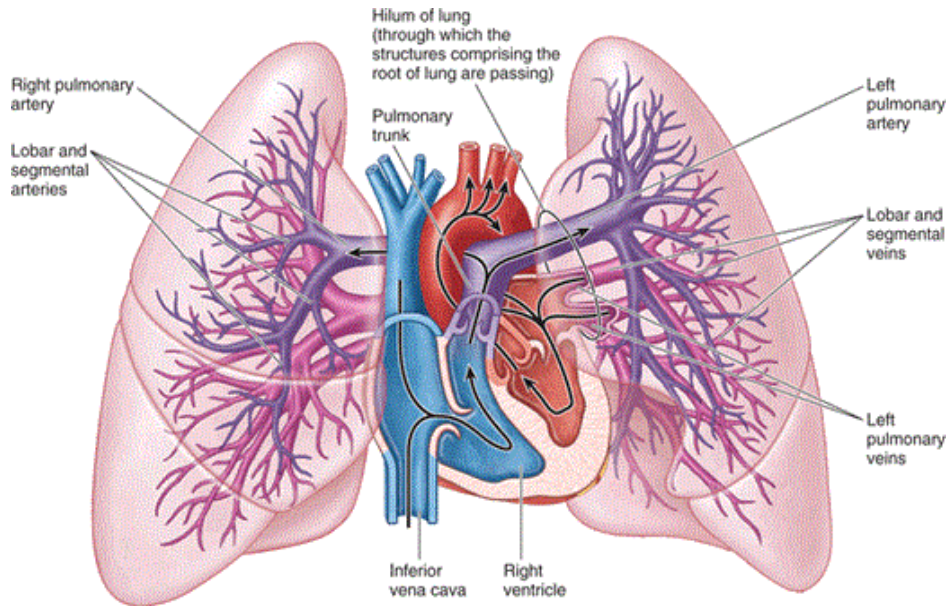


Figure 2.1: Pulmonary vascular system

(https://healtheappointments.com/wp-content/uploads/2016/11/m_Moore-ch001-image037.gif)

2.2 Learning outcomes

Upon completion of this learning unit you should be able to

- describe pulmonary embolism
- comprehend pulmonary infarction and pulmonary hypertension
- distinguish between primary pulmonary hypertension and pulmonary venous hypertension
- describe pneumonia and bronchiectasis
- discuss the clinical diagnosis of tuberculosis
- describe and discuss tuberculosis and its complications
- describe the relationship between HIV and TB
- define the causes and pathology of chronic obstructive pulmonary disease (COPD)
- describe the deficiency of alpha-1 antitrypsin
- describe the causes, epidemiology and pathogenesis of fibrosing and extrinsic allergic alveolitis
- describe the tumours and carcinomas of the lung and pleura.

Recommended reading: chapters 41-48 of Finlayson and Newell (2009).

Website: <http://www.webmd.com/lung/pulmonary-vascular-disease#1>

2.3 Pulmonary vascular disease

The definition of pulmonary vascular disease is simple: any condition that affects the blood vessels along the route between the heart and lungs. Blood travels from the heart to the lungs, and back to the heart. This process continually refills the blood with oxygen, and lets carbon dioxide be exhaled.

The process of pulmonary circulation operates in this manner:

- Oxygen-poor blood returns from the body's tissues through the veins back to the right side of the heart.
- The right heart pumps oxygen-poor blood through the pulmonary arteries into the lungs. This blood becomes filled with oxygen.
- The oxygen-rich blood returns from the lungs back to the left side of the heart. The left heart pumps the oxygen-rich blood into the body through the aorta and many other arteries.

Any part of the heart–lung blood circuit can become damaged or blocked, leading to pulmonary vascular disease. The causes of pulmonary vascular disease vary according to which of the lungs' blood vessels are affected. Pulmonary vascular disease is divided into several categories (see below).

2.3.1 Pulmonary embolism

Pulmonary embolism (PE) is a blockage in one of the pulmonary arteries in the lungs. It is a condition in which an embolus impacts within the pulmonary vasculature. In most cases, pulmonary embolism is caused by blood clots that travel to the lungs from the lower limbs or pelvis, but rarely from other parts of the body. PE occurs when a clump of material, most often a blood clot, becomes wedged in an artery in the lungs. Such blood clots most commonly come from the deep veins of the lower limbs and pelvis (deep vein thrombosis). The right side of the heart is a much rarer source of PE. Pulmonary emboli are thromboemboli and other rare sorts occur, stemming from

- bone marrow/mature adipose tissue (after fracture)
- amniotic fluids
- tumour cells and
- air.

The risk of blood clots is increased by

- cancer
- prolonged bed rest
- smoking
- stroke
- certain genetic conditions
- oestrogen-based therapy
- pregnancy
- obesity and
- types of surgery.



Figure 2.2: A clot in the pulmonary artery

(https://thoracickey.com/wp-content/uploads/2016/06/c00073_f073-005-9781455751341.jpg)

A small proportion of cases are due to the embolisation of **air**, **fat** or **amniotic fluid**. Symptoms of PE are typically sudden in onset and may include one or many of the following:

- dyspnea (shortness of breath)
- tachypnea (rapid breathing)
- chest pain of a “pleuritic” nature (worsened by breathing) and
- cough and haemoptysis (coughing up of blood).

More severe cases can include signs such as cyanosis (blue discoloration, usually of the lips and fingers), collapse, and circulatory instability because of decreased blood flow through the lungs and into the left side of the heart. About 15 per cent of all cases of sudden death are attributable to PE.

2.3.2 Pulmonary infarction

A pulmonary infarction is necrosis of one or more sections of lung tissue due to deprivation (inadequate blood supply), most commonly due to a blockage in the blood vessels supplying the lung tissue. Typically, a pulmonary infarction is accompanied by haemoptysis (coughing up of blood), fever, dyspnoea (shortness of breath) and/or pleurisy-like pain (chest pain in the area of the infarction, when drawing a breath).

By far the most common cause of pulmonary infarction is pulmonary embolism (a blood clot that travels to the lung). Several other medical conditions can, however, produce a pulmonary infarction, including cancer, autoimmune diseases such as lupus, various infections, sickle cell disease, infiltrative lung diseases such as amyloidosis or the embolisation of air or other materials from an intravenous catheter.

Whatever the cause, pulmonary infarction is relatively rare, because lung tissue has three potential sources for oxygen: the pulmonary artery, the bronchial artery (arteries that supply the bronchial tree) and the alveoli themselves (the air sacs in the lungs).

2.3.3 Pulmonary hypertension

Pulmonary hypertension (PHT) is high blood pressure in the heart-to-lung system that delivers fresh (oxygenated) blood to the heart while returning used (oxygen-depleted) blood back to the lungs. In one form of pulmonary hypertension, tiny arteries in the lungs (called pulmonary arterioles) and capillaries become narrowed, blocked or destroyed. As a result, it is harder for blood to flow through the lungs, and raises pressure within the lungs' arteries. As the pressure builds, the right ventricle must work harder to pump blood through the lungs, eventually causing the heart muscle to weaken and fail.

The World Health Organisation (WHO) divides pulmonary hypertension (PH) into five groups based on aetiology:

Group 1: Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a rare disease characterised by elevated pulmonary artery pressure, with no apparent cause. PAH (also termed precapillary pulmonary hypertension) was previously termed primary pulmonary hypertension. Primary hypertension is an arterial pressure within the pulmonary circulation of more than 30 mmHg. PAH with no identifiable cause is referred to as idiopathic pulmonary hypertension. PAH can be inherited

(genetically passed from parents to children), it can be caused by drugs or toxins, such as street drugs and certain diet-related medicines, or by conditions such as:

- Connective tissue diseases (connective tissue helps support all parts of the body, including the skin, eyes and heart)
- HIV infection
- Liver disease
- Congenital heart disease (present at birth)
- Sickle cell disease and
- Schistosomiasis (infection caused by a parasite).

Group 2: Pulmonary venous hypertension

Group 2 includes PH with left heart disease. Conditions that affect the left side of the heart, such as mitral valve disease or long-term high blood pressure, can cause left heart disease and PH. Left heart disease is likely the most common cause of PH. Pulmonary venous hypertension (PVH) is caused by diseases of the left side of the heart, such as heart failure or mitral valve disease.

Group 3: Pulmonary hypertension

Group 3 includes PH associated with lung diseases such as COPD (chronic obstructive pulmonary disease) and interstitial lung diseases, which cause scarring of the lung tissue. It includes PH associated with sleep-related breathing disorders, such as sleep apnea.

Group 4: Pulmonary hypertension

Group 4 includes PH caused by blood clots in the lungs or blood clotting disorders.

Group 5: Pulmonary hypertension

Group 5 includes PH caused by various other diseases or conditions.

Examples include:

- Blood disorders, such as polycythemia vera and essential thrombocythemia
- Systemic disorders, such as sarcoidosis and vasculitis. Systemic disorders involve many of the organs of the body
- Metabolic disorders, such as thyroid disease and glycogen storage disease. In glycogen storage disease, the cells of the body do not use a form of glucose (sugar) properly
- Other conditions, such as tumours that press on the pulmonary arteries, and kidney disease.

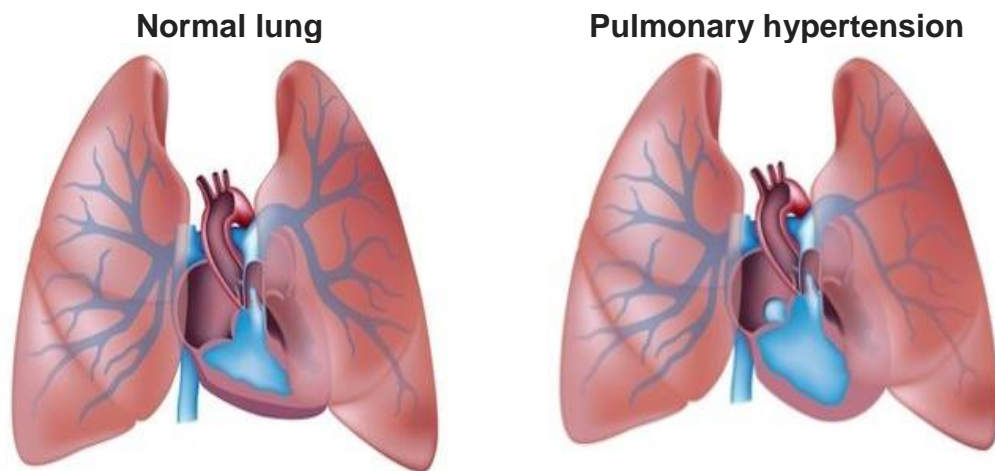


Figure 2.3: Pulmonary hypertension

(<http://www.thehealthsite.com/wp-content/uploads/2017/05/pulmonary-hypertension.jpg>)

Certain heart diseases, including aortic valve disease, left heart failure, mitral valve disease and congenital heart disease, can also cause pulmonary hypertension. Thromboembolic disease, a blood clot in a large pulmonary artery, can result in the development of pulmonary hypertension.

Pulmonary hypertension can be caused by

- certain drugs
- diseases (scleroderma, dermatomyositis, systemic lupus)
- infections (HIV, schistosomiasis)
- liver disease
- valvular heart disease
- congenital heart disease
- chronic obstructive pulmonary disease (COPD)
- blood clots in the lungs
- persistent pulmonary hypertension of the new-born (PPHN)
- rheumatoid arthritis
- parasitic lung disease
- sickle cell disease
- sarcoidosis and
- interstitial lung disease.

Risk factors for pulmonary hypertension include

- liver failure
- chronic lung disease
- blood clotting disorders
- underlying diseases such as scleroderma, dermatomyositis and systemic lupus erythematosus.

Signs and symptoms of pulmonary hypertension include

- shortness of breath
- difficulty breathing with exertion
- dizziness
- rapid breathing (tachypnea) and
- rapid heart rate (tachycardia).

Pulmonary hypertension is diagnosed by measuring pulmonary pressures by doing either an ultrasound of the heart (echocardiogram) or right heart catheterisation.

2.4 Pneumonia

Pneumonia is an acute disease marked by inflammation of the lung tissue, accompanied by the infiltration of alveoli and often bronchioles with white blood cells (such as neutrophils) and fibrinous exudate. It is characterised by

- fever
- chills
- cough
- difficulty breathing
- fatigue
- chest pain and
- reduced lung expansion (caused by infectious agents such as a bacterium, virus or fungus).

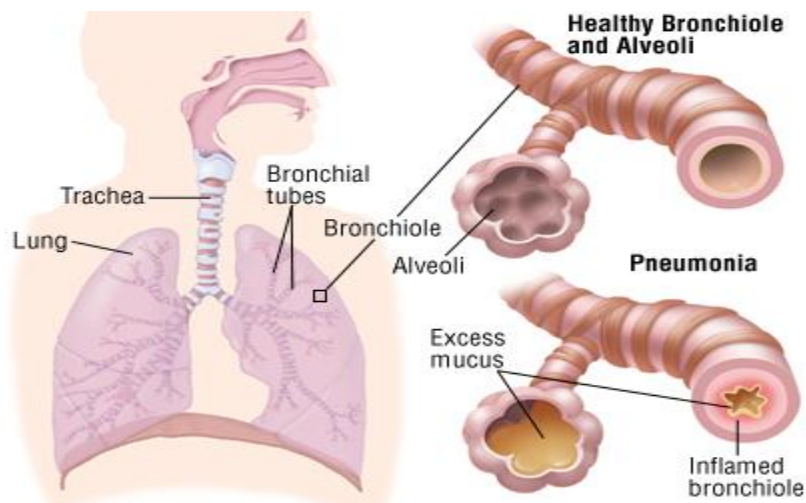


Figure 2.4: Pneumonia

(<https://www.drugs.com/health-guide/images/204871.jpg>)

2.4.1 Epidemiology

Pneumonia is a common illness with an incidence of 100-300 per 100 000 individuals per year. The disease tends to present in the very young and the elderly, although other age groups are not exempt. The overall rate of female to male is equal, although some variation occurs within the subtypes, especially *Klebsiella pneumoniae* which is more common in males.

Pneumonia can be caused by fungi, bacteria or viruses; *Streptococcus pneumoniae* I and *Mycoplasma pneumoniae* are the most common causes of bacterial pneumonia. People who suffer from chronic obstructive pulmonary disease (COPD) or alcoholism most often contract pneumonia from *Klebsiella pneumoniae* and *Haemophilus influenzae*.

Pneumonia can be divided into two main types, depending on the site of infection, namely

- lobar pneumonia and
- bronchopneumonia.

Other classifications reflect the pattern of acquisition and show a division into

- community acquired
- hospital acquired
- the immunocompromised and
- aspiration pneumonia.

a) Lobar pneumonia

Lobar pneumonia (also known as non-segmental or focal non-segmental pneumonia) is a radiological pattern associated with the homogenous, fibrinosupparative consolidation of one or more lobes of a lung in response to bacterial pneumonia. Lobar pneumonia evolves in four stages. Common to all stages is the enlargement of the affected lobe, with loss of its spongy appearance.

- In the **first stage**, congestion (days 1-2), the affected lung parenchyma is partially consolidated and red-purple, partially aerated. Microscopy: alveolar lumen contains serous exudate, bacteria and rare leucocytes.
- In the **second stage**, red hepatisation (days 3-4), the pulmonary lobe appears consolidated, red-brown, dry, firm, with a liver-like consistency. The cut surface is dry and rough. Microscopy: the characteristic aspect of this stage is determined by the accumulation in the alveolar spaces of an exudate (mainly) rich in fibrin, with bacteria,

leucocytes and erythrocytes. Alveolar walls are thickened due to capillary congestion and oedema.

- In the **third stage**, gray hepatisation (days 5-7), the affected lobe has a liver-like consistency, with a uniform gray colour. On the cut surface, a grayish purulent liquid drains. That is because the alveolar lumens are filled with leukocytic (suppurative) exudate (neutrophils and macrophages, in order to remove the fibrin). Capillary congestion and edema are still present, therefore the alveolar walls are thick.
- The **resolution stage** begins on day 8 and continues for three weeks (uncomplicated cases), while the exudate within the alveolar spaces will be drained through lymphatics and airways (“productive” cough), with the gradual aeration of the affected segment.

b) **Bronchopneumonia (lobular pneumonia)** is an acute exudative suppurative inflammation of the lungs, characterised by foci of consolidation surrounded by normal parenchyma. Generally, it is produced by bacteria:

- *Staphylococcus aureus*
- *Streptococcus*
- *Haemophilus influenzae*
- *Proteus mirabilis*
- *Escherichia coli*.

Bacteria are responsible for the transmission of bronchopneumonia. The disorder arises when bacteria enter the lungs. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most common forms of bacteria that lead to the development of bronchial pneumonia. When the pulmonary lobes are infected by bacteria, mucus produced by the lungs fills the alveolar sacs. This, in turn, results in a condition known as consolidation, which happens when the air space is reduced due to the build-up of mucus in the lungs. Reduced air space leads to respiratory difficulties such as shallow (laboured) breathing or shortness of breath.

2.5 Bronchiectasis

Bronchiectasis is a disease in which there is permanent enlargement of parts of the airways of the lung. Symptoms typically include a chronic cough producing mucus. Other symptoms include shortness of breath, coughing up of blood, and chest pain. Wheezing and nail clubbing may also occur.

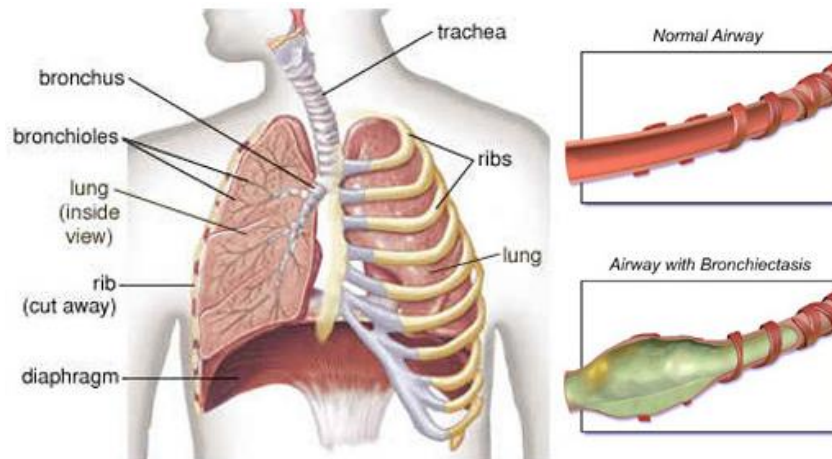


Figure 2.5: An airway affected with bronchiectasis

(<http://healthtips1.com/Bronchiectasis.jpg>)

ACTIVITY 2.1

- What are pulmonary diseases?
- Describe how pulmonary circulation operates.
- Name the three categories of pulmonary disease.
- Name the risk factors that increase the chances of blood clot formation.
- Write down the symptoms of pulmonary embolism.
- Write down the three potential sources of oxygen in the lungs.
- What is pulmonary hypertension?
- List the causes and risk factors of pulmonary hypertension.
- Define and write down the characteristics of pneumonia.
- Name two main types of pneumonia depending on the site of infection.
- Distinguish between lobar pneumonia and bronchopneumonia.
- Discuss the four evolutionary stages of lobar pneumonia.
- Define bronchiectasis.

