National Universities Commission

Core Curriculum and Minimum Academic Standards (CCMAS)

CCMAS Book Series

Fundamentals of Medicine and Dentistry

Book 1: Volume 2

HUMAN PHYSIOLOGY

Editors
Nimi Briggs
Eyitope Ogunbodede

General Editor: Abubakar Adamu Rasheed

Published by the National Universities Commission
26, Aguiyi Ironsi street PMB 237 Garki GPO, Maitama, Abuja.
Telephone: +2348027455412, +234054407741
Email: info@nuc.edu.ng

ISBN:

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Foreword

The National Universities Commission is empowered by the Education (National Minimum Standards and Establishment of Institutions) Act, CAP E3, Laws of the Federation of Nigeria, 2004, to lay down minimum academic standards in Nigerian Universities and to accredit the degrees therefrom. According to this and in its sustained commitment to the revitalisation of the Nigerian University System, the Commission launched the "Core Curriculum and Minimum Academic Standards (CCMAS)", in December, 2022. The document has been adjudged by both internationally and locally revered scholars, as a standard and fit-for-purpose, designed to meet the demands of the 21st Century.

To ensure the efficient delivery of the CCMAS, it has become fitting and necessary to develop a reference document that would contain innovative and simple topics for all disciplines/programmes to serve as a guide for students and lecturers. This novel idea informs the development of the CCMAS Book Series, which presents to Nigerian universities the fundamentals of each discipline, aimed at deepening the understanding of the CCMAS, for the overall improvement in teaching and learning, and ultimately, for the production of nationally relevant and globally competitive graduates from the System. The excitement and wide acceptance of the Book Series stems from the fact that several scholars in their respective disciplines sent in their contributions, which are rated topnotch in all ramifications. There is no gainsaying that the Book Series is a welcome masterpiece as it expounds what the CCMAS offers and the many lessons and motivations to draw from its optimal implementation, for the overall good of society.

The effort of the National Universities Commission in the development of the CCMAS and following up with associated innovative initiatives like the CCMAS book series is commendable. Consequently, I congratulate the Executive Secretary, National Universities Commission, Professor Abubakar Adamu Rasheed *mni, MFR, FNAL* for adding another feather to his feather-filled cap within his reltively short period in NUC. Kudos must be given to the Distinguished Emeritus Professor Okebukola led NUC Strategy and Advisory Committee (STRADVCOM) and staff of the National Universities Commission for driving this process to fruition. There is no way this initiative can become a reality without the contributions of the scholars who developed the texual materials. Consequently, I laud the erudite scholars of Nigerian universities, who have demonstrated their love for academic excellence in sharing their knowledge with humanity through the instrumentality of this project.

I commend the CCMAS Book Series to staff and students of Nigerian universities and indeed to scholars all over the globe as the contribution of the Nigerian University System to academic development and excellence. Happy reading.

Malam Adamu Adamu
Honourable Minister of Education

Preface

In keeping with its mandate of making university education in Nigeria more responsive to the needs of the society, the National Universities Commission commenced the journey to restructure the BMAS in 2018, introducing in its place, the Core Curriculum and Minimum Academic Standards (CCMAS), to reflect the 21st Century realities, in the existing and new disciplines and programmes in the Nigerian University System. The arduous process, which was birthed through continued stakeholder interactions over the course of four years, produced seventeen documents to cater for each of the disciplines in the Nigerian University System. A key feature of the CCMAS document is the unique structure that provides for 70% of core courses for each programme, while allowing universities to utilise the remaining 30% for other innovative courses in their peculiar areas of focus.

Following the conclusion of the development and review process as well as a series of editing, the CCMAS documents were launched in a grand ceremony on the 5th of December 2022. With the launch, the job of the Commission was far from over as this was only the beginning of a three-phase process in the development/review and implementation of the CCMAS document. Having completed phase one, which is the launching of the CCMAS, NUC proceeded to phase two, which involves the development of the 30% CCMAS by the universities. At the same time, the plan for capacity building for effective implementation of the CCMAS as well as the development of textual materials to support the implementation of the CCMAS were taken on board.

The need to have customised (bespoke) texts to support the implementation of the CCMAS was pointed out by an erudite Professor (President of the Nigerian academy of Education) during one of the General Assemblies and was processed through the NUC Strategy and Advisory Committee (STRADVCOM). Emeritus Professor Nimi Briggs was unanimously nominated as the Project Coordinator. The series of textual materials are called the *CCMAS Book Series* and titled *Fundamentals Series* in the first project.

The contributors across the 17 disciplines have been drawn from the six geopolitical zones and proprietorship of universities such that there is collective ownership. The major denominator for selection was scholarship in the discipline, which was reflected in the narrative of each book. The various chapters showcase and give examples from local published research so that visibility can be given to ideas from Nigeria and Africa on the topics. While definitions and models from "western" scholars are mentioned, these are de-emphasised as much as possible. The time is ripe to show the world, through this book, that Nigerian scholars, over the last 70 years at least, have been in the frontline of research in the published topics and now able to provide generic and contextual definitions, models and examples in the respective disciplines for scholarly work the world over.

The contents target the compulsory courses in the CCMAS and will be published in a series. As much as possible, the books attempt to sync with the levels of delivery of the curriculum

that is 100 level; 200 level and so on. The books are written in very simple English, well-illustrated and rendered in the typical course-material format of objectives, content to be learned, summary, evaluation, exercises and references.

The Commission is optimistic that these series will serve as a guide to support the implementation of the CCMAS documents in the Nigerian University System and beyond and adequately equip the trainers and students in making university education more responsive to the needs of society.

Professor Abubakar Adamu Rasheed, *mni, MFR, FNAL, HLR*
Executive Secretary

CCMAS BOOKS IN MEDICINE AND DENTISTRY
BOOK 1, VOLUME 1: HUMAN ANATOMY

With the launching of the 17 documents of the new Core Curriculum and Minimum Academic Standards (CCMAS) on Monday 5th December 2022 by Vice-President Professor Yemi Osinbajo, *GCON,* Nigeria's National Universities Commission (NUC) accomplished a major feat in its quest to rapidly revitalise the nation's university system.[1] In this regard, the Commission working though its *Strategy Advisory Committee (STRADVCOM),* had, in 2019, identified 10 priority areas that needed urgent attention, one of which is, the introduction of a reengineered curriculum that addresses 21st century challenges. Such a curriculum, it was envisaged, should lay emphasis on skills acquisition and learning outcomes and should be able to stand side by side with those from the World's best universities in the quality of its content as well as being relevant on issues affecting the local communities in which individual universities are located. Thus, CCMAS documents were developed to provide 70% of the contextual materials and compulsory credit units required for graduation at the bachelor's level across the entire chain of degree courses offered by all universities in the country.

That done, attention shifted towards enabling individual universities to develop the additional 30% of the curriculum from issues that are peculiar and relevant to their core mission and local circumstances, as approved by Senates of their individual universities, capacity building and training of staff on the delivery of the CCMAS and the production of books that would cover the contextual materials of the CCMAS.

For books in Medicine and Dentistry, the plan is to organise them in ways that mirror the various parts in which the courses are taught and professional examinations sat for. Consequently, CCMAS Medicine and Dentistry Book 1 will cover courses that are taught at the Basic Medical Sciences level, in the first part of the Medicine and Dentistry programme and for which students are examined at the First Professional Examination. Book 2 will cover courses taught at the Basic Clinical Sciences level, in the second part of the programme and for which students are examined at the Second Professional Examination. Books 3A and 3B will cover courses that are taught in the first part of the Clinical Sciences level (Bachelor of Medicine and Bachelor of Surgery and Bachelor of Dental Surgery options respectively) and for which students are examined in the Third Professional Examination. Books 4A and 4B will cover courses that are

taught in second part of the Clinical Sciences level (Bachelor of Medicine and Bachelor of Surgery and Bachelor of Dental Surgery options respectively) and are examined in the Fourth and Final Professional Examination.

This current CCMAS Medicine and Dentistry Book 1 is in three Volumes containing contextual materials for Human Anatomy (Volume 1), Human Physiology (Volume 2) and Medical Biochemistry (Volume 3). These courses are taught at the Basic Medical Sciences level and are examined at the First Professional Examination.

It is expected that utilisation of the CCMAS series in the Nigerian Universities System will commence in the 2023/2024 academic session. Stringent efforts were therefore made to conclude the production of this book, the first in the CCMAS Medicine and Dentistry series, well in advance of that period.

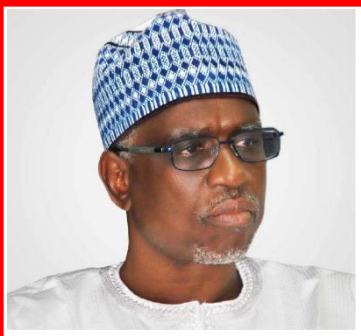
Nimi D. Briggs. Editor
Eyitope Ogunbodede. Co-Editor

February 2023.

Reference.

1. Blueprint on the Rapid Revitalisation of University Education in Nigeria 2019-2023. Abubakar Adamu Rasheed Ed. Sterling Publishers.

Note: Sadly, Emeritus Professor Nimi Briggs passed on April 10, 2023. He is resting in the realisation that this project is "safely delivered", he being a globally renowned scholar in obstetrics and gynecology.



PROF. ABUBAKAR A. RASHEED

Professor Abubakar Adamu Rasheed , mni, MFR, FNAL, HLR is a distinguished globally-acclaimed professor of English. He was Vice-Chancellor of one of Nigeria's foremost Universities - Bayero University, Kano where he raised to higher heights, the tradition of exemplary leadership. He was editor of the New Nigerian Newspapers. He served as the Executive Secretary of the National Universities Commission (NUC) till July 2023. He is the receipient of GUNi-Africa Award for the best Executive Secretary of NUC.