FEEDBACK ON ACTIVITY 2.1

- Did you mention blood vessels along the route between the heart and lungs?
- Did you mention CO_2 , O_2 , deoxygenated and oxygenated blood?
- Embolism, infarction and hypertension.
- (d–f) Study section 2.3 (1) above.
- Study sections 2.3 (3) and 2.3 (4) and pages 98–99 in the textbook.
- Look at section 2.3.3. and study pages 98–99 in the textbook.
- (i–m) Study sections 2.4 and 2.5 and pages 100–103 in the textbook.

LEARNING UNIT 3: GASTROINTESTINAL DISEASES

3.1 Introduction

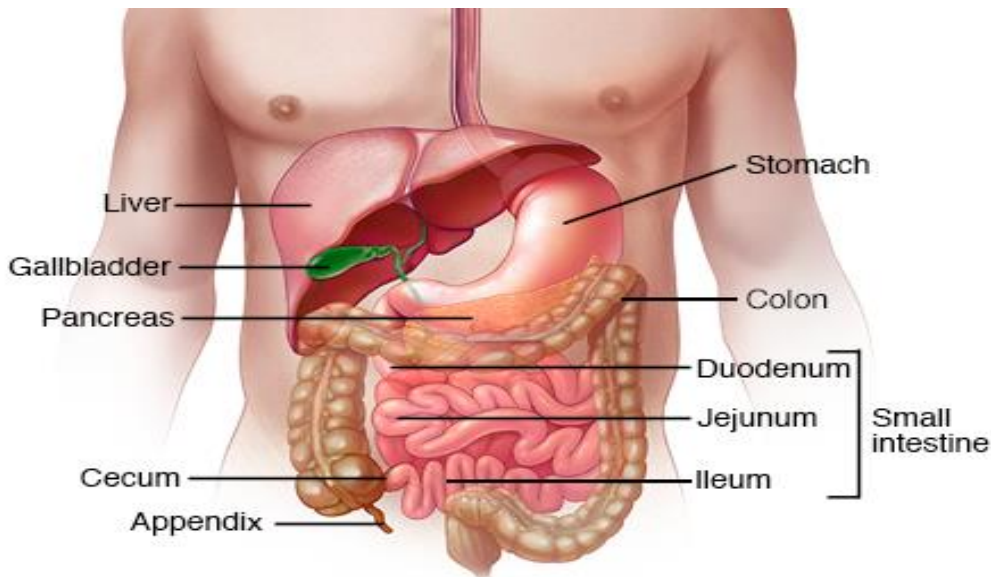


Figure 3.1: Gastrointestinal system

(https://www.mayoclinic.org/-/media/kcms/gbs/patient-consumer/images/2014/09/25/10/21/mcdc7_crohns.ashx) (Mayo Foundation for Medical Education and Research)

To complete this learning unit, you will need to refer to chapters 49–55 in Finlayson and Newell (2009).

3.2 Learning outcomes

Upon completion of this learning unit you should be able to

- define and describe the characteristics of malabsorption
- describe three conditions that predispose malabsorption
- discuss gluten-sensitive enteropathy
- show knowledge of diarrhoea and conditions that cause diarrhoea
- explain lactase deficiency or lactose intolerance
- describe coeliac diseases.
- discuss peptic ulcers
- describe the factors that cause lesions in the lining of the stomach, the oesophagus and the small intestine
- discuss gastroesophageal reflux disease
- write short notes on squamous cell carcinomas and gastric adenocarcinoma
- define lymphoma and distinguish between the two types
- recognise endocrine disorders, gastrointestinal stromal tumours, ulcerative colitis and Crohn's disease
- show knowledge of adenomas and polyps
- understand colorectal cancers and their types
- describe anal cancer.

3.3 Malabsorption

Malabsorption is a clinical term that encompasses defects occurring during the digestion and absorption of food nutrients by, and infections of, the gastrointestinal tract. The digestion or absorption of a single nutrient component may be impaired, as in lactose intolerance due to lactase deficiency. Malabsorption syndrome occurs when something prevents the bowel from absorbing important nutrients and fluids, including proteins, fats and vitamins.

Malabsorption can be caused by conditions such as

- coeliac disease
- Crohn's disease
- lactose intolerance
- intestinal damage.

Malabsorption can occur at any stage in the absorption pathway, and is characterised by the following:

1) Loss of digestive enzymes

- Brush border enzymes which digest lactose/milk fat: congenital disaccharidase deficiency
- Pancreatic enzymes which digest carbohydrates, fat or protein, e.g. the destruction of parenchyma in the pancreas or a stricture in the pancreatic duct due to cystic fibrosis.

2) Lack of bile salts for the emulsification of fats

- Common bile duct obstruction by gallstones
- Carcinoma of the head of the pancreas.

3) Loss or damaged absorptive surface

- gluten-sensitive enteropathy
- tropical sprue (rare chronic bacterial infection)
- Crohn's disease
- blockage in the absorptive pathway
- damage to the intestine from infection, inflammation, trauma or surgery
- prolonged use of antibiotics
- coeliac disease, chronic pancreatitis or cystic fibrosis
- lactase deficiency or lactose intolerance
- congenital biliary atresia (when the bile ducts do not develop normally and prevent the flow of bile from the liver)
- diseases of the gallbladder, liver or pancreas
- parasitic diseases
- scarring from radiation therapy, which may injure the lining of the intestine
- drugs which injure the lining of the intestine (tetracycline, colchicine or cholestyramine)
- malignant lymphoma
- congenital deficiency of transport proteins.

Certain diseases may cause malabsorption. These include tropical sprue, a condition most common in the Caribbean, India and other parts of Southeast Asia. This disease may be related to environmental factors, such as toxins in food, infection or parasites. An even rarer potential cause of malabsorption is Whipple's disease, which is the result of a bacterial infection.

3.4 Tumours of small intestines

Benign tumours of the small bowel are rare clinical entities that often remain asymptomatic throughout life. Despite comprising 75 per cent of the length and 90% of the surface area of the gastrointestinal (GI) tract, the small bowel harbours relatively few primary neoplasms and fewer than two per cent of GI malignancies.

Benign small-bowel tumours may develop as a single lesion or as multiple lesions of several subtypes, including hyperplastic polyps, adenomas, gut stromal tumours, lipomas, haemangiomas and those associated with Peutz-Jeghers syndrome.

Benign small-bowel tumours may be found throughout the duodenum, jejunum and ileum (in order of increasing frequency). Tumours may be single, multiple or widespread, that is, as part of a polyposis syndrome. Three growth patterns have been identified:

- intraluminal
- infiltrative
- serosal.

3.5 Gluten-sensitive enteropathy

Gluten-sensitive enteropathy (or, as it is more commonly called, coeliac disease) is an autoimmune inflammatory disease of the small intestine that is precipitated by the ingestion of gluten (a component of wheat protein) in genetically susceptible persons. The exclusion of dietary gluten results in healing of the mucosa, the resolution of the malabsorptive state, and the reversal of most (if not all) effects of coeliac disease. Recent studies in the United States suggest that the prevalence of coeliac disease is approximately one case per 250 persons. Gluten-sensitive enteropathy commonly manifests as "silent" coeliac disease (i.e. minimal or no symptoms). Serological tests for antibodies against endomysium, transglutaminase and gliadin identify most patients with the disease. Serological testing should be considered in patients who are at increased genetic risk of gluten-sensitive enteropathy (i.e. family history of coeliac disease or personal history of type I diabetes) and in patients who have chronic diarrhoea, unexplained anaemia, chronic fatigue or unexplained weight loss. Early diagnosis and management are important to forestall the serious consequences of malabsorption, such as osteoporosis and anaemia.

3.6 Diarrhoea

Acute **diarrhoea** is defined as the abrupt onset of three or more loose stools per day, lasting no longer than 14 days. Chronic or persistent diarrhoea is defined as an episode that lasts longer than 14 days.

Conditions that can cause persistent diarrhoea include

- irritable bowel syndrome – a poorly understood condition, where the normal functions of the bowel are disrupted
- laxatives and drugs which interfere with water absorption
- infection or toxins (*Vibrio cholera* and *Clostridium difficile*)
- coeliac disease – a digestive condition where the individual is intolerant of the protein gluten
- Crohn's disease – a condition that causes inflammation of the lining of the digestive system
- cystic fibrosis – an inherited condition that affects the lungs and digestive system
- diabetes – a condition where there is too much glucose in the blood
- diverticular disease – when small pouches (diverticula) form in the large intestine, causing symptoms such as diarrhoea
- failure to absorb bile salts if the small bowel is shortened or damaged (irritated colonic epithelium)
- gastrectomy – a surgical procedure to remove part of the stomach, for example, to treat stomach cancer
- lactose intolerance – lactose is a natural sugar found in milk
- microscopic colitis – a type of inflammatory bowel disease that causes watery diarrhoea
- neuroendocrine tumours (secrete gut-associated hormones)
- chronic pancreatitis – inflammation of the pancreas, a small organ that produces hormones and digestive juices
- ulcerative colitis – a condition that affects the colon (large intestine)
- bowel cancer – cancer in the bowel that can cause diarrhoea and blood in the stool.

3.7 Peptic ulcers

A peptic (stomach or duodenal) ulcer is a break in the inner lining of the oesophagus, stomach or duodenum. A peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the oesophagus, an oesophageal ulcer. Recent medical advances have increased our understanding of ulcer formation.



Figure 3.2: A gastric ulcer

(http://www.atlantaequine.com/images/gastric_ulcer.jpg)

Peptic ulcers result from an imbalance between factors that can damage the gastroduodenal mucosal lining and defence mechanisms that normally limit such injury. Aggressive factors include gastric juice (e.g. hydrochloric acid, pepsin and bile salts refluxed from the duodenum), *H pylori* and non-steroidal anti-inflammatory drugs (NSAIDs). Complications of peptic ulcer disease (PUD) include bleeding, perforation, penetration and gastric outlet obstruction.

- **Gastric ulcers** occur on the inside of the stomach
- **Duodenal ulcers** occur on the inside of the upper portion of the small intestine (duodenum).

Different factors can cause the lining of the stomach, the oesophagus and the small intestine to break down. These include

- *Helicobacter pylori* (*H. pylori*): bacteria that can cause a stomach infection and inflammation
- Drugs such as NSAIDs.

a) *H. pylori* is a type of bacteria. These germs can enter the body and live in the digestive tract. After many years they can cause sores, called ulcers, in the lining of the stomach or the upper part of the small intestine. For some people, an infection can lead to stomach cancer. After *H. pylori* enters the body it attacks the lining of the stomach, which usually protects the individual from the acid the body produces to digest food. Once the bacteria have done serious damage, acid can work through the lining, which leads to ulcers. These may bleed, cause infections or keep food from moving through the digestive tract.

b) NSAIDs are a drug class that group together drugs that provide analgesic (pain-killing) and antipyretic (fever-reducing) effects, and, in higher doses, anti-inflammatory effects. Most NSAIDs inhibit the activity of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) and thereby the synthesis of prostaglandins and thromboxanes. It is thought that inhibiting COX-2 leads to anti-inflammatory, analgesic and antipyretic effects, and that those NSAIDs also inhibiting COX-1 (particularly aspirin) may cause gastrointestinal bleeding and ulcers.

3.8 Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a digestive disorder that affects the lower oesophageal sphincter (LES), the ring of muscle between the oesophagus and the stomach. Many people, including pregnant women, suffer from heartburn or acid indigestion caused by GERD. Doctors believe that some people suffer from GERD due to a condition called hiatal hernia. In most cases, GERD can be relieved through diet and lifestyle changes; however, some people may require medication or surgery.

Gastroesophageal refers to the stomach and oesophagus; reflux means to flow back or return, therefore, gastroesophageal reflux is the return of the stomach's contents back up into the oesophagus. In normal digestion, the LES opens to allow food to pass into the stomach and closes to prevent food and acidic stomach juices from flowing back into the esophagus. Gastroesophageal reflux occurs when the LES is weak or relaxes inappropriately, allowing the stomach's contents to flow up into the oesophagus. One such cause of GERD is a hiatal (or hiatus) hernia. This is an anatomical abnormality, where a hole in the diaphragm allows the upper part of the stomach to enter the chest cavity, sometimes leading to GERD. Pregnancy can also cause acid reflux due to extra pressure being placed on the internal organs. GERD occurs when the quantity of gastric juice that refluxes into the oesophagus exceeds the normal limit, causing symptoms with or without associated oesophageal mucosal injury (i.e. oesophagitis).

3.9 Squamous cell carcinomas

Squamous cell carcinomas typically appear as persistent, thick, rough, scaly patches that can bleed if bumped, scratched or scraped. They often look like warts and sometimes appear as open sores with a raised border and a crusted surface. The two main sub-types of the disease are oesophageal squamous-cell carcinoma (ESCC), which is more common in the developing

world, and oesophageal adenocarcinoma (EAC), which is more common in the developed world. Squamous-cell carcinoma arises from the epithelial cells that line the oesophagus.

3.10 Gastric adenocarcinoma

Gastric adenocarcinoma is a cancer that affects the stomach. The stomach is an organ of the gastrointestinal tract which is responsible for digesting food that enters it from the oesophagus. Over 90 per cent of cancers that occur in the stomach are gastric adenocarcinomas.

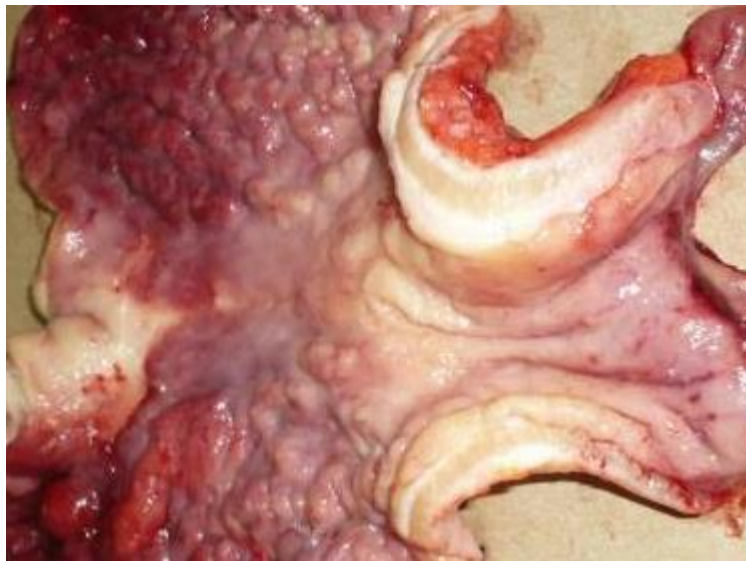


Figure 3.3: Gastric adenocarcinoma

(<https://medtube.net/images/min/9f03268e82461f179f372e61621f42d9/620/620/0>)

3.11 Lymphoma

Lymphoma is a form of cancer that affects the immune system, specifically, it is a cancer of immune cells called lymphocytes, a type of white blood cell. There are two broad types of lymphoma and many subtypes. The two types of lymphoma are Hodgkin's and non-Hodgkin's.

Lymphoma is typically associated with

- males
- 60 and older
- a weak immune system from HIV/Aids, an organ transplant or congenital autoimmune disease
- an immune system disease such as rheumatoid arthritis, Sjögren's syndrome, lupus or coeliac disease
- infection with a virus such as Epstein-Barr, hepatitis C, human T-cell leukemia/lymphoma (HTLV-1) or human herpesvirus 8 (HHV8)
- a close relative who had lymphoma

- exposure to benzene or chemicals that kill bugs and weeds
- having been treated for Hodgkin's or non-Hodgkin's lymphoma in the past
- having been treated for cancer with radiation
- being overweight.

Both Hodgkin's and non-Hodgkin's lymphoma are malignancies of a family of white blood cells known as lymphocytes, which fight off infections and other diseases. Hodgkin's lymphoma is marked by the presence of Reed-Sternberg cells, which are mature B-cells that have become malignant, are unusually large and carry more than one nucleus. The first sign of the disease is often the appearance of enlarged lymph nodes. Non-Hodgkin's lymphoma, by contrast, can be derived from B-cells or T-cells and can arise in the lymph nodes as well as other organs.

The two forms of lymphoma are marked by a painless swelling of the lymph nodes. Hodgkin's lymphomas are more likely to arise in the upper portion of the body (the neck, underarms or chest). Non-Hodgkin's lymphoma can arise in lymph nodes throughout the body, but also in normal organs. Patients with either type can have symptoms such as weight loss, fevers and night sweats.



Figure 3.4: Gastric lymphoma

(<http://www.gastrointestinalatlas.com/imagenes/Gastriclymphomazrt5.jpg>)

3.12 Neuroendocrine tumours

Neuroendocrine tumours (NETs) are neoplasms that arise from cells of the endocrine (hormonal) and nervous systems. Many are benign, while some are malignant. They most commonly occur in the intestines, where they are often called carcinoid tumours, but they are also found in the pancreas, lungs and the rest of the body.

3.13 Gastrointestinal stromal tumours

Gastrointestinal stromal tumours (GISTs) may be malignant (cancerous) or benign (not cancerous). They are most common in the stomach and small intestine, but may be found anywhere in or near the GI tract. Some scientists believe that GISTs begin in the interstitial cells of Cajal (ICC), in the wall of the GI tract.



Figure 3.5: Gastrointestinal stromal tumour

(<http://www.currentsurgery.org/index.php/jcs/article/viewFile/16/20/135>)

3.14 Ulcerative colitis

Ulcerative colitis is an inflammatory bowel disease (IBD) that causes long-lasting inflammation and ulcers (sores) in the digestive tract. Ulcerative colitis affects the innermost lining of the large intestine (colon) and rectum. A condition that causes inflammation of the intestines, such as ulcerative colitis or Crohn's disease, is known as IBD. Unlike IBD, inflammatory bowel syndrome (IBS) does not cause inflammation, ulcers or other damage to the bowel.

3.15 Crohn's disease

Crohn's disease is an inflammatory bowel disease (IBD). It causes inflammation of the lining of the digestive tract, which can lead to abdominal pain, severe diarrhoea, fatigue, weight loss and malnutrition.



Figure 3.6: Crohn's disease

(<https://i.ytimg.com/vi/hHM70EriFS4/maxresdefault.jpg>)

Inflammation caused by Crohn's disease can involve different areas of the digestive tract in different individuals and may affect any part of the gastrointestinal tract, from mouth to anus. Signs and symptoms often include abdominal pain, diarrhoea (which may be bloody if inflammation is severe), fever and weight loss.