PROF. NIMI BRIGGS

Nimi Briggs was Emeritus Professor of Obstetrics and Gynaecology at the University of Port-Harcourt, Port-Harcourt, Nigeria (UNIPORT) before his demise. He served as Vice-Chancellor of UNIPORT twice, from 1995 to 1996 and 2000 until 2005. He was Pro-Chancellor and Chairman of Council, Federal University, Lokoja, Nigeria. He was Pro-chancellor and Chairman of Council, Alex Ekwueme Federal University, Ndufu-Alike, Ebonyi State, Nigeria from May 2020 to April 2023. He was also pioneer Pro-Chancellor of Council, Bayelsa University of Medical Sciences.

PROF. EYITOPE OGUNBODEDE

Professor Eyitope Ogunbodede, BSc, BChD, MPH, PhD, DDPHRCS, FFDRCS, FICD, FNCS, FNAMed served as the 11th Vice-Chancellor of Obafemi Awolowo University (OAU), Ile-Ife from 2017 to 2022. He was Head of Department, Dean of the Faculty of Dentistry, and Provost of the College of Health Sciences, OAU. Professor Ogunbodede has led many outstanding research projects nationally and internationally. He was Convener and Foundation President of the Nigerian Division of International Association for Dental Research (IADR) and served on the International Council of the Association for 3 years.

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LIST OF AUTHORS AND CO-AUTHORS

TITLE	SURNAME	OTHER NAMES	INSTITUTION
PROFESSOR	ABDULWAHAB	Alhassan	Ahmadu Bello University, Zaria
PROFESSOR	AMAH-TARIAH	Fortune S.	Rivers State University, Port Harcourt
PROFESSOR	DAPPER	Victor D.	University of Port Harcourt, Port Harcourt
PROFESSOR	EGWURUGWU	Jude N.	Imo State University, Owerri
PROFESSOR	FASANMADE	Adesoji A.	University of Ibadan, Ibadan
PROFESSOR	MOHAMMED	Aliyu	Modibbo Adama University Yola
PROFESSOR	NWAFIA	Walter C.	Chukwuemeka Odumegwu Ojukwu University Awka
PROFESSOR	NWANGWA	Eze K.	Delta State University Abraka
PROFESSOR	ODEH	Samuel O.	University of Jos, Jos
PROFESSOR	OGUNLADE	Olawadare	Obafemi Awolowo University Ile-Ife
PROFESSOR	SALISU	Ahmed Ibrahim	Bayero University, Kano
PROFESSOR	TUKUR	Maisaratu Aminu	University of Maiduguri, Maiduguri

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Chapter 1

PHS 201: INTRODUCTORY PHYSIOLOGY AND AUTONOMIC NERVOUS SYSTEM

Victor D. Dapper, Walter C. Nwafia and Jude N. Egwurugwu

Introduction to Physiology and its place in Medicine

Overview

The subject of Physiology is as old as medicine. Indeed, Physiology has been described as the queen of medicine and the medical sciences. This is because a clear understanding of the subject of Physiology is critical for proper appreciation of the theory and practice of clinical medicine. Major and outstanding scientific breakthroughs in medicine or the medical sciences or the resolution of intractable clinical conditions are premised on an adequate understanding and application of the subject of Physiology.

As a branch of Biology, the subject of Physiology is a vast arena that includes human, animal, plant, viral, cellular, and comparative physiology and many more. Medical or Human Physiology is a study of how the human body functions in health and in disease. Physiology therefore has a critical place in the theory and practice of medicine. Physiology therefore has a critical place in the theory and practice of medicine. The autonomic nervous system is that part of the nervous system that controls most vegetative or visceral functions of the body such as gastrointestinal motility and secretion, sweating, arterial blood pressure, body temperature, heart rate, urinary bladder emptying. Its also called vegetative or involuntary nervous system. The central aspects of the ANS are located in hypothalamus, brain stem and spinal cord. Higher centers such as the limbic cortex and portions of the cerebral cortex also influence the activities of the ANS. The ANS is a motor or efferent system for the visceral organs, blood vessels and secretary glands.

One important feature of the ANS is the rapidity and intensity with which it can change visceral functions. It can increase heart rate to twice normal within 3-5 seconds, and sweating can start within seconds. It is often associated with some responses such as **"fight-or -flight** response (prepares the body to either run away from a threat or to stand and fight in the face of the threat); "**rest-and -digest**" response (after the encounter, body relaxes, heart reduces, etc) and emotional response. Genetics is described simply as the study of inheritance. Human society has always marvelled at the fact that a man's offspring always look like him: Semblance has therefore always been a way of person identification. Genetics attempts to provide a scientific basis for that resemblance.The presence of the DNA in the human chromosome provides the molecular basis of human inheritance and inheritance patterns. Biotechnology is broadly defined as the science of using living organisms or the products of living organisms for the benefit of humans or the improvement of human surroundings via making a new product or solving an identifiable problem. The human genome refers to the complete set of genes or indeed all the genetic material present in the human. Several benefits have arisen from the practice of biotechnology. These include the production of antibodies, transgenic animals, DNA fingerprinting and bioremediation