ACTIVITY 3.1

- (a) Define malabsorption.
- (b) Describe three conditions that predispose malabsorption.
- (c) Describe the characteristics of malabsorption.
- (d) Discuss gluten-sensitive enteropathy.
- (e) List five conditions that can lead to diarrhoea.
- (g) Serological tests test for antibodies against which substances in gluten-sensitive enteropathy?
- (h) What are peptic ulcers?
- (i) Describe lactose intolerance.
- (j) What factors are responsible for the formation of peptic ulcers?
- (k) What is meant by gastroesophageal reflux disease?
- (l) How does gastroesophageal reflux disease cause heartburn?
- (m) Distinguish between squamous cell carcinoma and gastric adenocarcinoma.
- (n) Define lymphoma and describe two types.
- (o) Distinguish between Hodgkin's and non-Hodgkin's lymphoma.
- (p) Describe neuroendocrine tumours and gastrointestinal stromal tumours.
- (q) Describe Crohn's disease and its symptoms.

FEEDBACK ON ACTIVITY 3.1

- (a) Did you mention digestion and absorption defects or the inability to ingest food?
- (b) Did you mention coeliac disease, Crohn's disease, lactose intolerance and intestinal damage?

(c–i) Study sections 3.4. and 3.5 above and pages 114–117 in the textbook by Finlayson and Newell.

(j–m) Study sections 3.4. and 3.5 above and pages 115–117 in the textbook by Finlayson and Newell.

(k) Gastroesophageal reflux disease (GERD); study section 3.5 and page 119 in the textbook by Finlayson and Newell.

(n–q) Refer to section 3.8 and pages 121–125 in the textbook by Finlayson and Newell.

3.16 Adenomatous polyps

Adenomatous polyps (also called adenomas) are gland-like growths that develop on the mucous membrane which lines the large intestines.

Adenoma is a type of non-cancerous or benign tumour of the epithelial tissue, of glandular origin or with glandular characteristics, or both.

A polyp is a projection (growth) of tissue from the inner lining into the lumen (hollow centre) of the colon. Different types of polyps look different under the microscope. Polyps are benign (non-cancerous) growths, but cancer can start in certain types of polyps.

- **Adenomatous polyps (adenomas)** – these polyps sometimes change into cancer. Because of this, adenomas are called a *pre-cancerous condition*
- **Hyperplastic polyps and inflammatory polyps** – these polyps are more common, but in general they are not pre-cancerous.

Adenomas can have several different growth patterns that a pathologist can view under the microscope. The two major growth patterns are tubular and villous. Many adenomas have a mixture of both growth patterns, and are thus called tubulovillous adenomas. Most adenomas that are small (less than 1.0 cm) have a tubular growth pattern. Larger adenomas may have a villous growth pattern, and more often have cancers developing in them.

3.17 Colorectal cancer

Colorectal cancer (CRC), also known as bowel cancer or colon cancer, is the development of cancer from the colon or rectum. Two types of colorectal cancer can be distinguished:

- a) **Hereditary non-polyposis colorectal carcinoma (HNPCC)**, also called Lynch syndrome – it increases the risk of colon and other cancers. People with HNPCC tend to develop colon cancer before age 50.

- b) **Familial adenomatous polyposis (FAP)** – a rare disorder that causes the development of hundreds (even thousands) of polyps in the lining of the colon and rectum, beginning during the teenage years. Another risk factor for colorectal cancer is genetic mutations that can be inherited.

3.18 Anal cancer

Anal cancer is very different from colorectal cancer, which is much more common. The causes, risk factors, clinical progression, staging and treatment of anal cancer are all very different from colorectal cancer. Anal cancer presents as a lump which is created by the abnormal and uncontrolled growth of cells in the anus.

ACTIVITY 3.2

- (a) What is an adenoma?
- (b) Define a polyp.
- (c) Name the three growth patterns of adenomatous polyps.
- (d) What is an adenomatous polyp?
- (e) Describe two examples of inherited colorectal carcinomas.
- (f) What are the characteristics of anal cancer?
- (g) Distinguish between colorectal and anal cancer.

FEEDBACK ON ACTIVITY 3.2

- (a–d) Study section 3.13 above and pages 126–127 in the textbook by Finlayson and Newell.
- (e–g) Study section 3.14 and pages 126–127 in the textbook by Finlayson and Newell.

LEARNING UNIT 4: GYNAECOLOGICAL DISEASES

4.1 Introduction

Gynaecological disorders affect the internal and external organs in the female pelvic and abdominal areas. These disorders include dysmenorrhoea (pain associated with menstruation), vulvodynia (unexplained chronic discomfort or pain in the vulva) and chronic pelvic pain (a persistent and severe pain primarily occurring in the lower abdomen, for at least six months). Some problems can affect the proper functioning of the reproductive system, as well as a woman's ability to fall pregnant. One example, polycystic ovary syndrome, occurs when immature follicles in the ovaries clump together to create a large cyst, preventing mature eggs from being released. Another reproductive disorder, endometriosis, occurs when the type of tissue that lines the uterus grows elsewhere, such as on the ovaries or on other abdominal organs. Uterine fibroids are non-cancerous tumours that grow in the uterine cavity, within the wall or on the outside of the uterus.

To complete this learning unit, you will need to refer to chapters 32–40 in Finlayson and Newell.

4.2 Learning outcomes

Upon completion of this learning unit you should be able to

- understand gynaecological diseases and their symptoms
- describe ovarian cancer
- discuss epithelial tumours
- describe germ cell carcinoma, teratomas and dysgerminoma
- describe a dermoid cyst
- classify sex cord stromal tumours
- distinguish the four types of uterine condition
- describe the four types of uterine cancer
- discuss cervical cancer
- define and explain the risk factors of cervical cancer.

4.3 Gynaecological diseases

A gynaecological disease is a condition that affects the female reproductive system or organs in the abdomen or pelvic area, namely the uterus, ovaries, fallopian tubes, vagina and vulva.

Such diseases include

- cancer and pre-cancerous diseases of the reproductive organs (including ovaries, fallopian tubes, uterus, cervix, vagina and vulva)

- urinary incontinence
- amenorrhoea (absent menstrual periods)
- dysmenorrhoea (painful menstrual periods) and
- infertility.

4.3.1 Ovarian cancer

Ovarian cancer refers to any cancerous growth that occurs in the ovary. The majority of ovarian cancers arise from the epithelium (outer lining) of the ovary.



Figure 4.1: Ovarian cancer

(<http://img.medscapestatic.com/pi/meds/ckb/15/38015tn.jpg>)

Different types of ovarian cancer are classified according to the type of cell from which they originate:

- Epithelial tumours – about 90 per cent of ovarian cancers develop in the epithelium, the thin layer of tissue covering the ovaries
- Germ cell carcinoma tumours
- Stromal carcinoma tumours
- Small cell carcinoma.

- a) **Epithelial tumours** – there are several types of benign epithelial tumours, including serous adenomas, mucinous adenomas and Brenner tumours. Cancerous epithelial tumours are carcinomas, meaning they begin in the tissue that lines the ovaries. These are called borderline tumours or tumours of low malignant potential (LMP tumours).
- b) **Germ cell carcinoma tumours** – a germ cell tumour (GCT) is a neoplasm derived from germ cells. GCTs can be cancerous or non-cancerous. Germ cells normally occur inside the gonads (ovaries and testes).
- c) **Teratomas** – a teratoma is a tumour with tissue or organ components resembling normal derivatives of more than one germ layer. Although the teratoma may be

monodermal or polydermal (originating from one or more germ layers), its cells may differentiate in ways suggesting other germ layers. A mature teratoma (also known as a dermoid cyst) contains tissues from the three embryonic layers. A dermoid cyst is a saclike growth that is present at birth. It contains structures such as hair, fluid, teeth or skin glands that can be found on or in the skin. Dermoid cysts grow slowly and are not tender unless ruptured

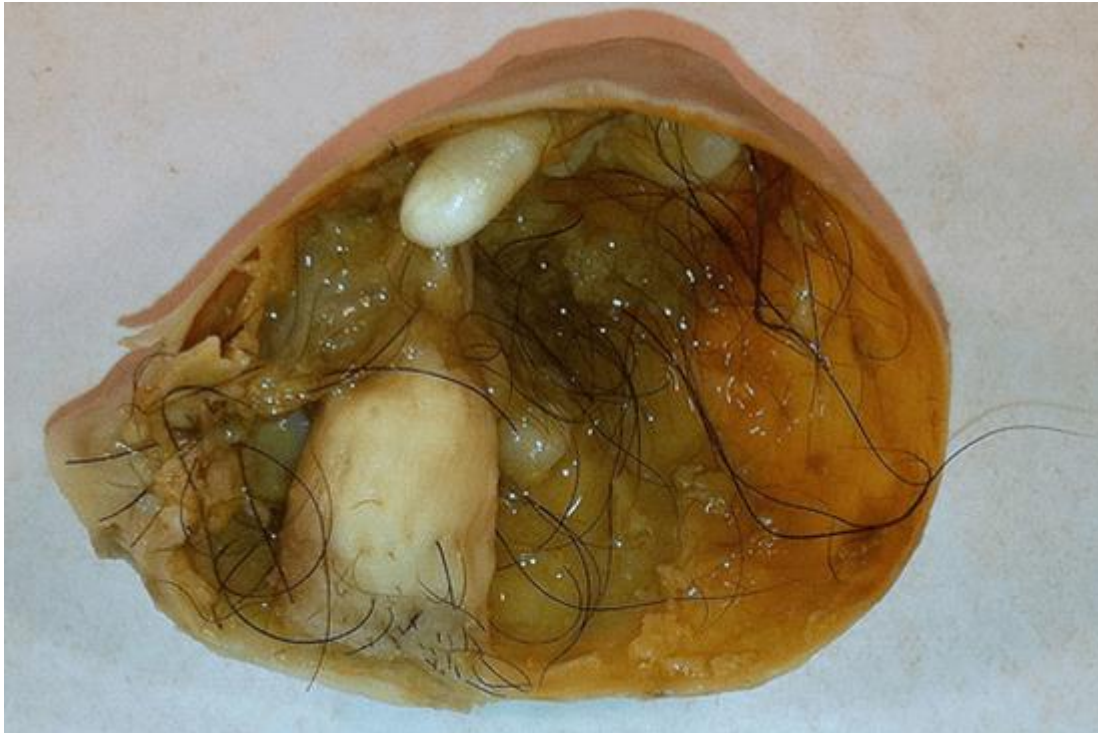


Figure 4.2: Mature teratoma (dermoid cyst) showing structures such as hair, skin and teeth.

(https://i0.wp.com/alterreddimensions.net/main/wp-content/uploads/2016/01/image_thumb-29-1.png?fit=550%2C366)

4.3.2 Dysgerminoma

A dysgerminoma is a type of germ cell tumour; it is malignant and usually occurs in the ovary. A tumour with the identical histology but not occurring in the ovary may be described by an alternate name: seminoma in the testes or germinoma in the central nervous system or other parts of the body.



Figure 4.3: Ovarian dysgerminoma

(https://farm9.staticflickr.com/8832/17324694382_bba1797460_b.jpg)

A dysgerminoma is a tumour of the ovary that is composed of primitive, undifferentiated germ cells. Germ cell tumours arise from the primordial germ cells of the ovaries and the testes.

4.3.3 Sex cord stromal tumours

Sex cord stromal tumours are groups of tumours composed of granulosa cells, theca cells, Sertoli cells, Leydig cells and fibroblasts of stromal origin, singly or in various combinations.

Sex cord-stromal tumours are classified into the following categories:

- Adult granulosa-stromal cell tumours
- Juvenile granulosa cell ovarian tumours
- Gynandroblastoma
- Benign ovarian fibroma
- Malignant ovarian fibroma
- Sertoli cells
- Leydig cells
- Sertoli-Leydig cells
- Mixed variants.

4.3.4 Benign uterine conditions

Uterine growths are tissue enlargements of the womb (uterus). These growths can be caused by either harmless or dangerous conditions. Four types are distinguished:

- Fibroids
- Adenomyosis
- Endometriosis
- Salpingitis.

4.3.5 Uterine cancer

Endometrial cancer (also called uterine cancer) begins in the uterus. The uterus is the hollow, pear-shaped pelvic organ in women where foetal development occurs. Endometrial cancer begins in the layer of cells that form the lining (endometrium) of the uterus.

There are four major types of uterine cancer:

- a) **Endometrial carcinoma** is a cancer that arises from the endometrium (the lining of the uterus or womb). It is the result of the abnormal growth of cells that have the ability to invade or spread to other parts of the body.
- b) **Carcinosarcomas** are malignant tumours that consist of a mixture of carcinoma (or epithelial cancer) and sarcoma (or mesenchymal/connective tissue cancer). Carcinosarcomas are rare tumours which can arise in diverse organs such as the skin, salivary glands, lungs, oesophagus, pancreas, colon, uterus and ovaries.
- c) **Leiomyosarcoma** (LMS) is a type of soft tissue sarcoma. Soft tissue sarcomas can develop in muscle, fat, blood vessels or any of the other tissues that support, surround and protect the organs of the body. Leiomyosarcoma is one of the more common types of soft tissue sarcomas to develop in adults.
- d) **Endometrial stromal sarcoma** is a malignant subtype of endometrial stromal tumour arising from the stroma (connective tissue) of the endometrium, rather than the glands.

4.3.6 Cervical cancer

Cervical cancer occurs in the cells of the cervix, the lower part of the uterus that connects to the vagina. Various strains of the human papillomavirus (HPV), a sexually transmitted infection, play a role in incidences of cervical cancer.

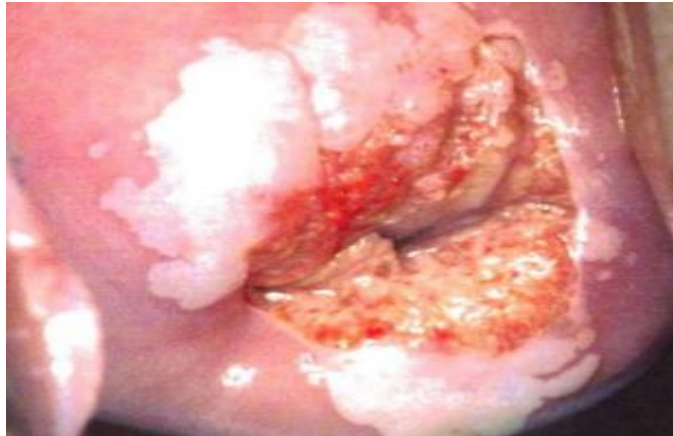


Figure 4.4: Cervical cancer

(<https://image.slidesharecdn.com/nownfs68spk8qkmb5cbb-signature-cervical-cancer-17-638.jpg>)

Causes and risk factors for cervical cancer include

- human papillomavirus (HPV) infection
- having many sexual partners
- smoking
- taking birth-control pills
- engaging in early sexual contact.

ACTIVITY 4.1

- (a) What are gynaecological diseases?
- (b) Classify ovarian cancers according to the type of cell from which they originate.
- (c) Name three types of epithelial cell tumour.
- (d) What are germ cell carcinomas?
- (e) Distinguish between teratoma and dysgerminoma and germ cell carcinomas.
- (f) Classify the cells of the sex cord tumours.
- (g) Write down the four types of benign uterine tumours.
- (h) Describe the four types of uterine cancer.
- (i) Define cervical cancer and list the risk factors.
- (j) Distinguish between amenorrhoea and dysmenorrhoea.

FEEDBACK ON ACTIVITY 4.1

(a–d) Look at section 4.3 above and study pages 164–167 in the textbook by Finlayson and Newell.

(e–l) Refer to section 4.3 (c–h) and pages 168–171 of the textbook by Finlayson and Newell.

LEARNING UNIT 5: CENTRAL NERVOUS SYSTEM DISEASES

5.1 Introduction

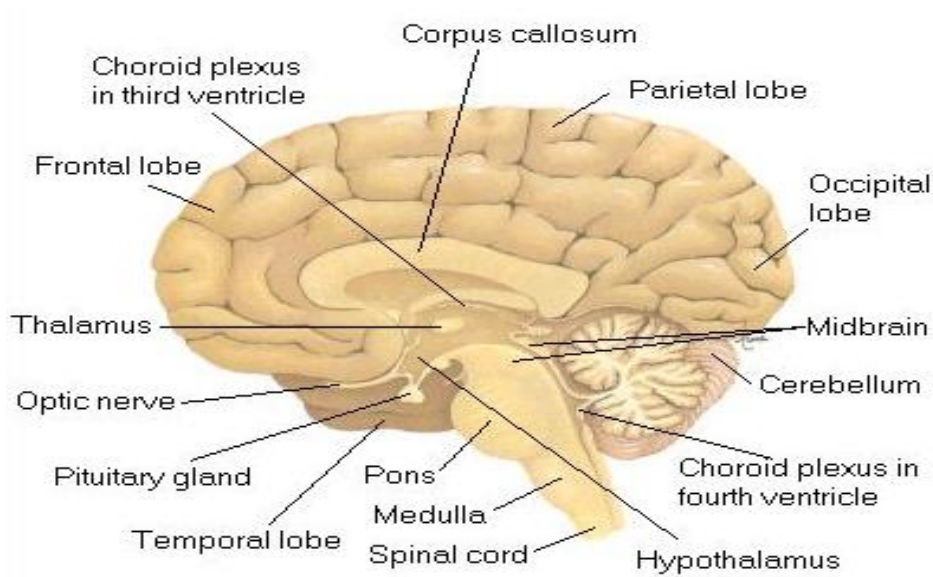


Figure 5.1: Internal structures of the brain

(<https://s-media-cache-ak0.pinimg.com/736x/bb/38/7c--cross-section-brain-health.jpg>)

Central nervous system (CNS) disease is a broad category of conditions in which the brain does not function as it should, limiting health and the ability to function. The condition may be an inherited metabolic disorder, the result of damage from an infection, a degenerative condition, stroke, a brain tumour or other problems, or may arise from unknown or multiple factors. Movement disorders such as Parkinson's disease, dystonia and essential tremor are central nervous system conditions. What they have in common is the loss of sufficient, intact nervous system circuits that orchestrate functions as varied as memory formation (in Alzheimer's) or voluntary motion (in movement disorders).

To complete this learning unit, you will need to refer to chapters 79–87 in Finlayson and Newell.

5.2 Learning outcomes

Upon completion of this learning unit you should be able to

- define central nervous system disorders
- distinguish between primary and secondary brain tumours
- define cerebrovascular accidents and types of cerebrovascular accidents
- describe strokes and their symptoms
- Name the risk factors for stroke
- explain what traumatic brain injury and intercranial haemorrhage are

- describe epidural and extradural haemorrhage
- explain what brain contusion is
- explain what brain tumours are
- distinguish between primary and secondary brain tumours
- define meningitis and explain the types (bacterial, viral and fungal)
- explain brain and intracranial abscesses
- describe Parkinson's disease
- describe Huntington's disease
- describe multiple sclerosis
- describe Guillain-Barre syndrome
- define dementia
- describe prion diseases.

5.3 Central nervous system disorders

The central nervous system (CNS) controls most functions of the body and mind. It consists of two parts: the brain and the spinal cord. The brain is the centre of all thought, the interpreter of the external environment, and the origin of control over bodily movements. A CNS disease can affect either the brain or the spinal cord, resulting in neurological or psychiatric disorders.

Causes of CNS diseases include

- trauma
- infections
- degeneration
- autoimmune disorders
- structural defects
- tumours
- stroke.