Objectives

At the end of this chapter, students should be able to:

1. Define and have a clear understanding of the subject of Physiology
2. Differentiate between cells, tissues, organs, and organ systems
3. Understand fully the concept of the *milieu intérieur* (The internal environment).
4. Understand the terms homeostasis, homeostatic mechanisms and the concept of Homeostasis including the roles of the various organ systems in its maintenance.
5. Understand the importance of physiological control both negative and positive control mechanisms.
6. Appreciate the importance of physiology and its critical role in the theory and practice of clinical medicine.
7. Describe the components of the ANS
8. Differentiate between the structures of the sympathetic and parasympathetic divisions of the ANS
9. Describe the functions of the ANS
10. Describe how the CNS coordinates and contributes to autonomic functions.
11. Define genetics and understand the scientific basis of inheritance
12. Appreciate the role of chromosomes in the inheritance process
13. Understand the roles of DNA and other nucleotides in genetic expression
14. Understand cellular divisions: meiosis and mitosis and their role in genetics
15. Understand how genes code for proteins via the transcription and translation process
16. Define the terms genotype, phenotype and haplotype
17. Define biotechnology and describe the benefits of biotechnology to humanity.
18. Understand the potential ethical issues in biotechnology research.
19. Define the human genome and describe the potential benefits of unravelling the human genome.
20. Understand the human genome as a basis for human diversity

What is Physiology?

Physiology is the science of life. The word physiology is derived from two Greek words *phúsis* meaning 'nature, origin' and *logía* meaning 'study of.' The term was first introduced by a French physician Jean Francois Fernel (ca. 1497–1558) in 1542 to describe the study of the function of the healthy body as distinguished from Pathology, the study of disease processes. With his description of the circulatory system, the English physician and physiologist William Harvey (1578–1657) was the first to use carefully designed human and animal experiments to establish the function of a major organ and organ system.

Over the centuries however, the extent, and the scope of Physiology as an area of study has expanded. Physiology attempts to explain the physical and chemical factors that are responsible for the origin, development, and progression of life. Physiology aims at understanding the mechanisms of living things from the basic functional unit of the cell to the molecular, ionic, and elemental level and from the organs and organ systems to the general adaptive behaviour of the whole organism to the internal and external environment. This deliberate emphasis at integrating molecular, cellular, organ, and organ systems and whole-body function is what distinguishes Physiology from the other life sciences.

As a branch of Biology, the subject of Physiology is a vast area that includes human physiology, animal physiology, plant physiology, viral physiology, cellular physiology, and comparative physiology and many more. Medical or Human Physiology is a study of how the human body functions in health. Human Physiology attempts to explain the cellular and molecular mechanism that ensures the maintenance of human life and our continued survival as individuals and evolution as a distinct modern species: *Homo sapiens sapiens*. Basically, Human Physiology attempts to understand how the human body works in health and how it responds and adapts to the challenges of living. These challenges may arise from either the internal or external environment.

A few basic concepts in Human Physiology

Cells, Tissues, Organs, and Organ Systems

The cell is the basic functional unit of the human body. Typically, the human cell is described as eukaryotic as opposed to prokaryotic cell types found in lower forms of life. A detailed discourse of the basic physiology of the cell, cellular organelles and other processes would be provided subsequently. As shown in Figure 1.1 below, the human cell is composed of atoms, molecules, genetic materials, and various cellular organelles. There are about 100 trillion cells in the human body.

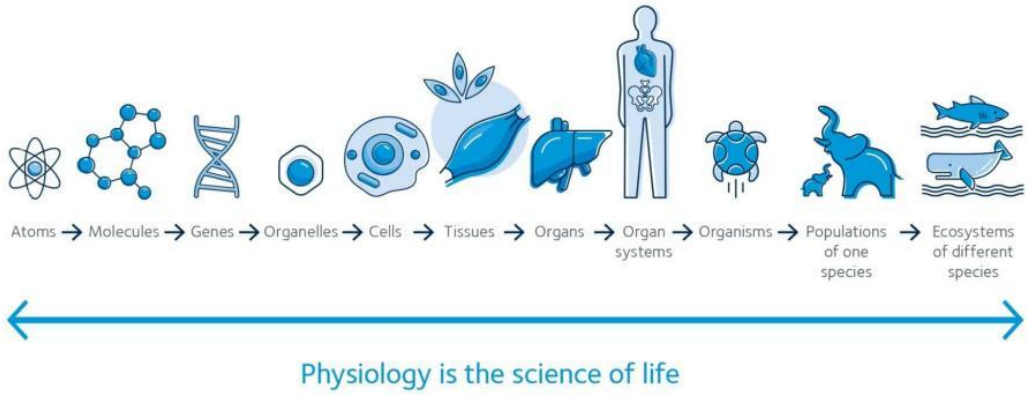


Figure 1.1: The Science of Physiology

Source: https://www.physoc.org/explore-physiology/what-is-physiology/

There are several different types of cells in the human body, examples include, muscle cells, fat cells, nerve cells and bone cells. Each cell type is specially adapted to perform a specific set of bodily function thus each cell type differs evolutionarily, morphologically, and functionally from the other.