5.3.1 Cerebrovascular accident

Cerebrovascular accident (CVA) is the medical term for a stroke. A stroke is when blood flow to a part of the brain is stopped either by a blockage in, or the rupture of, a blood vessel. There are two main types of cerebrovascular accident or stroke: an ischemic stroke is caused by a blockage, while a haemorrhagic stroke is caused by the rupture of a blood vessel. Both types of stroke deprive part of the brain of blood and oxygen, causing brain cells to die. The result is sudden loss of speech, weakness, paralysis on one side of the body and lasting brain damage.

a) Ischemic stroke

An ischemic stroke is the most common and occurs when a blood clot blocks a blood vessel and prevents blood and oxygen from reaching a part of the brain.

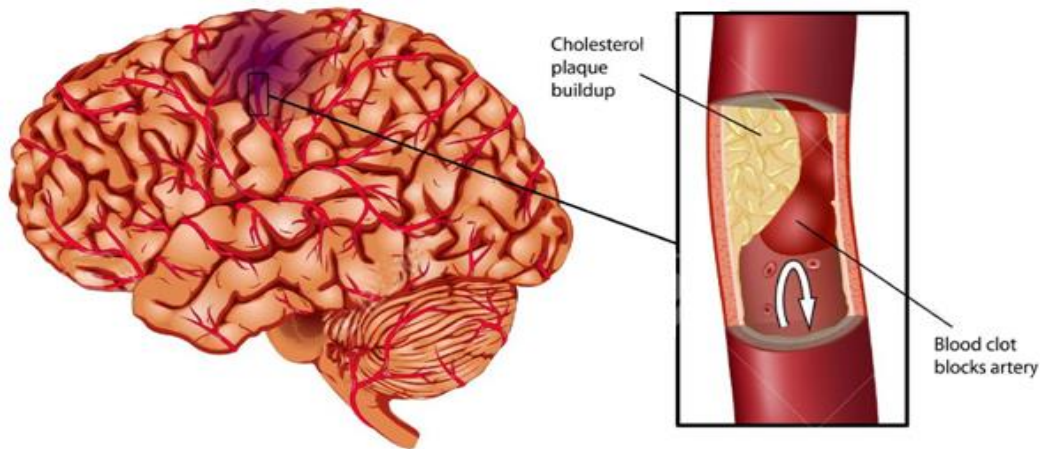


Figure 5.2: Ischaemic stroke

(<http://www.biaia.org/stroke.htm>)

There are two ways in which this can happen. One way is an embolic stroke, which occurs when a clot forms somewhere else in the body and lodges in a blood vessel in the brain. The other way is a thrombotic stroke, which is when a clot forms in a blood vessel in the brain. An ischemic stroke occurs when a blood vessel that supplies blood to the brain is blocked by a blood clot or plaque. A clot, or thrombus, may form in an artery that is already narrow. A stroke happens when the lack of blood supply results in the death of brain cells.

b) Haemorrhagic stroke

A haemorrhagic stroke occurs when a blood vessel ruptures (haemorrhages) and this prevents blood from reaching a part of the brain.

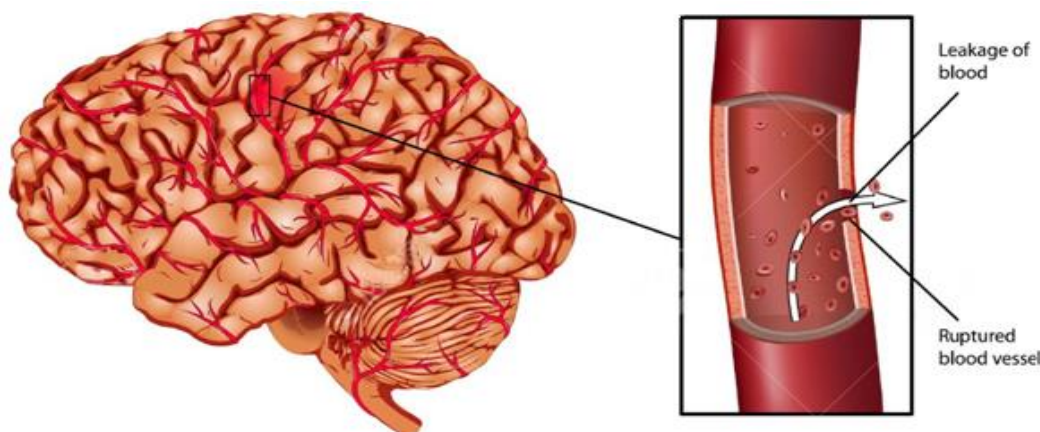


Figure 5.3: Haemorrhagic strokes

(<http://www.biaia.org/stroke.htm>)

The haemorrhage may occur in any blood vessel in the brain, or in the membrane surrounding the brain. A haemorrhagic stroke occurs when a blood vessel in part of the brain becomes weak and bursts open, causing blood to leak into the brain. This puts pressure on the brain tissue, causing tissue damage. The haemorrhage can also cause a loss of blood supply to other parts of the brain.

Stroke symptoms include

- difficulty walking
- dizziness
- loss of balance and coordination
- difficulty speaking or understanding others who are speaking
- numbness or paralysis in the face, leg or arm (most likely on one side of the body)
- blurred or darkened vision
- a sudden headache, especially when accompanied by nausea, vomiting or dizziness
- severe and sudden headache
- paralysis on one side (hemiplegia)
- weakness on one side (hemiparesis)
- confusion
- difficulty communicating, including slurred speech
- limited loss of vision
- loss of balance
- loss of consciousness.

Cerebrovascular disease happens for a variety of reasons. Atherosclerosis is one type of cerebrovascular disease. It occurs when high cholesterol levels, together with inflammation in the arteries of the brain, cause cholesterol to build up in the vessel as a thick, waxy plaque that can narrow (or block blood flow in) the arteries. This plaque can limit or completely obstruct blood flow to the brain. In time, this can cause a cerebrovascular attack, such as a stroke or a transient ischemic attack (TIA). The signs and symptoms of cerebrovascular disease or a cerebrovascular attack depend on where the blockage or damage occurs, and how much cerebral tissue is affected.

Causes of strokes include:

- a) **an aneurysm** or a subarachnoid haemorrhage, which can result from defects in the blood vessels of the brain. If a blood vessel ruptures, the flow of blood that follows can damage brain cells.
- b) **an embolism**, which happens when a clot breaks off from elsewhere in the body and travels up to the brain to block a smaller artery. This may cause an embolic stroke. This is more common in people who have arrhythmias, such as atrial fibrillation.

- c) **a tear in the lining of the carotid artery**, which can lead to ischemic stroke in people younger than 40. The tear lets blood flow between the layers of the carotid artery, narrowing the artery and reducing blood flow to the brain.

A stroke is the most common type of cerebrovascular event. It is more likely among males aged over 65 years, and especially if they or a close relative have previously had a stroke.

Factors that increase the risk of stroke and other types of cerebrovascular disease include

- hypertension, or blood pressure of 140/90 mm Hg and above
- smoking
- obesity
- poor diet and lack of exercise
- diabetes
- high blood cholesterol of 240 milligrams per decilitre (mg/dl) and over.

5.3.2 Traumatic injury and intracranial haemorrhage

Traumatic brain injury (TBI), also known as intracranial injury, occurs when an external force injures the brain. TBI can be classified based on severity, mechanism (closed or penetrating head injury) or other features (e.g. occurring in a specific location or over a widespread area).

Traumatic injury is a term which refers to physical injuries of sudden onset and severity which require immediate medical attention. Intracerebral haemorrhage is a common complication of traumatic brain injury. Traumatic brain injuries can be classified into three major groups:

- Closed head injury
- Penetrating injury
- Explosive blast injury.

Blast injuries appear to have a high risk for traumatic pseudoaneurysm formation. Differentiating between an intracerebral haemorrhage and haemorrhagic contusion is difficult. Epidural, subdural and subarachnoid haemorrhages are extra-axial bleeds, occurring outside of the brain tissue, while intra-axial haemorrhages (including intraparenchymal and intraventricular haemorrhages) occur within the brain.

Intracranial haemorrhage (ICH), also known as intracranial bleed, is bleeding in the skull. This type of brain haemorrhage includes the following kinds of bleeds:

- Intracerebral (intraventricular and intraparenchymal)

- Subarachnoid
- Epidural
- Subdural.

Intracerebral bleeding affects 2.5 per 10 000 people each year. Intracranial bleeding occurs when a blood vessel in the skull is ruptured or leaks. It can result from physical trauma (head injury) or non-traumatic causes (haemorrhagic stroke) such as a ruptured aneurysm. Anticoagulant therapy, as well as blood-clotting disorders can heighten the risk of an intracranial haemorrhage occurring.

The causes include

1) Trauma

- extradural
- chronic subdural
- acute subdural or
- cerebral haemorrhage

2) Subarachnoid haemorrhage

3) Arteriovenous malformation

4) Cerebrovascular accidents

5) Tumour.

a) **Epidural or extradural haemorrhage** – this type of haematoma (also known as epidural haemorrhage) is a TBI in which a build-up of blood occurs between the dura mater (the tough outer membrane of the central nervous system) and the skull.

b) **Chronic subdural haemorrhage** – a chronic subdural haematoma (SDH) is a collection of blood on the brain's surface, under the outer covering of the brain (dura). It usually begins forming several days or weeks after bleeding initially starts. Bleeding is usually due to a head injury.

c) **Acute subdural haemorrhage** – an acute subdural haematoma (SDH) is a clot of blood that develops between the surface of the brain and the dura mater, the brain's tough outer covering, usually due to stretching and tearing of veins on the brain's surface. These veins rupture when a head injury suddenly jolts or shakes the brain.

d) **Subarachnoid haemorrhage (SAH)** – this non-traumatic (or spontaneous) haemorrhage involves bleeding into the subarachnoid space, the area between the arachnoid membrane and the pia mater surrounding the brain. Symptoms of SAH include a severe headache with a rapid onset (“thunderclap headache”), vomiting, confusion or a lowered level of consciousness, and sometimes seizures. Neck stiffness or neck pain are also relatively common. In some cases, trauma to the brain during an injury can cause aneurysms and result in a subarachnoid haemorrhage. Another cause of SAH is bleeding from an arteriovenous malformation (AVM).

e) **Brain contusions** – an accident or injury to the brain can lead to a brain contusion. A contusion is essentially a bruise that affects the tissue of the brain. The prognosis of the condition is usually good, and patients can lead long and happy lives after receiving a diagnosis.

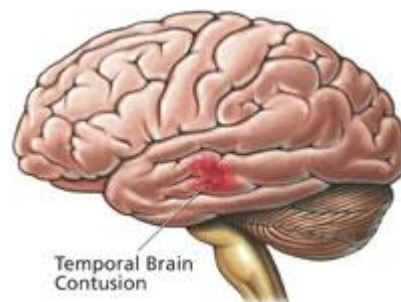


Figure 5.4: Temporal brain contusion
(<http://brainmind.com/BrainLecture11.html>)

ACTIVITY 5.1

- (a) Define central nervous system disorders.
- (b) What causes central nervous system disorders?
- (c) What are cerebrovascular accidents? List the various types.
- (d) Define stroke, and list four symptoms.
- (e) What are the risk factors for strokes?
- (f) Explain what traumatic brain injury and intercranial haemorrhage entail.
- (g) Describe an epidural haemorrhage.
- (h) Describe what a brain contusion involves.

FEEDBACK ON ACTIVITY 5.1

- (a–e) Refer to section 5.3 and pages 176–179 in the textbook by Finlayson and Newell.
(f–h) Look at section 5.3.1 above and pages 178–181 in the textbook by Finlayson and Newell.

5.4 Central nervous system tumours

5.4.1 Brain tumours

A central nervous system (CNS) tumour begins when healthy cells in the brain or spinal cord change and grow out of control, forming a mass. A tumour can be cancerous or benign. A cancerous tumour is malignant, meaning it can grow and spread to other parts of the body.



Figure 5.5: Brain tumour
(https://1.imimg.com/data/X/E/MY-1616075/tt_500x500.jpg)

There are two main types of tumour: malignant/cancerous and benign/non-cancerous tumours. Brain tumours are categorised as primary or secondary. A primary brain tumour originates in the brain. Many primary brain tumours are benign. A secondary brain tumour, also known as a metastatic brain tumour, occurs when cancer cells spread to the brain from another organ, such as the lung or breast.

There are many types and subtypes of primary brain tumours – some are benign, others malignant.

Examples include

- Acoustic Neuroma
- Pituitary adenomas
- Astrocytoma: Grade I – Pilocytic Astrocytoma; Grade II – Low-grade Astrocytoma; Grade III – Anaplastic Astrocytoma
- Chordoma
- CNS Lymphoma
- Craniopharyngioma
- Other gliomas: Brain Stem Glioma, Ependymoma
- Medulloblastoma
- Meningioma.

Secondary brain tumours (metastases) are cancers that have spread to the brain from another part of the body. This is more likely to happen with certain types of cancer, such as lung, breast, bowel, kidney and melanoma (skin cancer). Symptoms can include headaches and a feeling of uneasiness.

5.5 Meningitis

Meningitis is a serious inflammation of the meninges, the three membranes that envelop the brain and spinal cord. Meningitis can be caused by infection by bacteria, viruses and protozoa.

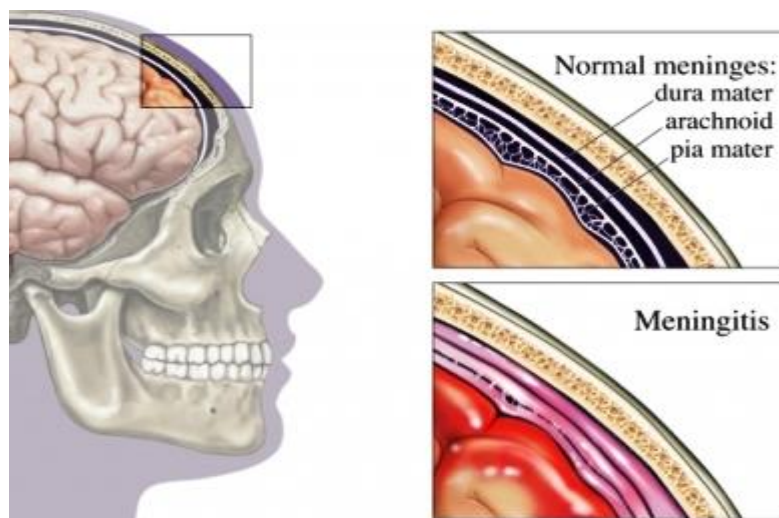


Figure 5.6: Meningitis

(<http://services.epnet.com/getimage.aspx?imageid=7307>)

There are actually five types of meningitis, each classified by the cause of the disease, namely

- bacterial
- viral
- parasitic
- fungal
- non-infectious.

Bacterial meningitis is caused by several different types of bacteria, including *Streptococcus pneumoniae*, also called pneumococcus; *Neisseria meningitidis*, also called meningococcus and *Haemophilus influenzae*, also called Hib.

Other forms of meningitis include:

- **Tuberculous (TB)** – meningitis occurs when tuberculosis bacteria (*Mycobacterium tuberculosis*) invade the membranes and fluid surrounding the brain and spinal cord. The infection frequently begins elsewhere in the body (usually in the lungs) and

then travels through the bloodstream to the meninges, where small abscesses (called microtubercles) are formed. When these abscesses burst, TB meningitis is the result.

- **Fungal meningitis** – two types of fungus can cause cryptococcal meningitis (CM). They are *Cryptococcus neoformans* (*C. neoformans*) and *Cryptococcus gattii* (*C. gattii*). This disease is rare in healthy people. CM is more common in people who have compromised immune systems, such as those living with Aids.
- **Viral meningitis** – this is an inflammation of the layers of tissue that cover the brain and spinal cord (meninges) and of the fluid-filled space between the meninges (subarachnoid space). Viral meningitis usually begins with symptoms of a viral infection such as fever, a general feeling of illness, headache and muscle aches. Herpes viruses include the herpes simplex viruses (HSVs) and varicella zoster virus – the same virus that causes chickenpox and shingles. HSVs can cause meningitis or encephalitis (inflammation of the brain itself, which is much more serious).

5.6 Encephalitis

Encephalitis is a complex and severe disease that can occur in people of all ages, anywhere in the world. It is defined as an inflammation of the brain substance or brain tissue, together with evidence of brain dysfunction. The most common cause is viral infection, but in rare cases it can be caused by bacteria or even fungi.

There are two main types of encephalitis: primary and secondary.

- a) **Primary encephalitis** (infectious encephalitis) occurs when a germ (viruses and small bacteria) directly infects the brain and spinal cord.
- b) **Secondary encephalitis** (autoimmune encephalitis) occurs when an infection starts elsewhere in the body and then travels to the brain.

5.7 Brain or intracranial abscess

A brain abscess is a collection of pus, immune cells and other material in the brain, usually from a bacterial or fungal infection. Intracranial abscesses are uncommon, serious, life-threatening infections. They include brain abscess and subdural or extradural empyema, and are classified according to the anatomical location or the aetiological agent.

Other neurological infections include

- a) **Tetanus** – a serious bacterial infection that affects the nervous system and causes muscles throughout the body to tighten. Tetanus is also called lockjaw, because the infection often causes muscle contractions in the jaw and neck, but it can eventually spread to other parts of the body.
- b) **Botulism** – a serious illness that causes flaccid paralysis of muscles. It is caused by a neurotoxin, generically called botulinum toxin, produced by the bacterium *Clostridium botulinum*.
- c) **Polio** (also known as poliomyelitis) – a highly contagious disease caused by a virus that attacks the nervous system.

5.8 Motor neuron disease

Motor neuron disease is a rare condition that progressively damages parts of the nervous system. This leads to muscle weakness, often with visible wasting. Motor neuron disease, also known as amyotrophic lateral sclerosis (ALS), occurs when specialist nerve cells (motor neurons) in the brain and spinal cord stop working properly (neurodegeneration).

Motor neurons control important muscle activity related to

- gripping
- walking
- speaking
- swallowing
- breathing.

a) **Parkinson's disease** (PD) – this is a chronic and progressive movement disorder caused by progressive impairment or deterioration of dopaminergic neurons (nerve cells) in an area of the brain known as the substantia nigra. Parkinson's involves the malfunction and death of vital nerve cells (neurons) in the brain. It is associated with the degeneration of the basal ganglia of the brain and a deficiency of the neurotransmitter dopamine. When functioning normally, these neurons produce a vital brain chemical known as dopamine.

b) **Huntington's disease** (HD), also known as Huntington's chorea – this is an inherited progressive brain disorder that results in the death of brain cells. The earliest symptoms are

often subtle problems with mood or mental ability. There is a general lack of coordination and an unsteady gait, and uncontrolled movements, emotional problems and loss of thinking ability (cognition) often follow. The HTT gene provides instructions for making a protein called huntingtin. Although the function of this protein is unknown, it appears to play an important role in nerve cells (neurons) in the brain. The HTT mutation that causes Huntington's disease involves a DNA segment known as a CAG trinucleotide repeat.

c) **Multiple sclerosis** – an abnormal hardening of body tissue, this chronic, typically progressive disease involves damage to the myelin sheaths of nerve cells in the brain and spinal cord, whose symptoms may include numbness, the impairment of speech and muscular coordination, blurred vision and severe fatigue.