Cells of a particular type aggregate to form tissues, two or more different tissues coming together constitutes an organ in the body, while different organs make up an organ system. Organs, such as the heart, the lungs, the stomach, the kidneys, the skin, and the liver, are made up of two or more types of tissue organized to serve a particular function. The functional activity of an organ system is dependent on the various activities of its various component organs. To ensure optimum effectiveness, the activities of the various organs systems are usually coordinated and controlled by both the endocrine and the nervous system.

Briefly, the digestive system oversees ingestion, digestion, and absorption of nutrients into the body; the respiratory system along with the cardiovascular system oversees oxygen intake and carbon dioxide removal; the excretory system eliminates all waste products of metabolism; the muscular and skeletal systems working together with the nervous system is responsible for movement while the endocrine and reproductive systems are

critical for reproduction. Each of these systems are fully integrated and dependent on one another and are critical for the continued survival of the human species.

The concept of the milieu intérieur (The internal environment)

The concept of the *milieu interieur* or the internal environment was first proposed in the 19th century by the French physiologist Claude Bernard (1813-1878). The internal environment refers to the environment in which all the cells of the body are found. Basically, it refers to all the fluid within the human body but located outside of the cells of the body.

Approximately 67% of the human body is fluid or water; for an average 70kg adult male, this translates to about 42 litres. This fluid is unevenly distributed in the body as both intracellular fluid of about 28 litres and extracellular fluid of about 14 litres. As the name implies, the intracellular fluid refers to the fluid located inside the about 100 trillion cells of the human body; while the extracellular fluid refers to the fluid located outside these numerous cells. The two largest components of the extracellular fluid are the interstitial fluid of about 11 litres and the plasma of about 3 litres. The interstitial fluid are the fluids that lie in the interstices between the cells of the body, while the plasma is the fluid or noncellular portion of blood. The interstitial spaces are the potential spaces that surround all the cells of the human body. Except for the presence of plasma proteins in plasma, interstitial fluid is fairly homogenous in chemical composition to plasma. Other portions of the extracellular fluid include lymphatic fluids or lymph found in the lymphatic system, synovial fluids found in the joints, both aqueous and vitreous humour found in the eyes and cerebrospinal fluid found in the ventricular system of the central nervous system.

The extracellular fluid is the fluid that surround and bathes all the 100trillion cells of the body. It contains electrolytes, nutrients and various other molecules that are essential to cellular life. The extracellular fluid bathes all cells of the human body and is constantly being transported by the circulatory system to all parts of the body where its content diffuses to reach all cells of the body. Despite the varied portions enumerated above, the composition of the extracellular fluid is fairly homogenous all through the body. Therefore, on account of its homogenous composition, the extracellular fluid is regarded as one continuous large fluid portion designated as the *milieu interieur* or the internal environment.

All the cells of the body are capable of optimal activities with the correct and fairly constant composition of the internal environment. The internal environment is therefore critical to cellular survival. Several homeostatic processes involving organs and the organ systems described below ensure a relative constancy of the various constituents of the internal environment.

Finally, the concept of the milieu intérieur refers to the ability to ensure a protective stability for the cells, tissues, and organs of various multicellular organism by ensuring a near constant chemical composition of the extracellular fluid compartment. This internal stability buffers and protects the whole organism against a constantly changing flux external environment. For instance, these mechanisms operate in a coordinated fashion to maintain a relatively constant temperature and blood glucose concentration of the extracellular fluid compartment vital for the survival of the organism.

Homeostasis, homeostatic mechanisms and the concept of Homeostasis

The word homeostasis is coined from two Greek words *Omoio/ (hómoios)* meaning 'similar' and *st´asi/ (stásis)* meaning 'standing still' when read in context it means 'staying similar but not necessarily staying the same.' Homeostasis describes process that ensure the maintenance of a near constancy in the chemical and physical

conditions of the internal environment. Homeostasis is essentially a self-regulating process through which a biological system maintains internal stability while adjusting to a diverse and indeed rapidly changing external circumstances. This maintenance of internal stability via the coordinated response of its various parts to any situation or stimulus that disturbs normal conditions or equilibrium.

The concept of Homeostasis: The concept of a constant internal environment (*milieu intérieur*) was first proposed by the American Physiologist, Walter B Cannon (1871–1945) building on the concept of the *milieu intérieur* as developed by Claude Bernard (1813–1878). The concept of homeostasis is therefore basically an extension the concept of the internal environment (*milieu intérieur*). Since its proposition, the concept of homeostasis has become the central unifying concept and one of the central principles of Physiology. It has enabled the full comprehension of the functions of the human body in both health and in disease conditions. Homeostasis is antecedent to and a requirement for physiological processes and not necessarily the consequence or outcome of such processes.