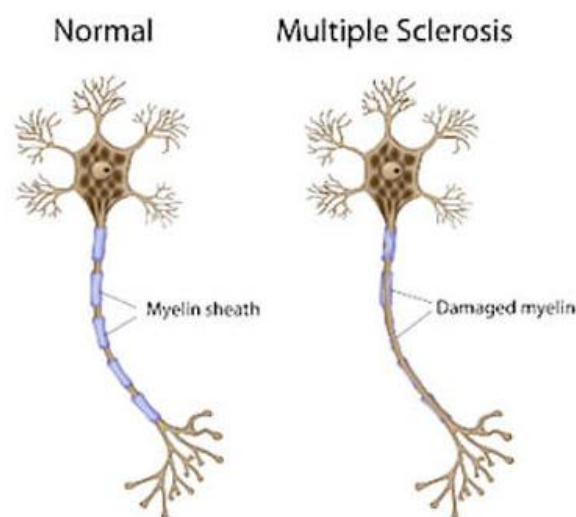


Figure 5.7: Multiple sclerosis

(<https://dailyhealthguard.com/wp-content/uploads/2017/04/multiple-sclerosis-treatment.jpg>)

Multiple sclerosis (MS) is a chronic autoimmune disorder affecting movement, sensation and bodily functions. It is caused by the destruction of the myelin insulation. It is considered an autoimmune disease in which the body's immune system attacks its own tissues, destroying myelin (the fatty substance that coats and protects nerve fibres in the brain and spinal cord).

Other forms of CNS demyelination include

- acute disseminated encephalopathy
- acute necrotising haemorrhage encephalopathy
- central pontine myelinolysis.

d) **Guillain-Barre syndrome** – this is a rare but serious autoimmune disorder in which the immune system attacks healthy nerve cells in the peripheral nervous system. This leads to weakness, numbness and tingling. It can eventually cause paralysis. The disorder is characterised by an assault on the peripheral nervous system, leading to weakness and paralysis that can last months or years. It frequently follows a mild viral infection which may be flu-like, or even a case of gastroenteritis, with symptoms starting 10–14 days after the infection. Both sexes can develop Guillain-Barre syndrome, and it can strike at any age, although it is slightly more common in older male adults. The precise cause is not known, but the condition usually begins shortly after an individual has experienced an infectious disease.

e) **Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)** – this is a rare neurological disorder in which there is inflammation of the nerve roots and peripheral nerves, and the destruction of the fatty protective covering (myelin sheath) around the nerves. CIDP manifests as weakness, numbness and pain that can occur at any stage of an individual's life. Nerve roots swell and destroy the myelin sheath (fatty tissue) around the nerves, which causes CIDP.

f) **Dementia** – this is a general term that describes a group of symptoms such as loss of memory, judgement, language, complex motor skills and other intellectual functions, caused by the permanent damage or death of the brain's nerve cells or neurons. Dementia is not a specific disease. It is an overall term that describes a wide range of symptoms associated with a decline in memory or other thinking skills, severe enough to reduce a person's ability to perform everyday activities. There are different types of dementia and each form is partially manageable, but they are not reversible and worsen over time.

Examples include

- Alzheimer's disease
- vascular dementia
- dementia from Parkinson's disease and similar disorders
- dementia with Lewy bodies
- frontotemporal dementia (Pick's disease)
- Creutzfeldt-Jakob disease.

g) **Prion diseases** (also known as transmissible spongiform encephalopathies/TSEs; the name is derived from proteinacious infectious particle) are a group of progressive

neurodegenerative conditions. These illnesses, which exist in both animals and humans, describe the pathogen that causes TSEs or neurodegenerative diseases in mammals.

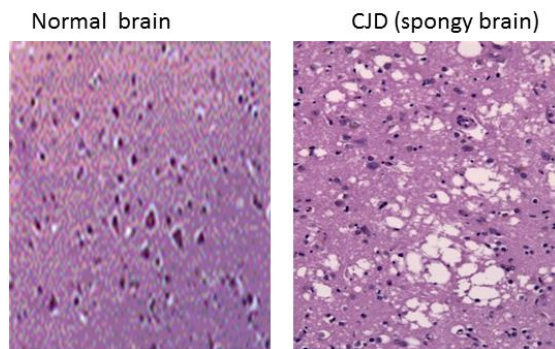


Figure 5.8: Prion disease

(http://www.dovemed.com/uploads/images/CJD_spongiosis_temporal_lobe.max-1000x800.jpg)

- 1) **Alzheimer's disease** is a progressive, degenerative disorder that attacks the brain's nerve cells or neurons, resulting in loss of memory, thinking and language skills, and behavioural changes. It is a type of dementia that causes problems with memory, thinking and behaviour. Alzheimer's disease accounts for 60–80 per cent of dementia cases. Frontotemporal dementia (FTD) or Pick's disease is a syndrome featuring the shrinking of the frontal and temporal anterior lobes of the brain. The symptoms of frontotemporal dementia fall into two clinical patterns that involve either changes in behaviour or problems with language.
- 2) **Creutzfeldt-Jakob disease (CJD)** is a rare, incurable and invariably fatal neurodegenerative brain disease. CJD is a human form of mad cow disease known as bovine spongiform encephalopathy (BSE). CJD is a degenerative brain disorder that leads to severe memory problems, behavioural changes, poor coordination, visual disturbances and later dementia, involuntary movement, blindness, weakness, coma and ultimately death. It is estimated that about one person is diagnosed with CJD per million people per year, worldwide. Ninety per cent of people are reported to die within a year of diagnosis. CJD is caused by an abnormal infectious protein in the brain called a prion, which is dangerous because it promotes the refolding of the native prion protein from the dominantly alpha helical regions into beta pleated sheets. This change in conformation disables the ability of the protein to undergo degradation, leading to a large quantity of insoluble protein being deposited in affected cells, with a sponge-like appearance (see Figure 5.8). The defective proteins invade the brain and induce other prion protein molecules to misfold in a

self-sustaining feedback loop. This mass of misfolded proteins disrupts neuronal cell function and causes cell death.

3) Other prion diseases include

- Gerstmann-Sträussler-Scheinker syndrome (GSS) – a very rare, usually familial, fatal neurodegenerative disease that affects patients from 20–60 years of age. It forms part of a group of hereditary prion protein diseases known as transmissible spongiform encephalopathies (TSEs).
- Fatal familial insomnia (FFI) is an extremely rare autosomal dominant inherited prion disease of the brain. It is almost always caused by a mutation of the protein PrPC, but can also develop spontaneously in patients with a non-inherited mutation variant called sporadic fatal insomnia (SFI).

h) Vascular dementia – this is a general term describing problems with reasoning, planning, judgement, memory and other thought processes caused by brain damage from impaired blood flow to the brain. Vascular dementia occurs when the vessels that supply blood to the brain become blocked or narrowed. Strokes take place when the supply of blood carrying oxygen to the brain is suddenly cut off. However, not all people with stroke will develop vascular dementia.

ACTIVITY 5.2

- (a) Write short explanatory notes on brain tumours.
- (b) Distinguish between primary and secondary brain tumours.
- (c) What is meningitis?
- (d) List five types of meningitis.
- (e) Describe tuberculous, viral and fungal meningitis.
- (f) Define encephalitis.
- (g) Distinguish between primary and secondary encephalitis.
- (h) What is meant by a brain abscess?
- (i) Write short notes on tetanus, botulism and polio.
- (j) Name the muscle activities affected by motor neuron disease.
- (k) Distinguish between Parkinson's and Huntington's diseases.
- (l) What is multiple sclerosis? Give three examples.
- (m) What is dementia?
- (n) Distinguish between Alzheimer's and Creutzfeldt-Jakob disease.
- (o) What are prion diseases? Discuss two types.
- (p) Discuss vascular dementia.

FEEDBACK ON ACTIVITY 5.2

(a–h) Section 5.4–5.7 above will provide you with in-depth knowledge about brain tumours and encephalitis. Also study pages 182–185 in the textbook by Finlayson and Newell.

(i–p) Study section 5.8 (a–h) above and revisit pages 186–191 in the textbook by Finlayson and Newell.

LEARNING UNIT 6: ENDOCRINE DISEASES

6.1 Introduction

The endocrine system is the collection of glands that produce hormones which regulate metabolism, growth and development, tissue function, sexual function, reproduction, sleep and mood, among other things. The endocrine system influences how your heart beats, how your bones and tissues grow, even your ability to reproduce. It plays a vital role in whether or not you develop diabetes, thyroid disease, growth disorders, sexual dysfunction, and a host of other hormone-related disorders.

When hormone levels reach a certain normal amount, the endocrine system helps the body to keep that level of hormone in the blood. For example, if the thyroid gland has secreted the right amount of thyroid hormones into the blood, the pituitary gland senses the normal levels of thyroid hormone in the bloodstream. In addition to the specialised endocrine organs mentioned above, many other organs that are part of other bodily systems, such as bone, kidney, liver, heart and gonads, have secondary endocrine functions. For example, the kidney secretes endocrine hormones such as erythropoietin and renin.

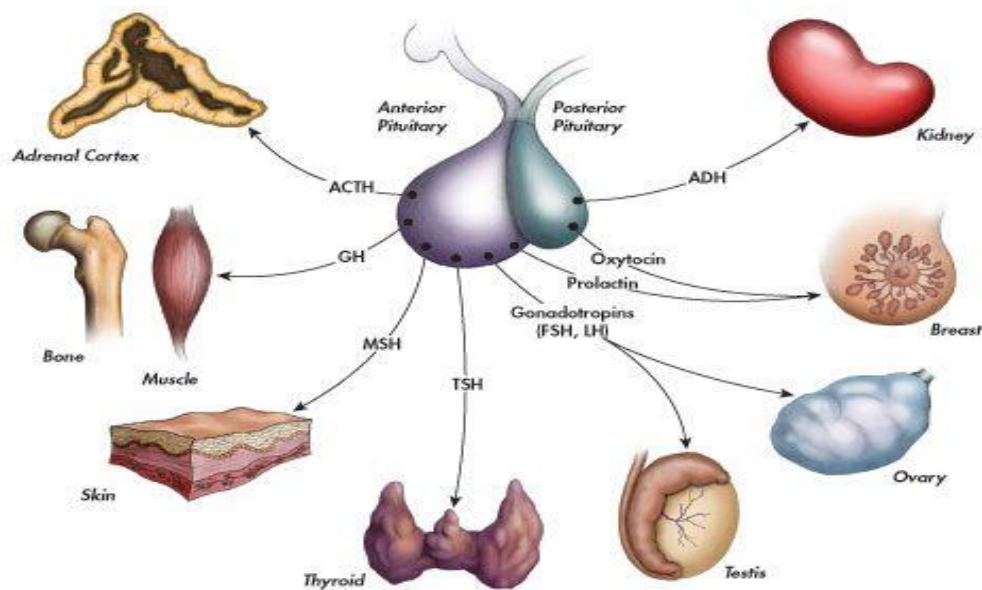


Figure 6.1: The endocrine system

(<http://square-one.mokshayoga.ca/files/2017/06/hormones.jpg>)

The hypothalamus links the nervous and endocrine systems by way of the pituitary gland. Its function is to secrete releasing and inhibiting hormones that stimulate or inhibit (as the names

imply) the production of hormones in the anterior pituitary. The pituitary gland is often dubbed the “master gland” because its hormones control other parts of the endocrine system, namely the thyroid gland, adrenal glands, ovaries and testes.

Endocrine diseases present in three ways, namely as

- hypofunction
- hyperfunction
- local effects.

For example, a pituitary tumour may present with acromegaly (hyperfunction), hypogonadism and hypothyroidism due to compression of the pituitary (hypofunction) and headaches or bitemporal hemianopia.

To complete this learning unit, you will need to refer to chapters 56–63 in Finlayson and Newell.

6.2 Learning outcomes

Upon completion of this learning unit you should be able to

- define and describe pituitary diseases
- explain what is meant by inappropriate ADH secretion
- discuss diabetes insipidus
- describe hypopituitarism
- name the causes of hypopituitarism
- describe pituitary tumours
- distinguish between hypothyroidism and hyperthyroidism
- describe the pathology of Graves’ disease and goitre
- identify the types of thyroiditis
- distinguish between primary and secondary hyperthyroidism
- explain what thyroid neoplasm is.

6.3 Pituitary diseases

Pituitary disease is a disorder primarily affecting the pituitary gland. The over- or underproduction of a pituitary hormone will affect a particular end organ. For example, insufficient production (hyposcretion) of thyroid stimulating hormone (TSH) in the pituitary gland will cause hypothyroidism, while overproduction (hypersecretion) of TSH will cause hyperthyroidism. Thyroidisms caused by the pituitary gland are uncommon, accounting for less than ten per cent of all hypothyroidism cases and much less than one per cent of hyperthyroidism cases.

6.3.1 Inappropriate ADH secretion

The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterised by the excessive release of antidiuretic hormone from the posterior pituitary gland or another source. The increase in blood volume (hypervolemia) often results in true hyponatremia, in which the plasma sodium levels are lowered and total body fluid is increased. Although the sodium level is low, SIADH is brought about by an excess of water rather than a deficit of sodium. SIADH is defined by hyponatremia and hypo-osmolality resulting from the inappropriate, continued secretion or action of the antidiuretic hormone arginine vasopressin (AVP), despite normal or increased plasma volume, which results in impaired water excretion. Hyponatremia is a decrease in serum sodium concentration < 136 mEq/L caused by an excess of water relative to solute. Treatment involves restricting water intake and promoting water loss, replacing any sodium deficit, and correcting the underlying disorder. Signs and symptoms of hyponatremia can include altered personality, lethargy and confusion. Severe hyponatremia can cause seizures, coma and even death.

6.3.2 Diabetes insipidus

Diabetes insipidus (DI) is defined as the passage of large volumes (>3 L/24 hr) of dilute urine (< 300 mOsm/kg). It has the following two major forms:

- **Central (neurogenic, pituitary, or neurohypophyseal) or cranial DI** – characterised by the decreased secretion of ADH, also referred to as arginine vasopressin (AVP). Decreased secretion of ADH reduces the ability to concentrate urine and so causes polyuria and polydipsia.
- **Nephrogenic DI** – characterised by a decreased ability to concentrate urine because of resistance to ADH in the kidney, resulting in poor kidney response to this chemical messenger, which is also called antidiuretic hormone.

6.3.3 Hypopituitarism

Hypopituitarism (also called pituitary insufficiency) is a rare condition in which the pituitary gland does not produce enough of certain hormones. The body cannot work properly when important glands, such as the thyroid and adrenal, do not receive the hormones they need from the pituitary. Hypopituitarism is frequently triggered by a tumour of the pituitary gland. As

a pituitary tumour increases in size, it can compress and damage pituitary tissue, interfering with hormone production.

Possible causes include

- head injuries
- brain or pituitary tumours, e.g. non-functioning (chromophobe adenoma, craniopharyngioma) or functioning pituitary tumours, hypothalamic tumours
- brain surgery
- radiation treatment
- autoimmune inflammation (hypophysitis)
- stroke
- infections of the brain, such as meningitis
- tuberculosis
- infiltrative diseases such as sarcoidosis (an inflammatory disease occurring in various organs); Langerhans cell histiocytosis (in which abnormal cells cause scarring in numerous parts of the body, such as the lungs and bones) and hemochromatosis (which causes excess iron deposition in the liver and other tissues)
- severe loss of blood during childbirth, which may cause damage to the front part of the pituitary gland (Sheehan syndrome or postpartum pituitary necrosis)
- genetic mutations resulting in impaired pituitary hormone production.

6.3.4 Pituitary tumours

Diseases of the hypothalamus, a portion of the brain situated just above the pituitary, can also cause hypopituitarism. The hypothalamus produces hormones of its own that directly affect the activity of the pituitary. Craniopharyngioma is a type of brain tumour derived from pituitary gland embryonic tissue that occurs most commonly in children, but also in adults in their 50s and 60s. People may present with bitemporal inferior quadrantanopia leading to bitemporal hemianopsia, as the tumour may compress the optic chiasm.

6.4 Thyroid gland

Hyperthyroidism most commonly occurs in three ways, namely as

- thyroiditis or an inflammation of the thyroid
- a thyroid nodule that produces too much T4 hormone
- an autoimmune condition known as Graves' disease.

6.4.1 Clinical features of thyroid gland disease

a) **Hyperthyroidism and Graves' disease** – hyperthyroidism is a condition that occurs due to the excessive production of thyroid hormone by the thyroid gland. Thyrotoxicosis is a condition that occurs due to excessive thyroid hormone of any cause, and therefore includes hyperthyroidism. Graves' is an autoimmune disease in which the over activity of the thyroid gland causes the overproduction of thyroid hormones (hyperthyroidism). A number of conditions can cause hyperthyroidism, but Graves' disease is the most common. Graves' is often the underlying cause of hyperthyroidism.

Pathology

Depending on the underlying cause, Graves' is an autoimmune disease caused by the production of auto-antibodies against thyroid stimulating hormone receptors which are involved in stimulating follicular cells to produce thyroid hormone. These antibodies are called thyroid-stimulating immunoglobulins (TSIs)

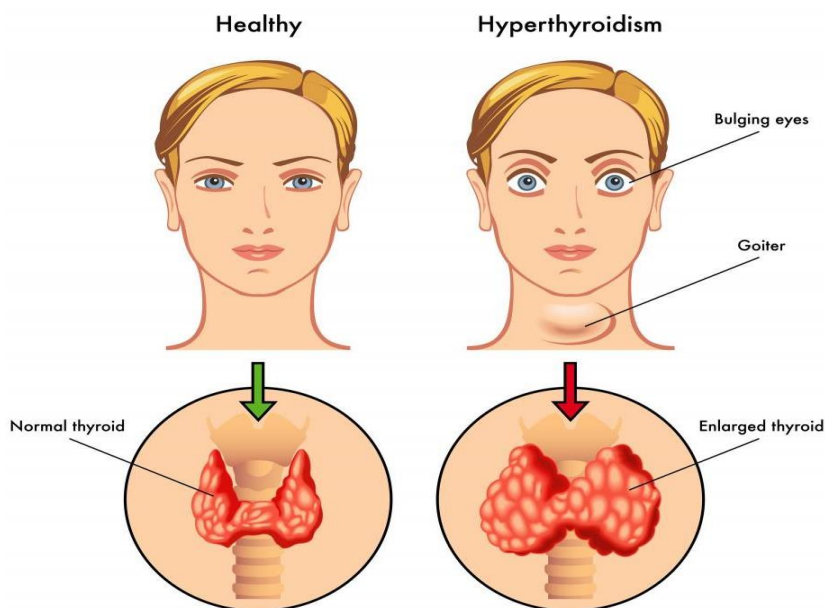


Figure 6.2: Clinical features of Graves' disease

(http://www.planetayurveda.com/media/wysiwyg/planet/hyperthyroidism_2.jpg)(<https://cdn1.healthambition.com/wp-content/uploads/2016/05/28095309/2015.jpg>)

Types of hyperthyroidism

1) **Primary hyperthyroidism** – intrinsic thyroid abnormality, low TSH, high free T4, normal TRH stimulation test.