The concept of Homeostasis does not propose that the internal conditions or the internal environment are unchanging or stagnant, but rather that the internal conditions could vary, could be similar, but are not necessarily always identical. This homeostatic stability attempts to keep conditions within a range of values that allows the whole organism the freedom and ability to adapt.

Homeostatic mechanisms: These are processes the various organs and organ systems utilizes to achieve homeostasis. These self-regulating mechanisms that essentially allows any biological system to adapt and survive in the face of a changing and often hostile external environment. Obviously, disruption of homeostatic mechanisms leads to disease and any effective treatment must aim at re-establishing homeostasis. Homeostasis mechanisms are not static and unvarying but are rather dynamic process that can change internal conditions on a need-to-need basis to survive various environmental and external challenges.

A brief review of how each of each of the major organ systems achieves homeostasis is summarized as follows:

Cardiovascular system: This system includes the heart (cardiac) and the blood vessels (vascular). The cardiovascular system functions in the transport of oxygen and other nutrients including glucose, amino acids, fats, hormones, vitamins, and other substances from their site of production or absorption to various cells where they are needed. Conversely, the system transports waste products of metabolism including carbon dioxide and other noxious substances away from the cells facilitating their removal from the body and avoiding cellular damage. The system also helps maintain body temperature and pH within acceptable ranges.

Gastrointestinal tract and system: The gastrointestinal tract consist of the buccal cavity, oesophagus, stomach, small and large intestines, rectum, and anal canal; inclusion of the accessory organs like the salivary glands, liver, gallbladder, exocrine pancreas constitutes the gastrointestinal system. The gastrointestinal system ensures the proper digestion and absorption of ingested nutrients, minerals and vitamins, water, and dietary fibre, thus providing the basic fuel needed for the sustenance of human life.

Endocrine system: This system includes the several endocrine glands located at various parts of the human body: the pituitary, pineal, thyroid, parathyroids, endocrine pancreas, adrenals, testes, heart, and ovaries. The endocrine system ensures homeostasis by providing a system of communication within the body via hormones. These hormones in turn regulate several metabolic processes in various tissues, organs and organ systems in the body ensuring on a long term, a constancy of the internal environment. As shall be shown later, the endocrine

system along with the nervous system provides coordinated short-term and long-term control of various processes thus ensuring homeostasis.

Haemopoietic system: This system includes blood and various haemopoietic tissues located in the marrow of long bones of the body like the tibia, spleen etc. The system is involved in the production of erythrocytes, leucocytes and platelets. Erythrocytes serve vital roles in the transport of oxygen, and carbon dioxide; leucocytes are vital in the response of the body to invading bacteria and other foreign bodies; while platelets are essential in ensuring blood clotting (haemostasis) thereby reducing blood loss during injury. These roles are important in ensuring survival of the human species from unfavourable external conditions.

Immune system: This system consists of the cells called leucocytes produced by organs like the tonsils, adenoids, thymus, and spleen. By defending the body against microbial pathogens and other disease-causing agents they facilitate homeostasis.

Integumentary system: This system includes the skin and its appendages: hairs, sebaceous glands, and nails. By ensuring control of body temperature, providing an immediate protective interphase from injury, and reducing body fluid loss this system contributes to homeostasis.

Lymphatic system: This system includes the special fluid called lymph, the various lymph nodes located strategically all over the body and the lymphatic vessels that connect them. It is regarded essentially as accessory to the circulatory system. The system ensures homeostasis by defending the body against infection and disease via an isolation and containment effect. It also functions to transfer lymphatic fluid between tissues and the blood stream. As described earlier, this is an important portion of the extracellular fluid compartment.

Musculo-skeletal system: This system as the names implies includes the skeleton and the muscles of the body: skeletal, cardiac, and smooth muscles. The skeleton and the skeletal muscle facilitate support for the human organism and enables movement from one place to another. While the cardiac and the smooth muscles of the body enables the heart and the various hollow organs to provide their physiological functions.

Nervous system includes both the central nervous system: cerebrum, cerebellum, medulla, pons etc; the peripheral nervous system: spinal cord, peripheral nerves and various sensory organs and the special sense organs for hearing, equilibrium, smelling, taste, and sight. The nervous system facilitates homeostasis by acting as a source for the collection, transfer, and processing of neural information. The system along with the endocrine system controls various organs systems by directing short-term changes in these organ systems.

Reproductive system: This system includes the fallopian tubes, uterus, vagina, ovaries, mammary glands of the female and the testes, vas deferens, seminal vesicles, prostate, and penis of the male. The system is vital for the continued survival and existence of the human species via the production of oocytes and spermatocytes as well as production of sex hormones.

Respiratory system this includes the nose, pharynx, larynx, trachea, bronchi, lungs, and diaphragm. The respiratory system functions to deliver oxygen from the environment to where gaseous exchange can occur and functions also to remove carbon dioxide from the body to the environment.