2) **Secondary hyperthyroidism** – high TSH, abnormal TRH stimulation test.

- Subclinical hyperthyroidism – low TSH ($< 0.1 \mu\text{IU/ml}$), normal T3 and T4. May be attributed to exogenous thyroid hormone, due to TSH suppressive therapy with L-thyroxine or hormone overreplacement. Excessive thyroid hormone may be due to differentiated thyroid cancer. Patients have increased risk of coronary heart disease.
- T3 hyperthyroidism: 1–4 per cent of hyperthyroid patients. Low TSH, high free T3, normal free T4. Associated with early treatment of hyperthyroidism with antithyroid drugs.
- T4 hyperthyroidism: high T4, normal T3. Due to primary hyperthyroidism causes, also iodine, amiodarone, pregnancy (transient gestational hyperthyroidism syndrome, 1–3%).

b) **Hypothyroidism and cretinism** – hypothyroidism, also called underactive thyroid or low thyroid, is a common disorder of the endocrine system in which the thyroid gland does not produce enough thyroid hormone. It can cause a number of symptoms, such as poor ability to tolerate cold, a feeling of tiredness, constipation, depression and weight gain. Occasionally there may be swelling of the front part of the neck due to goitre. Untreated hypothyroidism during pregnancy can lead to delays in growth and intellectual development in the baby, which is called cretinism.

c) **Hashimoto's thyroiditis** – also known as chronic lymphocytic thyroiditis or Hashimoto's disease, this is an autoimmune disease in which the thyroid gland is gradually destroyed. Early on, there may be no symptoms. Over time the thyroid may enlarge to form a painless goitre (hyperthyroidism). In some instances, people eventually develop hypothyroidism with its accompanying weight gain, fatigue, constipation, depression and general pains. After many years the thyroid typically shrinks in size. Potential complications include thyroid lymphoma. Hashimoto's is the most common type of thyroiditis.

d) **De Quervain's thyroiditis** – also called subacute or granulomatous thyroiditis, it was first described in 1904 and is much less common than Hashimoto's thyroiditis. The thyroid gland generally swells rapidly and is very painful and tender. The gland discharges thyroid hormone into the blood and the patients become hyperthyroid; however, the gland stops taking up iodine (radioactive iodine uptake is very low) and the hyperthyroidism generally resolves over the next several weeks.

e) **Riedel's thyroiditis** (RT), also called Riedel's struma – this is a rare chronic inflammatory disease of the thyroid gland, characterised by a dense fibrosis that replaces normal thyroid parenchyma. It is now believed that Riedel's thyroiditis is one manifestation of a systemic disease called IgG4-related disease, which can affect many organ systems.

f) **Goitre** – this describes a condition where the thyroid gland, located in the neck, becomes enlarged. Iodine deficiency is the world's leading cause of goitre, but this is rare in North America. In developed countries, goitre is usually caused by an autoimmune disease. A goitre can sometimes occur when the thyroid gland produces too much thyroid hormone (hyperthyroidism). In Graves' disease, antibodies produced by the immune system mistakenly attack the thyroid gland, causing it to produce excess thyroxine. This overstimulation causes the thyroid to swell.

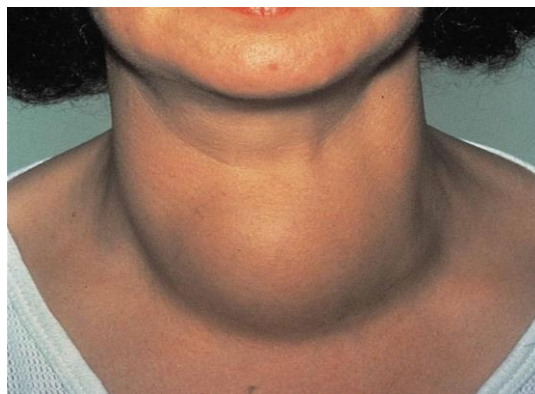


Figure 6.3: Clinical features of goitre

(<https://s3.amazonaws.com/classconnection/503/flashcards/1790503/jpg/goiter-14B898DCF026F24DAEF.jpg>)

Hyperthyroidism creates excess thyroid hormone. Since the thyroid gland produces hormones that regulate the body's metabolism, not surprisingly, the disease increases the body's normal metabolic functions. Goitre (an enlarged thyroid gland) is another way in which hyperthyroidism affects the body.

6.5 Thyroid neoplasm

Thyroid neoplasm is a neoplasm or tumour of the thyroid. It can be a benign tumour such as a thyroid adenoma, or it can be a malignant neoplasm (thyroid cancer).

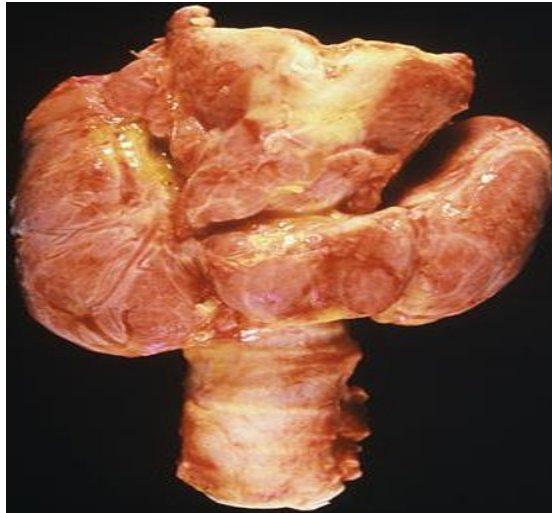


Figure 6.4: Thyroid neoplasm

(https://upload.wikimedia.org/wikipedia/commons/thumb/8/8a/Thyroid%2C_Diffuse_Hyperplasia.jpg/300px-Thyroid%2C_Diffuse_Hyperplasia.jpg)

Examples of thyroid neoplasms are papillary, follicular, medullary or anaplastic thyroid cancer.

- a) **A follicular adenoma** is a benign, encapsulated tumour of the thyroid gland. It is a firm or rubbery, homogeneous, round or oval tumour surrounded by a thin, fibrous capsule. A follicular adenoma is a common neoplasm of the thyroid gland.
- b) **Papillary carcinoma** (PTC) is the most common form of well-differentiated thyroid cancer, and the most common form of thyroid cancer to result from exposure to radiation. Papillary carcinoma appears as an irregular solid or cystic mass or nodule in a normal thyroid parenchyma.
- c) **Medullary thyroid cancer** (MTC) is a form of thyroid carcinoma which originates in the parafollicular cells (C-cells), which produce the hormone calcitonin. Medullary tumours are the third most common of all thyroid cancers, making up about three per cent of cases.
- d) **Anaplastic thyroid carcinoma** (ATC) is an aggressive form of cancer of the thyroid gland. It is one of the fastest-growing tumours in humans. Unlike other forms of thyroid cancer (papillary, follicular, medullary and their variants) it spreads quickly to other organs. ATC occurs most often in people over 60.

6.6 Parathyroid gland diseases

The single major disease of the parathyroid glands is due to the over-activity of one or more of the parathyroid lobes, which produce too much parathyroid hormone, causing a potentially serious calcium imbalance. As the blood filters through the parathyroid glands, they detect the amount of calcium present in the blood and react by making more or less parathyroid hormone (PTH). When the calcium level in the blood is too low, the cells of the parathyroids sense it and produce more parathyroid hormone.

- a) **Primary hyperparathyroidism** is a disorder of one or more of the parathyroid glands. The parathyroid gland(s) becomes overactive and secretes excess amounts of parathyroid hormone (PTH). As a result, the blood calcium rises to a level that is higher than normal (called hypercalcemia). If the blood calcium level is too low, the parathyroid glands release more PTH. This causes the bones to release more calcium into the blood and reduces the amount of calcium released by the kidneys into the urine.
- b) **Secondary hyperparathyroidism** (SHPT) refers to the excessive secretion of parathyroid hormone (PTH) by the parathyroid glands in response to hypocalcaemia (low blood calcium levels) and associated hyperplasia of the glands. This disorder is especially seen in patients with chronic kidney failure.
- c) **Tertiary hyperparathyroidism** is a state of excessive secretion of parathyroid hormone (PTH) after a long period of secondary hyperparathyroidism and resulting in a high blood calcium level. It reflects the development of an autonomous (unregulated) parathyroid function, following a period of persistent parathyroid stimulation.
- d) **Bone changes** – the parathyroid hormone regulates serum calcium through its effects on bone, the kidneys and the intestines: in bone, PTH enhances the release of calcium from the large reservoir contained in the bones. Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH.
- e) **Hypoparathyroidism** is the state of decreased secretion or activity of the parathyroid hormone (PTH). This leads to decreased blood levels of calcium (hypocalcemia) and increased levels of blood phosphorus (hyperphosphatemia). Hypocalcemia is caused by loss of calcium from, or insufficient entry of calcium into, the circulatory system. Hypoparathyroidism is the

most common cause of hypocalcaemia and often develops because of surgery in the central neck, requiring radical resection of head and neck cancers.

f) **Pseudohypoparathyroidism** is a condition primarily associated with resistance to the parathyroid hormone. Those with the condition have a low serum calcium and high phosphate, but the parathyroid hormone level (PTH) is appropriately high (due to the low level of calcium in the blood). It is usually an inherited disorder that clinically resembles hypoparathyroidism, but results from the body's inability to respond normally to parathyroid hormone rather than from a deficiency of the hormone itself.

g) **Pseudopseudohypoparathyroidism** is genetically similar to pseudohypoparathyroidism in that both conditions share the same signs and symptoms (such as skeletal defects) but with pseudopseudohypoparathyroidism the body can manage calcium, phosphorus and vitamin D levels. An inherited disorder that closely simulates the symptoms but not the consequences of pseudohypoparathyroidism, it thus has mild or no manifestations of hypoparathyroidism or tetanic convulsions.

6.7 Multiple endocrine neoplasia

Multiple endocrine neoplasia is a group of disorders that affect the body's network of hormone-producing glands (the endocrine system). Hormones are chemical messengers that travel through the bloodstream and regulate the function of cells and tissues throughout the body. Multiple endocrine neoplasia syndromes are rare, inherited disorders in which several endocrine glands develop non-cancerous (benign) or cancerous (malignant) tumours or grow excessively without forming tumours. Multiple endocrine neoplasia syndromes are caused by gene mutations, so they tend to run in families. The major forms of multiple endocrine neoplasia are called type 1, type 2 and type 4. These types are distinguished by the genes involved.

- a) **Multiple endocrine neoplasia type 1 (MEN 1)** is a hereditary condition associated with tumours of the endocrine (hormone-producing) glands. MEN 1 was originally known as Wermer syndrome. The most common tumours seen in MEN 1 involve the parathyroid gland, islet cells of the pancreas and the pituitary gland.
- b) **Multiple endocrine neoplasia type 2 (MEN 2)** is a hereditary condition associated with three primary types of tumour: medullary thyroid cancer, parathyroid tumours and

pheochromocytoma. MEN 2 is classified into three subtypes based on clinical features: medullary thyroid cancers, pheochromocytoma and neuromas.

- c) **Multiple endocrine neoplasia type 2B (MEN 2B)** is an autosomal dominant syndrome characterised by medullary thyroid carcinoma, pheochromocytoma, multiple mucosal neuromas and intestinal ganglioneuromas, and often a marfanoid habitus and other skeletal abnormalities. Symptoms depend on the glandular elements present.

6.8 Adrenal gland diseases

The adrenal glands are small glands located on top of each kidney. They produce hormones that are essential to life, including sex hormones and cortisol (which helps the body respond to stress and has many other important functions). With adrenal gland disorders, the glands produce too much or not enough hormones. Two of the most important adrenal hormones are cortisol and aldosterone. The adrenal glands also produce adrenaline and small amounts of sex hormones called androgens, among other hormones. Adrenal disorders can be caused by too much or too little of a particular hormone. The adrenal hormone aldosterone may also be lacking. Secondary adrenal insufficiency occurs when the pituitary gland fails to produce enough adrenocorticotropin (ACTH), a hormone that stimulates the adrenal glands to produce cortisol. If ACTH output is too low, cortisol production drops.

- a) **Pheochromocytoma** is a rare tumour of the adrenal gland tissue. It results in the release of too much epinephrine and norepinephrine – hormones that control heart rate, metabolism and blood pressure. Sometimes pheochromocytomas arise from chromaffin cells located outside of the adrenal gland. In this case, they are termed extra-adrenal pheochromocytomas or paragangliomas, and are usually located in the abdomen.

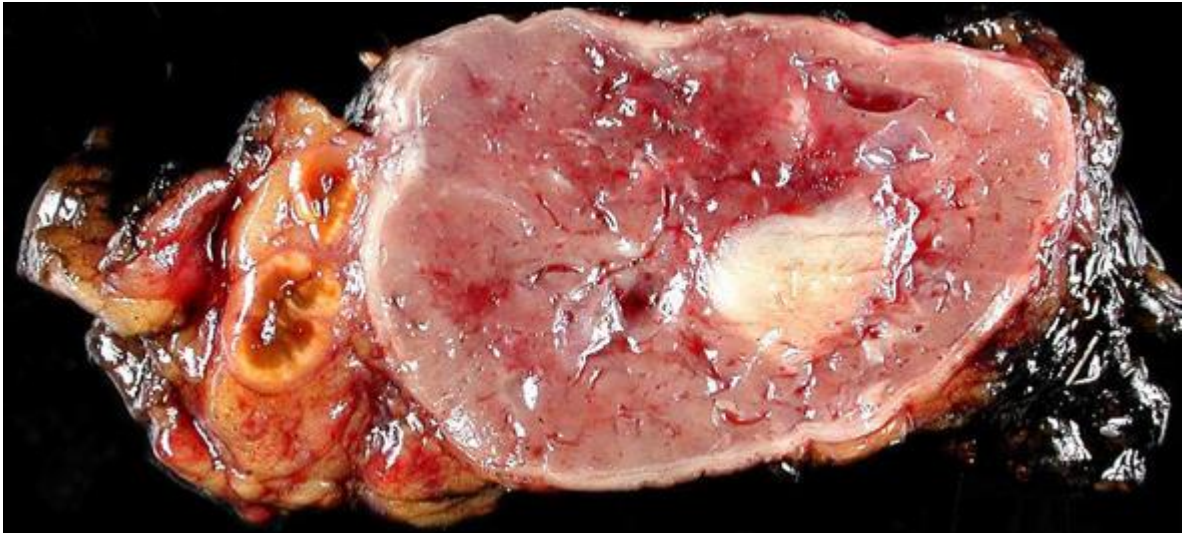


Figure 6.5: Pheochromocytoma

(<http://img.medscapestatic.com/pi/features/slideshow-slide/pheochromocytoma/fig1.jpg?resize=645:439>)

b) **Addison's disease** occurs when the body's adrenal glands are not able to produce enough of the hormones cortisol or aldosterone. Autoimmune disease accounts for 70 per cent of Addison's disease. This occurs when the body's immune system mistakenly attacks the adrenal glands and destroys the outer layer of the glands. Long-lasting infections such as tuberculosis, HIV and some fungal infections can harm the adrenal glands.

c) **Cushing's syndrome** occurs due to abnormally high levels of the hormone cortisol. This can happen for a variety of reasons. The most common cause is overuse of corticosteroid medications, resulting in excessive corticosteroids in the body. The main cause is overproduction of the adrenocorticotropin hormone (ACTH) in the pituitary gland. ACTH causes the adrenal glands to produce corticosteroids, so too much ACTH means too much corticosteroid. Under stressful conditions, cortisol provides the body with glucose by tapping into protein stores via gluconeogenesis in the liver. This energy can help an individual fight or flee a stressor. However, elevated cortisol over the long term consistently produces glucose, leading to increased blood sugar levels.

d) **Apparent mineralocorticoid excess (AME)** is an autosomal recessive disorder causing hypertension (high blood pressure) and hypokalaemia (abnormally low levels of potassium).

ACTIVITY 6.1

- (a) Describe pituitary diseases.
- (b) What is the function of the hypothalamus?
- (c) Name three ways in which endocrine diseases generally present themselves.
- (d) Discuss the consequences of inappropriate ADH secretion.
- (e) Define diabetes insipidus.
- (f) Describe the two major forms of diabetes insipidus.
- (g) Distinguish between diabetes insipidus and diabetes mellitus.
- (h) Discuss the causes of hypopituitarism.
- (i) Describe craniopharyngioma and its presentation.
- (j) Describe the four types of thyroid cancer.
- (k) Describe the clinical features of thyroid gland diseases.
- (l) Distinguish between hypothyroidism and hyperthyroidism.
- (m) Describe the characteristics of secondary hyperthyroidism.
- (n) Describe the pathology of Graves' disease and goitre.
- (o) Distinguish between goitre and cretinism.
- (p) Describe the types of thyroiditis.
- (q) Distinguish between primary, secondary and tertiary hyperparathyroidism.
- (r) Describe the characteristics of parathyroid gland diseases.
- (s) Describe the characteristics of hypoparathyroidism.
- (t) Discuss pseudohypoparathyroidism and pseudopseudohypoparathyroidism.
- (u) Describe the different types of multiple endocrine neoplasia.
- (v) Describe pheochromocytoma.
- (w) Distinguish between Cushing's and Addison's disease.
- (x) Describe apparent mineralocorticoid excess.

FEEDBACK ON ACTIVITY 6.1

(a–x) Understanding pituitary diseases will be very helpful. Read sections 6.3–6.7 above and also review pages 192–201 in the textbook by Finlayson and Newell.

LEARNING UNIT 7: GENITOURINARY DISEASES

7.1 Introduction

The kidneys have a pivotal role in a number of basic physiological functions, including blood pressure control, salt and water homeostasis, blood cell production, acid-base balance and calcium homeostasis. It is therefore not surprising that renal dysfunction can result from, or cause, a variety of pathologies. Congenital anomalies of the kidney and urinary tract (CAKUT) comprise a spectrum of structural abnormalities that occur in one in 500 fetuses and cause death early after birth in one in 2 000 live-born children. The CAKUT spectrum encompasses the absence of kidneys (renal agenesis), hypoplasia (reduced number of nephrons), malformed cystic kidneys (multicystic dysplasia), a double renal collecting system and abnormalities of the tracts which connect the kidneys with the bladder (ureters).