Urinary system this system includes the kidneys, ureters, urinary bladder, and urethra. The system provides homeostasis by removing excess water, salts, and waste products of metabolic processes from the body. It also

ensures and controls the pH of body fluids. Clearly, these various homeostatic regulatory processes are not achieved by a single negative feedback cycle. They are the product of a complex interaction of multiple feedback systems inherently modifiable by higher centres. The health and vitality of human is the result of these various homeostatic regulatory mechanisms. Disruption of these of homeostatic mechanisms invariably leads to disease. This is the arena of Pathophysiology that would later be discussed with each organ and organ system.

The importance of physiological control

Control or regulation of the body function is critical for the maintenance of homeostasis. To this end, the human body has a complex myriad of physiological control systems ensuring homeostasis. These control systems involves either single organs or several organ systems working in tandem. For instance, the regulation of blood glucose concentration involves several organs including the liver, muscles, kidneys, and several hormone including insulin, glucagon, adrenaline, growth hormone, cortisol, estrogens and other hormones depending on the physiological circumstance. Aside blood glucose, all the chemical constituents of the extra cellular fluid are controlled or regulated within physiological limits. Significant deviations with either a decrease or increase can become pathologic or life threatening.

Examples of physical characteristics and chemical constituents of the extra cellular fluid compartment that are controlled in the human body are illustrated in the Table below:

Physical and chemical characteristics		**Normal value and range**
Respiratory	Respiratory rate	12-20 breaths/minute
	Vital capacity	3-5 liters
	Tidal volume	400-500mL/cycle
Cardiovascular	Heart rate	60-80 beats/minute
	Blood pressure	>120/80 mmHg
	Cardiac output	5-6litres/minute
Renal and body fluid	Daily urinary output volume	800-2000mL/day
	Blood volume	5 liters
	Renal blood flow	1.2-1.3L/minute
Others	Body temperature	36.5-37.5 °C
	Blood pH	7.35-7.45
	Blood glucose	90-150md/dL
	Concentration	

All the physiological control processes in the body operate via a physiological feedback mechanism. A feedback mechanism in a physiological system is a biological process involving the partial reversion of the effects of a particular process to its initial originating source or to subsequent preceding steps. This essentially results in a self regulatory process. Physiological feedback mechanisms may be either reductive (negative) or additive (positive) in nature and functions to maintain the constancy of the internal environment and thus ensuring homeostasis.

Negative feedback: Negative feedback occurs when an initial increase in the concentration of a particular constituent (in the ECF) elicits processes that result in a decrease in the concentration of that particular chemical. Conversely, a decrease in the concentration of the chemical elicits mechanisms that result in an increase. In other words, the ultimate result of a negative feedback process is the opposite of the initial stimulus: an initial increase response with a decrease while an initial decrease results in an increase.

A typical example is in the regulation of blood glucose concentration. Simplified, an initial reduction in blood glucose concentration causes an increase in glucagon secretion and a decrease in insulin secretion. Increased glucagon causes an increase in blood glucose concentration by stimulating the breakdown of stored glycogen in both the liver and muscle cells. This causes glucose to be released from the liver and from the muscle and an increase in blood glucose concentration. Similarly, the decrease in insulin concentration halts the cellular uptake of glucose thereby stopping a further reduction in blood glucose concentration. This feedback regulation of blood glucose concentration typifies a negative feedback mechanism and ensures a fairly normal range of blood glucose concentration despite erratic feeding habits and binges. This is as summarized in Figure 1.2 below.

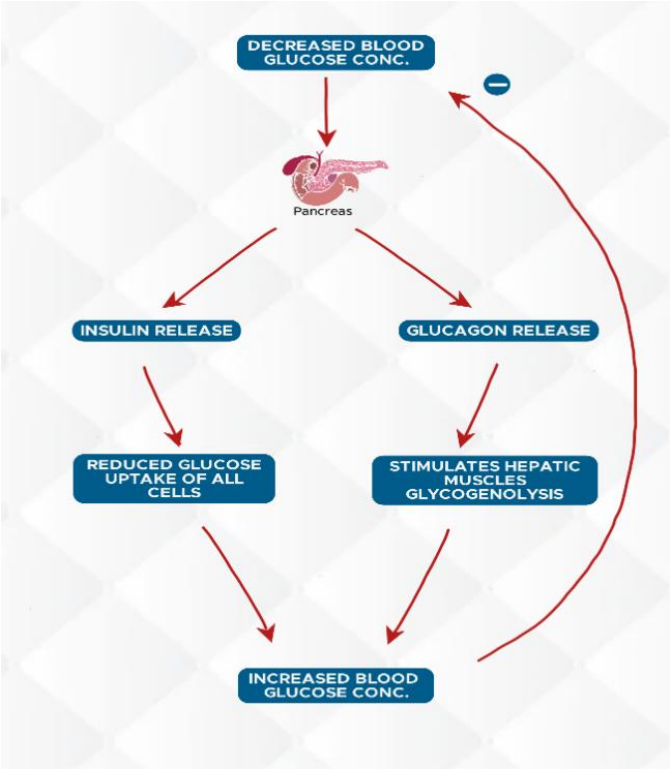


Figure 1.2: Schematic representation of negative feedback in the regulation of blood glucose concentration

Importance of feedback gain: Feedback gain refers to the effectiveness of negative feedback mechanisms. The degree of effectiveness of a control system to maintain homeostasis is usually determined by the gain of negative feedback. This emphasizes the importance of negative feedback processes in maintaining homeostasis. Although negative feedback does not return the status back to status immediately, normality is re-established gradually over time.