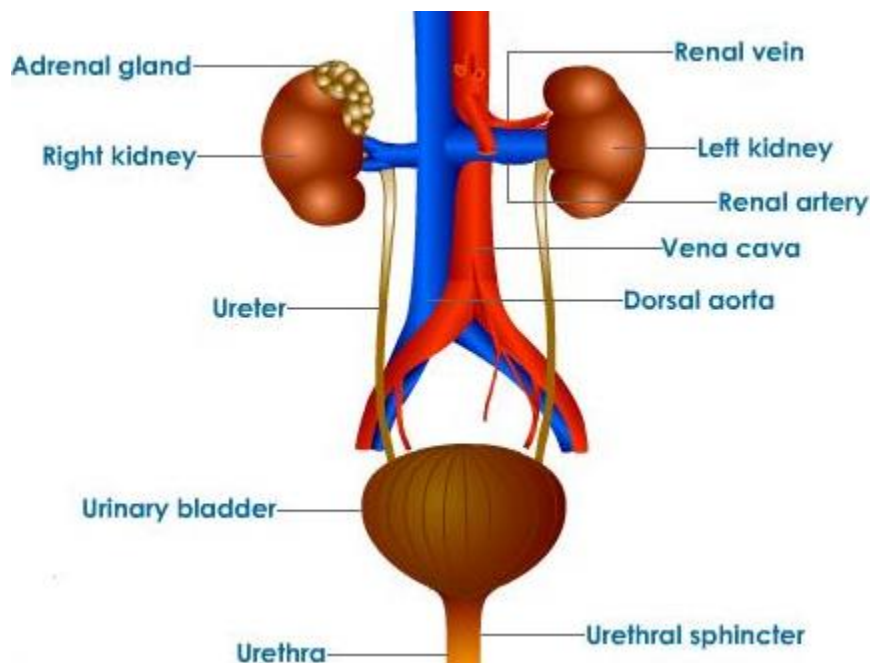


Figure 7.1: Genitourinary system

(<http://images.tutorvista.com/content/excretion-and-osmoregulation/urinary-system-of-man.jpeg>)

CAKUT constitutes the major cause (70%) of end-stage renal disease in children, which is a devastating disease with a major impact on growth, maturation and cognitive development. Patients become dependent on chronic dialysis and/or transplantation, and have a poor life expectancy. Therefore knowledge of the causes of CAKUT and the identification of reliable prognostic biomarkers are essential for early and correct diagnosis, for predicting the risk of progressive disease, and for developing personalised therapies to protect the function of the kidneys. Congenital and inherited anomalies of the urinary system comprise a group of

anatomic defects that, although uncommon, may have subclinical to serious functional consequences.

To complete this learning unit, you will need to refer to chapters 64–72 in Finlayson and Newell.

7.2 Learning outcomes

Upon completion of this learning unit you should be able to

- understand the basic physiological functions of the kidneys
- describe polycystic kidney diseases
- differentiate between autosomal dominant and recessive polycystic kidney disease
- distinguish between acute and chronic kidney diseases
- define renal agenesis, horseshoe kidney and foetal pelvic kidney
- explain what ureteral duplication is
- describe bladder exstrophy and urethral hypospadias
- discuss Potter's syndrome
- describe the vascular diseases of the kidney
- give details of acute and chronic kidney injury
- explain the risk factors of kidney diseases
- comprehend the factors affecting the kidneys or patterns of kidney disease
- distinguish between nephrotic and nephritic kidney diseases
- identify the presenting factors of nephrotic and nephritic kidney diseases
- distinguish between acute and chronic glomerulonephritis
- identify possible causes of glomerulonephritis
- differentiate between proliferative and nonproliferative glomerulonephritis
- understand tubulointerstitial diseases
- discuss nephrocalcinosis
- describe renal neoplasm, bladder cancer and testicular neoplasm.

7.3 Basic physiological functions of the kidney

- 1) Excretory function, excreting
 - metabolites
 - drugs
 - toxins.
- 2) Homeostatic
 - maintenance of water, electrolyte and acid-base balance.
- 3) Endocrine (hormonal) secretory function of
 - renin by the juxtaglomerular cells
 - erythropoietin hormone by endothelial cells of peritubular capillaries of renal cortex
 - prostaglandins.
- 4) Endocrine (hormonal) metabolic function
 - a) converts vitamin D₃ to active 1.25-dihydroxycholecalciferol by 1- α -hydroxylase enzyme in cells of PCT under effect of PTH.

7.4 Polycystic kidney disease

Polycystic kidney disease (PKD or PCKD, also known as polycystic kidney syndrome) is a genetic disorder in which abnormal cysts develop and grow in the kidneys. Cystic disorders can express themselves at any point during infancy, childhood or adulthood.

There are two types of polycystic kidney disease, caused by different genetic flaws:

- Autosomal dominant polycystic kidney disease (ADPKD)
- Autosomal recessive polycystic kidney disease (ARPKD).

Kidney diseases are typically classified as either chronic or acute. Whereas acute kidney injury (AKI) is commonly associated with bacterial infection, sepsis or ischemia-reperfusion injury (I/R that can transition to chronic renal disease), chronic kidney disease (CKD) typically results from diabetic complications, hypertension, obesity and autoimmunity.

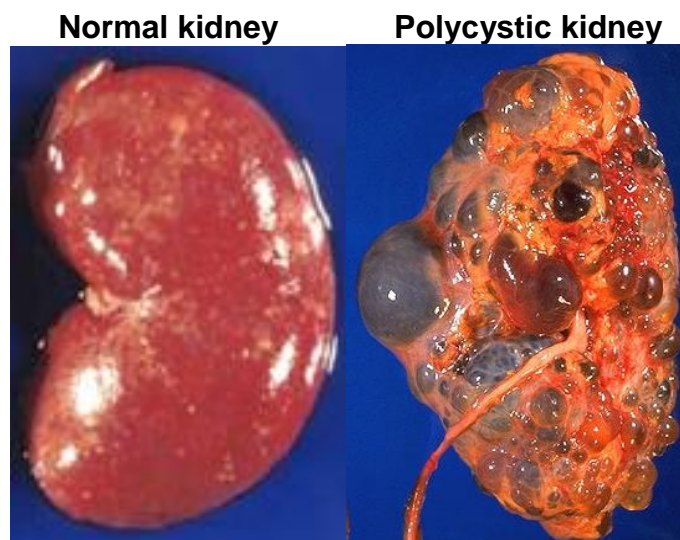


Figure 7.2: Polycystic kidney disease

(https://upload.wikimedia.org/wikipedia/commons/6/68/Polycystic_kidneys%2C_gross_pathology_20G0027_lores.jpg)

The initiating events that promote renal disease can be quite different, however AKI can lead to CKD and, if unchecked, both can lead to end-stage renal disease (ESRD).

7.5 Congenital developmental abnormalities of the kidney

a) Kidney

- Renal agenesis, the complete absence of one or both kidneys, is always accompanied by ureteral aplasia and may be associated with aplastic reproductive tissues on the same side
- Horseshoe kidney, also known as *ren arcuatus* (in Latin), renal fusion or super kidney, is a congenital disorder affecting about one in 600 people, and is more common in men. In this disorder, the patient's kidneys fuse to form a horseshoe-shape during development in the womb
- A foetal pelvic kidney is a condition that results when the kidneys fail to ascend to their normal position above the waist, and remain in the pelvis because they are blocked by blood vessels in the aorta.

b) **Ureter** – ureteral duplication (bifid ureters) is a congenital malformation of the urinary tract, quite common in women, affecting about one per cent of the general population. In ureteral duplication the ureteral bud splits or arises twice before metanephric blastema formation, causing multiple forms of abnormalities of the ureters or of the renal pelvis (duplication of ureters is often associated with duplication of the renal pelvis).

c) **Bladder** – bladder exstrophy (meaning “turned inside out”) is a congenital abnormality that occurs when the skin over the lower abdominal wall (bottom part of the tummy) does not form properly. The bladder is open and exposed on the outside of the abdomen. In epispadias, the urethra does not form properly.

d) **Urethra** – hypospadias is a congenital disorder of the urethra, where the urinary opening is not at the usual location on the head of the penis. Shiny tissue seen extending from the meatus to the tip of the glans, which would have made the urinary channel, is referred to as the urethral plate.

e) **Urachal remnant** – the urachus is a fibrous remnant of the allantois, a canal that drains the urinary bladder of the foetus, that joins and runs within the umbilical cord. The fibrous remnant lies in the space of Retzius, between the transverse fascia anteriorly and the peritoneum posteriorly.

f) **Potter's syndrome** – this refers to the typical physical appearance and associated pulmonary hypoplasia (limited lung development) of a new-born as a direct result of kidney

failure, oligohydramnios (lack of amniotic fluid) and compression while in the uterus. In Potter's syndrome, the primary problem is kidney failure. The kidneys fail to develop properly as the baby is growing in the womb. The kidneys normally produce the amniotic fluid (as urine).

Potter's phenotype refers to a typical facial appearance that occurs in a new-born when there is no amniotic fluid. Without amniotic fluid, the infant is not cushioned from the walls of the uterus. The pressure of the uterine wall leads to an unusual facial appearance, including widely separated eyes. Potter's phenotype may also lead to abnormal limbs, or limbs that are held in abnormal positions or contractures. Oligohydramnios also stops the development of the lungs, so that they do not work properly at birth.

7.6 Vascular diseases of the kidney

a) **Renal artery stenosis** – this is the narrowing of one or more arteries that carry blood to the kidneys (renal arteries). Narrowing of the arteries prevents normal amounts of oxygen-rich blood from reaching the kidneys, which need adequate blood flow to help filter waste products and remove excess fluids. Reduced blood flow may increase blood pressure in the entire body (systemic blood pressure or hypertension) and injure kidney tissue.

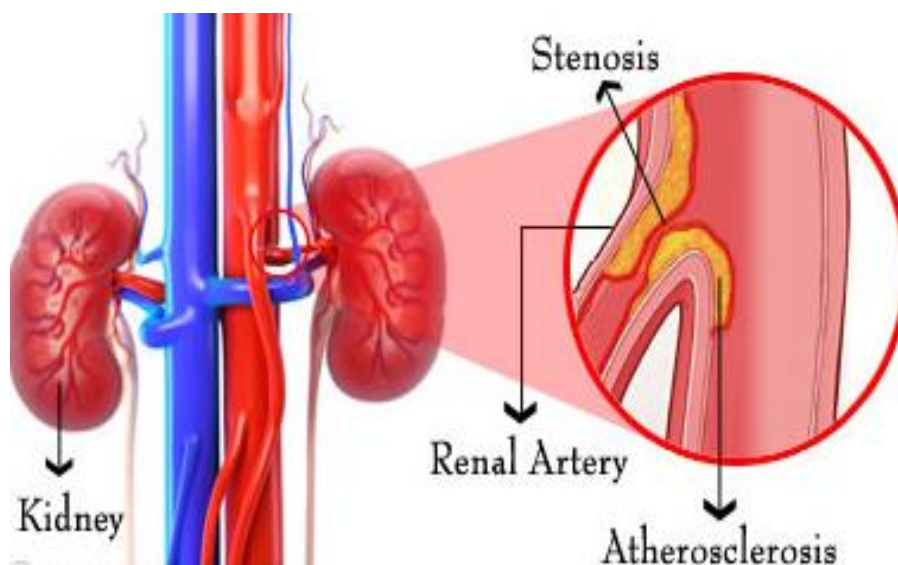


Figure 7.3: Renal artery stenosis

(<http://www.medindia.net/patients/patientinfo/images/renal-artery-stenosis.jpg>)

b) Renal arteriole immune-mediated damage

- Polyarteritis nodosa (PAN) is a rare disease that results from blood vessel inflammation (“vasculitis”) causing injury to organ systems. In addition to the kidneys, the areas most commonly affected by PAN include the nerves, intestinal tract, heart and joints.
- Wegener's granulomatosis (WG) (also known as granulomatosis with polyangiitis [GPA]) is a rare disease in which blood vessels become inflamed (a condition called vasculitis) and localised, nodular collections of abnormal inflammatory cells (granulomas) are found in affected tissues.

c) Glomerular damage

- hypertension
- immune complex disorders
- disseminated intravascular coagulation
- haemolytic uraemia syndrome

d) **Hypertensive damage** – “hypertensive” refers to high blood pressure and “nephropathy” means damage to the kidney; hence this condition is where chronic high blood pressure causes damage to kidney tissue; this includes the small blood vessels, glomeruli, kidney tubules and interstitial tissues.

7.7 Kidney diseases

Kidney diseases occur when the kidneys are damaged and cannot function properly. Numerous conditions and diseases can result in damage to the kidneys, thus affecting their ability to filter waste from the blood while reabsorbing important substances.

Generally, kidney diseases may present or develop in a few different ways:

- a) **Acute kidney injury (AKI)** – this is the rapid loss of kidney function. It may be recognised when a person suddenly produces urine much less frequently and/or has a dramatic increase in the level of waste products in the blood that the kidneys normally filter out. AKI is often the result of trauma, illness or a medication that damages the kidneys. It is most common in people who are already hospitalised, such as those who are critically ill and in the intensive care unit. If the damage caused by AKI persists, it can eventually progress to chronic kidney disease.

- b) **Chronic kidney disease (CKD)** – this occurs over time and is usually defined as lasting more than three months. The most common causes are diabetes and high blood pressure (hypertension). According to the National Kidney Foundation, 26 million American adults have CKD and many more are at risk. However, in some cases it is preventable or, if detected early enough, treatable to prevent or delay progression to kidney failure.
- c) **Kidney failure** – also called end-stage renal disease or ESRD, this is the total or near total loss of kidney function and is permanent. The only two options are treatment with haemodialysis or a kidney transplant. Various factors can cause different patterns of injury to the kidneys and can affect kidney function. Some factors affect the blood-filtering units (the nephrons) or parts of the nephrons, such as the glomeruli or the tubules.

Some factors affect the passage of urine from the kidney, while others cause damage to the kidney(s) as a whole, namely:

- **Obstruction** – the urinary tract can become blocked or obstructed by a kidney stone or tumour. The blockage can lead to infection and injury to the kidney.
- **Autoimmune** disease – sometimes an autoimmune disorder such as systemic lupus erythematosus or Goodpasture syndrome can lead to glomerular disease and affect the kidneys. In autoimmune diseases, the body's immune system mistakenly attacks and damages its own tissue and organs, including the kidneys.
- **Infections** – certain bacteria and viruses can infect the kidneys and cause damage, e.g. repeated urinary tract infections (UTIs) that spread to the kidneys.
- **Immune response** – infections in other parts of the body can stimulate an immune response that has an adverse effect on the kidneys. Examples include strep infection of the throat or skin, the skin infection impetigo, an infection inside the heart (endocarditis) or a viral infection such as HIV, hepatitis B or hepatitis C.
- **Congenital defects** – defects present at birth, such as those that impede the normal flow of urine.
- **Injury** – trauma to the kidneys can cause AKI that can lead to chronic kidney disease.

- **Toxins** – some contrast dyes used for imaging procedures and certain medications can have toxic effects on the kidneys.
- **Drugs** – use and/or overuse of non-steroidal anti-inflammatory drugs (NSAIDs), such as over-the-counter ibuprofen and various prescription drugs, can damage the kidneys. The use of analgesics (painkillers) has been associated with two different forms of kidney damage: acute renal failure and a type of chronic kidney disease called analgesic nephropathy. Certain antibiotics can be directly toxic to the kidneys if their levels are too high. Other drugs may trigger an immune response by the body that subsequently causes kidney damage.
- **Pre-renal azotaemia** – any situation in which there is severe blood loss or reduced blood flow may prevent the kidneys from working properly, such as a blood clot, severe burn, severe dehydration or septic shock.

The most common causes of and main risk factors for kidney diseases are

- **diabetes** – a sustained high level of blood glucose from uncontrolled diabetes can, over time, damage the nephrons in the kidneys. This can be avoided by maintaining good glucose control.
- **high blood pressure** (hypertension) – this can damage blood vessels within the kidneys, preventing them from filtering wastes from the blood as they should. Hypertension can therefore cause CKD, but having CKD can cause high blood pressure as well.
- **family history** of kidney disease – for example, polycystic kidney disease (PKD) is an inherited disorder in which cysts grow in the kidneys, reducing kidney function over time and eventually leading to kidney failure.

Other examples of factors affecting the kidneys or patterns of kidney disease include the following.

- 1) **Glomerulonephritis** (also called chronic nephritis or nephritic syndrome) – a group of diseases that cause inflammation and damage to the blood-filtering units of the kidneys (glomeruli) and the third most common type of kidney disease. As blood filtering becomes impaired urine output decreases, water and waste products accumulate in the blood, and blood appears in the urine. Because the blood cells break down, urine often becomes brown instead of red. Certain body tissues swell with the excess water (a condition called oedema). Outcomes can vary: the condition

may go away in a few weeks, permanently reduce kidney function or progress to end-stage renal disease.

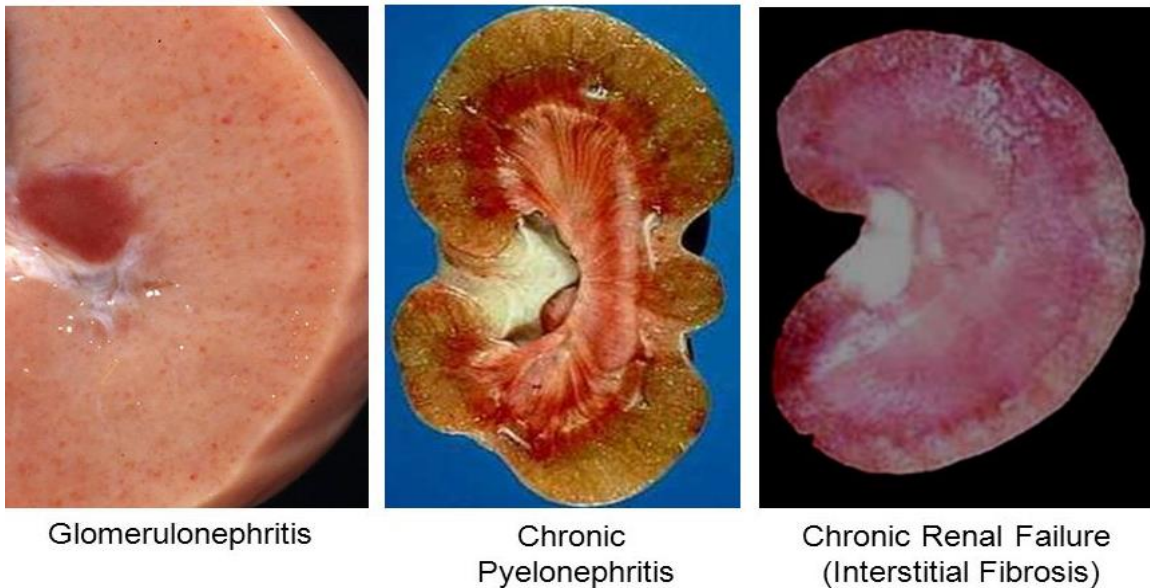


Figure 7.4: Common types of renal disease

(http://images.slideplayer.com/12/3375715/slides/slide_20.jpg)

- 2) Nephritic syndrome** – this is characterised by haematuria (blood in the urine), variable degrees of proteinuria (usually dysmorphic red blood cells [RBCs]), and often RBC casts on microscopic examination of urinary sediment. Often ≥ 1 of the following elements are present: 1) oedema, 2) hypertension, 3) elevated serum creatinine and 4) oliguria. It has both primary and secondary causes. In this syndrome, inflammatory damage to cells lining the glomerulus are thought to result in the destruction of the epithelial barrier, leading to blood being found in the urine. At the same time, reactive changes such as the proliferation of mesangial cells may result in a decrease in kidney blood flow, thus leading to a decrease in the production of urine. The renin-angiotensin system may subsequently be activated, because of the decrease in perfusion of the juxtaglomerular apparatus, which may result in hypertension.

Presenting factors include

- haematuria
- oliguria
- hypertension
- mild proteinuria and oedema.

3) **Nephrotic syndrome** – this often occurs in glomerulonephritis, which is characterised by a thin glomerular basement membrane and small pores in the podocytes of the glomerulus, large enough to permit proteins and red blood cells to pass into the urine (yielding proteinuria and haematuria). By contrast, nephrotic syndrome is characterised by only proteins moving into the urine. Nephrotic syndrome is a kidney disorder that causes the body to excrete too much protein in the urine. Nephrotic syndrome is usually caused by damage to the clusters of small blood vessels in the kidneys that filter waste and excess water from the blood. Nephrotic syndrome causes swelling (oedema), particularly in the feet and ankles, and increases the risk of other health problems. The syndrome is characterised by oedema and increased protein in the urine, decreased protein in the blood, with increased fat in the blood. Inflammation that affects the cells surrounding the glomerular podocytes increases the permeability to proteins, resulting in an increase in excreted proteins. When the level of proteins excreted in the urine exceeds the liver's ability to compensate, fewer proteins are detected in the blood, in particular albumin, which makes up the majority of circulating proteins. With decreased proteins in the blood, there is a decrease in the oncotic pressure of the blood.

The result is oedema, as the oncotic pressure in tissue remains the same. Note that although decreased intravascular oncotic (i.e. osmotic) pressure partially explains the patient's oedema, more recent studies have shown that extensive sodium retention in the distal nephron (collecting duct) is the predominant cause of water retention and oedema in nephrotic syndrome. This is worsened by the secretion of the hormone aldosterone by the adrenal gland, which is secreted in response to the decrease in circulating blood, and causes sodium and water retention. Hyperlipidaemia is thought to be a result of the increased activity of the liver.

Presenting factors include

- proteinuria
- oedema
- hyperlipidaemia.

The differences between nephrotic and nephritic syndrome are easily forgotten. At the most basic level, remember that nephrotic syndrome involves the loss of a lot of protein, whereas nephritic syndrome involves the loss of a lot of blood in urine.

- 4) **Interstitial nephritis** – this is a kidney disorder in which the spaces between the kidney tubules become inflamed and swollen. It is associated with decreased urine output, blood in the urine and oedema. Usually, it is a short-term condition which may be acute or chronic.

Causes of interstitial nephritis include

- side effects of certain medications
 - certain autoimmune disorders
 - having a low blood potassium level (hypokalaemia) or a high blood calcium level (hypercalcaemia) or uric acid (hyperuricaemia).
- 5) **Acute tubular necrosis (ATN)** – a kidney disorder involving damage to the tubules in the kidneys. It is one of the most common causes of kidney failure in hospitalised patients. ATN is caused by a lack of oxygen to the kidney tissues or from damage to the kidneys by toxic substances such as contrast dyes used for x-ray studies and certain medications. In most cases, ATN is reversible.



Figure 7.5: Acute tubular necrosis, with dusky red medulla and a pale cortex
(http://peir.path.uab.edu/library/_data/i/upload/2013/08/01/20130801094322-d94d0c0c-me.jpg)

Numerous causes of secondary glomerulonephritis exist.

a) **Acute glomerulonephritis**

Acute glomerulonephritis can be a response to an infection such as strep throat or an abscessed tooth. It may be due to problems with the immune system overreacting to the

infection. This can go away without treatment. If it does not resolve, prompt treatment is necessary to prevent long-term damage to the kidneys.

Certain illnesses are known to trigger acute glomerulonephritis, including

- strep throat
- systemic lupus erythematosus (also called lupus)
- Goodpasture syndrome, a rare autoimmune disease in which antibodies attack the kidneys and lungs
- amyloidosis, which occurs when abnormal proteins that can cause harm build up in the organs and tissues
- Wegener's granulomatosis, a rare disease that causes inflammation of the blood vessels
- polyarteritis nodosa, a disease in which cells attack arteries.

b) **Chronic glomerulonephritis**

The chronic form of glomerulonephritis can develop over several years, with no or very few symptoms. This can cause irreversible damage to the kidneys and ultimately lead to complete kidney failure. Chronic glomerulonephritis does not always have a clear cause – genetic disease is a possibility. Hereditary nephritis occurs in young men with poor vision and poor hearing.

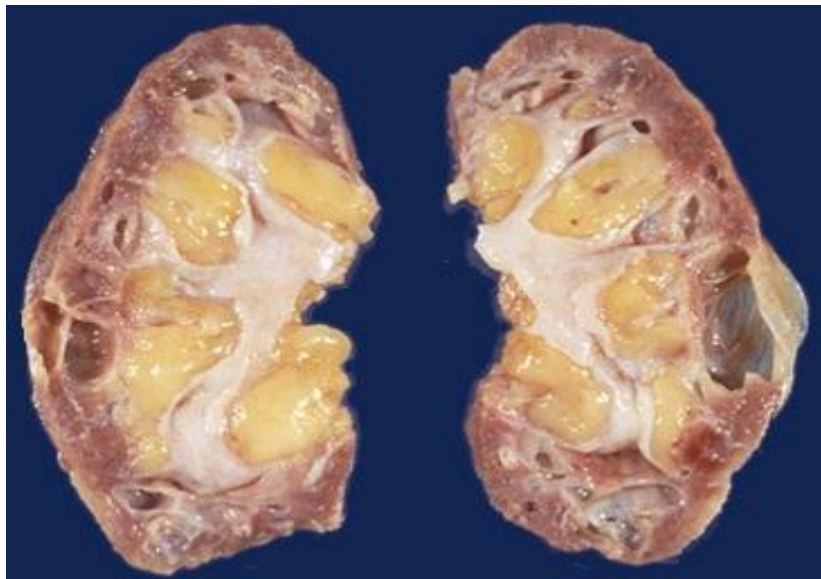


Figure 7.6: Chronic glomerulonephritis

(https://classconnection.s3.amazonaws.com/451/flashcards/929451/png/screen_shot_2012-01-05_at_4.42.29_pm1325810563892-thumb400.png)

7.8 Other possible causes of glomerulonephritis

- a) **Certain immune diseases**, a history of cancer and exposure to certain hydrocarbon solvents.
- b) **Systemic lupus erythematosus (SLE)** is an autoimmune disease where the body's immune system mistakenly attacks healthy tissue. It can affect the skin, joints, kidneys, brain and other organs.
- c) **Henoch-Schönlein purpura (HSP)** (also known as IgA vasculitis, anaphylactoid purpura, purpura rheumatica and Schönlein-Henoch purpura) is a disease of the skin, mucous membranes, and sometimes other organs. It most commonly affects children. In the skin, the disease causes palpable purpura (small, raised areas of bleeding below the skin), often with joint and abdominal pain. With kidney involvement, there may be a loss of small quantities of blood and protein in the urine (haematuria and proteinuria), but this usually goes unnoticed; in a small proportion of cases, the kidney involvement proceeds to chronic kidney disease. HSP is often preceded by an infection, such as a throat infection. HSP is a systemic vasculitis (inflammation of blood vessels) and is characterised by the deposition of immune complexes containing the antibody immunoglobulin A (IgA); the exact cause of this phenomenon is unknown. It usually resolves within several weeks and requires no treatment apart from symptom control, but may relapse in a third of cases and cause irreversible kidney damage in about one in a hundred cases.
- d) **Goodpasture syndrome** is an autoimmune disorder. It occurs when the immune system mistakenly attacks and destroys healthy body tissue. People with this syndrome develop substances that attack a protein called collagen in the tiny air sacs in the lungs and the filtering units (glomeruli) of the kidneys.
- e) **Diabetic nephropathy** (or diabetic kidney disease) is a progressive kidney disease involving damage to the capillaries in the kidneys' glomeruli because of longstanding diabetes mellitus. It is characterised by nephrotic syndrome and diffuse scarring of the glomeruli. A common complication of diabetes, it is a prime reason for dialysis in many developed countries.

7.9 Proliferative glomerulonephritis

Proliferative glomerulonephritis is characterised by an increased number of cells in the glomerulus. These forms usually present with a triad of blood in the urine, decreased urine

production and hypertension, i.e. nephritic syndrome. The disease usually progresses to end-stage kidney failure (ESKF) over weeks to years (depending on type).

7.10 Non-proliferative glomerulonephritis

This is characterised by forms of glomerulonephritis in which the number of cells is not changed. These forms usually result in nephrotic syndrome.

a) **Minimal change disease (MCD)** is a kidney disease in which large amounts of protein are lost in the urine. Worldwide, it is one of the most common causes of nephrotic syndrome (see below). The kidneys normally work to clean the blood of natural waste products that build up over time.

b) **Focal segmental glomerulosclerosis (FSGS)** is one of the most common causes of primary glomerular diseases in adults. The condition causes asymptomatic proteinuria or nephrotic syndrome with or without renal insufficiency. It can have many different causes. Scarring may happen because of an infection, a drug or a disease that affects the entire body, like diabetes, HIV infection, sickle cell disease or lupus. FSGS can also be caused by another glomerular disease that occurred prior to FSGS.

c) **Membranous glomerulonephritis** – membranous nephropathy (MN) is a kidney disease that can occur by itself (primary) or in conjunction with several other diseases (secondary). MN is one of the most common causes of nephrotic syndrome in adults. Over time this can lead to kidney failure as well. MN is caused by the build-up of circulating immune complexes, within the kidney itself, against hepatitis B, syphilis, DNA or certain drugs or tumours. Immune complexes are made when a person's antibodies attack something they consider foreign to the body (an antigen).

d) **Thin basement membrane disease (TBMD)**, also known as benign familial haematuria and thin basement membrane nephropathy) is, along with IgA nephropathy, the most common cause of asymptomatic haematuria. This disease is characterised by abnormal thinning of the basement membrane of the glomeruli in the kidneys.

e) **IgA nephropathy**, also known as Berger's disease, occurs when an antibody called immunoglobulin A (IgA) lodges in the kidneys. This results in local inflammation that, over time, may hamper the kidneys' ability to filter wastes from the blood.

f) **Post-infectious glomerulonephritis** – this is a common complication of bacterial infections, typically skin infection by Streptococcus bacteria types 12, 4 and 1 (impetigo), but also after streptococcal pharyngitis, for which it is also known as postinfectious or poststreptococcal glomerulonephritis. It can be a risk factor for future albuminuria.

7.11 Tubulointerstitial diseases

Tubulointerstitial nephritis is a primary injury to the renal tubules and interstitium, resulting in decreased renal function. The acute form is most often due to allergic drug reactions or infections.

a) **Acute tubular necrosis (ATN)** is a medical condition involving the death of tubular epithelial cells that form the renal tubules of the kidneys. ATN presents with acute kidney injury (AKI) and is one of the most common causes of AKI. Common causes of ATN include low blood pressure and the use of nephrotoxic drugs

b) **Interstitial nephritis** (or tubulointerstitial nephritis) is a form of nephritis affecting the interstitium of the kidneys surrounding the tubules, i.e. inflammation of the spaces between renal tubules.

c) **Nephrocalcinosis**, once known as Albright's calcinosis after Fuller Albright, or Anderson-Carr kidneys, is a term originally used to describe the deposition of calcium salts in the renal parenchyma due to hyperparathyroidism.

7.12 Physical agents

- Radiation and obstruction
- Immune-mediated disease – vasculitis: polyarteritis nodosa
- Infection
- Acute pyelonephritis, which is a sudden and severe kidney infection. It causes the kidneys to swell and may permanently damage them. Pyelonephritis can be life-threatening. When repeated or persistent attacks occur, the condition is called chronic pyelonephritis.

Other renal and tubular tract infections include

- bacterial
- TB
- viral
- fungal
- parasitic

7.13 Renal neoplasms

a) **Renal cell carcinoma (RCC)** is a kidney cancer that originates in the lining of the proximal convoluted tubule, a part of the very small tubes in the kidney that transport primary urine. RCC is the most common type of kidney cancer in adults, responsible for approximately 90–95 per cent of cases.



Figure 7.7: Renal cell carcinoma

(http://webpathology.com/slides-13/slides/Kidney_RCC_Gross17.jpg)

b) **Transitional cell carcinoma (TCC)** (TCC, also known as urothelial carcinoma [UCC]) is a type of cancer that typically occurs in the urinary system. It is the most common type of bladder, ureter, urethra and urachus cancer.

7.14 Bladder tumours

a) **Squamous cell carcinoma** – these tumours typically appear as persistent, thick, rough, scaly patches that can bleed if bumped, scratched or scraped. They often look like warts and sometimes appear as open sores with a raised border and a crusted surface.

b) **Adenocarcinoma** (plural: adenocarcinomas or adenocarcinomata) is a type of cancerous tumour that can occur in several parts of the body. It is defined as the neoplasia of epithelial tissue that has a glandular origin, glandular characteristics, or both.

Bladder cancer begins when cells in the bladder start to grow uncontrollably. As more cancer cells develop, they form a tumour and spread to other areas of the body. Most bladder cancers start in the innermost lining of the bladder, which is called the urothelium or transitional epithelium. As the cancer grows into or through the other layers in the bladder wall, it becomes more advanced and can be more difficult to treat.

Bladder cancers are often described based on how far they have invaded into the wall of the bladder:

- **Non-invasive cancers** are still in the inner layer of cells (the transitional epithelium), but have not grown into the deeper layers.
- **Invasive cancers** have grown into the deeper layers of the bladder wall. These cancers are more likely to spread and are more difficult to treat.

7.15 Testicular cancer

Testicular cancer is cancer that develops in the testicles, which are part of the male reproductive system.

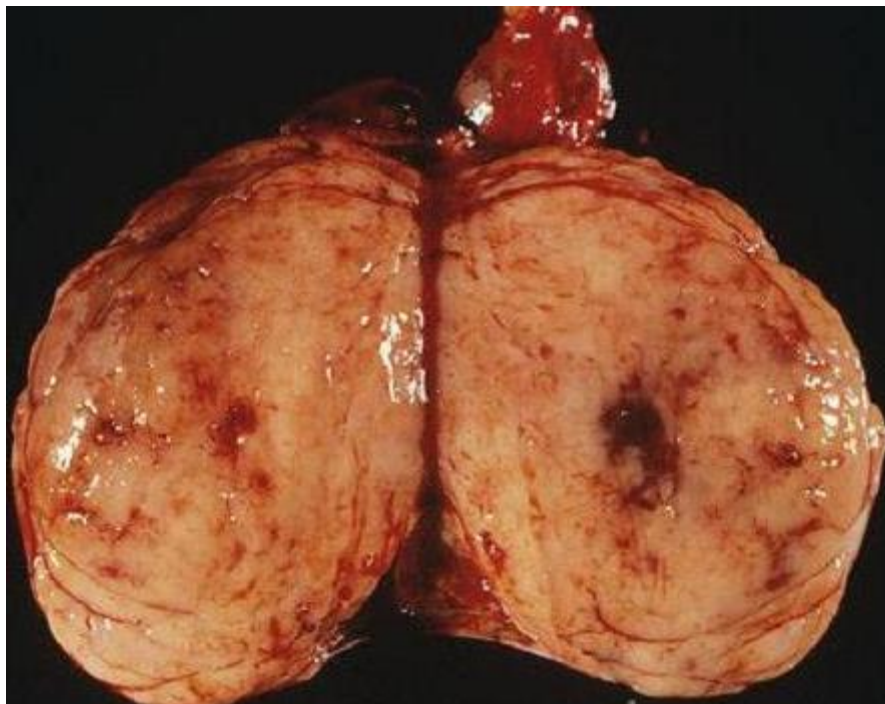


Figure 7.8: Testicular cancer

(<https://medicaldailyjournal.com/wp-content/uploads/sites/5/2017/10/Testicular-Cancer-2.jpg>)

a) **Intratubular germ cell neoplasia** (abbreviated as ITGCN or IGCN, also known as testicular intratubular germ cell neoplasia and intratubular germ cell neoplasia of the testis) is considered a precursor lesion for many types of testicular germ cell tumours.

b) **Seminoma** (also known as pure seminoma or classical seminoma) is a germ cell tumour of the testicle or, more rarely, the mediastinum or other extra-gonadal locations. A malignant neoplasm, it is one of the most treatable and curable cancers, with a survival rate above 95 per cent if discovered in the early stages.

c) **Nonseminoma** is a type of testicular cancer that arises in specialised sex cells called germ cells, which give rise to sperm. Nonseminomas include embryonal carcinoma, teratoma, choriocarcinoma and yolk sac tumour.

d) **Testicular sex cord stromal tumours** include Leydig cell tumours, Sertoli cell tumours and granulosa cell tumours. Leydig cell tumours are derived from normal Leydig cells that produce testosterone and are located in the interstitium of the testis.

e) **Testicular lymphoma** is a rare extranodal presentation of non-Hodgkin's lymphoma. Extranodal means the location of the malignant cells was found outside the lymphoid organs (lymph nodes). Prognosis depends on the type and stage of the lymphoma.

f) **Prostate cancer** occurs in a man's prostate – a small, walnut-shaped gland that produces the seminal fluid that nourishes and transports sperm. Prostate cancer is one of the most common types of cancer in men.

ACTIVITY 7.1

- (a) Describe the physiological functions of the kidney.
- (b) Describe the types of kidney disease.
- (c) Define polycystic kidney diseases.
- (d) Differentiate between autosomal dominant and recessive polycystic kidney disease.
- (e) Distinguish between acute and chronic kidney disease.
- (f) Define renal agenesis, horseshoe kidney and foetal pelvic kidney.
- (g) What is ureteral duplication?
- (h) Describe bladder exstrophy and urethral hypospadias.
- (i) Discuss Potter's syndrome.
- (j) Describe the vascular diseases of the kidney.
- (k) Give details of acute and chronic kidney injury.
- (l) Explain the risk factors of kidney diseases.
- (m) Explain the factors affecting the kidneys or patterns of kidney disease.

- (n) Distinguish between nephrotic and nephritic kidney diseases.
- (o) What are the presenting factors of nephrotic and nephritic kidney diseases?
- (p) What are the causes of interstitial nephritis?
- (q) Distinguish between acute and chronic glomerulonephritis.
- (r) Describe the possible causes of glomerulonephritis.
- (s) Differentiate between proliferative and nonproliferative glomerulonephritis.
- (t) Explain tubulointerstitial diseases.
- (u) Discuss nephrocalcinosis.
- (v) Describe renal neoplasm, bladder cancer and testicular neoplasm.
- (w) Name the five types of testicular cancer.

FEEDBACK ON ACTIVITY 7.1

(a–e) Sections 7.1–7.5 may be very helpful in answering the questions. Also see pages 148–155 in the textbook by Finlayson and Newell.

(f–w) The study guide provides further enlightenment regarding the above questions. Study sections 7.6–7.9 in addition to pages 148–155 in the textbook by Finlayson and Newell.

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