Positive feedback: This is not as common as negative feedback and indeed occurs in very few specific circumstances to ensure normal physiological functioning and homeostasis. Positive feedback usually leads to a vicious cycle which can be life threatening. Positive feedback occurs when an initial increase in the concentration of a particular constituent (in the ECF) causes a further increase in the concentration of that same constituent. A typical example of positive feedback occurs in the concentration of Luteinizing Hormone (LH) and Follicular Stimulating Hormone (FSH) during the menstrual cycle. Despite the rising concentration of LH, a pre ovulatory surge (increase) seen as a further increase in the concentration of LH is critical for ovulation to occur. The pre-ovulatory surge of luteinizing hormones occurs approximately 16 hours prior ovulation, this is despite the increased secretion of luteinizing hormones 24 hours prior ovulation. A similar pre-ovulatory surge of FSH also occurs prior ovulation. The essential mechanism is that the initial increase in the secretion of LH or FSH causes a further increased secretion of each hormone. This stimulation of increased secretion occurs via a self-induced increase. This is positive feedback mechanism.

Despite the danger inherent in positive feedback, it is a physiologic advantage in certain circumstances. However, most instances where positive is useful, it is essentially an integral part of an overall negative feedback process. The precise mechanism of positive feedback is a described above and is illustrated in the Figure 1.2 below.

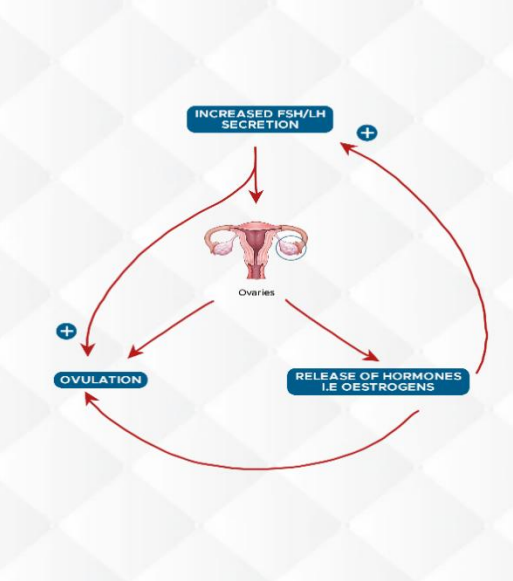


Figure 1,2: Schematic representation of positive feedback for the induction of ovulation

Another important positive feedback mechanism occurs during childbirth and in the process of infant breastfeeding. For example, positive feedback is important to fully contract the uterus to enable childbirth during the labour.

The place of Physiology in Medicine.

Physiology is an experimental scientific discipline that is of vital import to medicine and indeed all health-related sciences. Physiology provides a basis for the proper understanding of human body function to enable a proper appreciation of deviations in disease and determination of appropriate treatment. Research in physiology advances our understanding of the detailed mechanisms that control and regulate the behaviour of living things.

The Nobel Prize in the field of the life sciences or medicine is actually in the subject of Physiology and is called the *Nobel Prize in Physiology or Medicine*. The subject of Physiology was indeed amongst the first five subjects to benefit from a Nobel Prize in 1901: underscoring the importance of the subject Physiology to the theory and practice of medicine and the medical and life sciences as a whole. Therefore, understanding human physiology is vital and appropriate in the determination of deviations during disease, such understanding facilitates the development of new and appropriate treatments and maintenance of overall health.

A concise understanding of the subject of human physiology is therefore central to proper interpretation of laboratory and clinical signs of disease and pivotal an excellent medical practice. Any proper and appropriate medical intervention is premised on a clear understanding of basic principles of physiological function. This caveat applies to all areas of medical sciences including but not excluded to pharmacy, nursing, medical laboratory sciences, physiotherapy, radiography, and public health.

For instance, diagnostic tests like measurement of electrolytes and plasma creatinine give possible valuable insight into the pathophysiology of diseases. Furthermore, many physiological principles are the basis of such clinical tests as the electrocardiogram (ECG), electromyogram (EMG), measurements of blood pressure both direct and indirect methods, exercise based “stress tests,” renal clearance measurements to determine renal function, gastrointestinal motility studies, all the numerous tests of pulmonary function, and many others. Physiology as an experimental discipline has been involved in elucidating both the theory (academic) and practice of clinical medicine.

A cell can be defined as the basic living unit of the body. It is made up of the protoplasm. Structurally as components of tissues, they exhibit special adaptations to suit the tissue function. However cells have a common basic structure and they are as follows:

(1) Cell membrane

(2) Mitochondria

(3) Endoplasmic reticulum

(4) Golgi apparatus

(5) Lysosomes

(6) Micro filaments and microtubules

(7) Nucleus

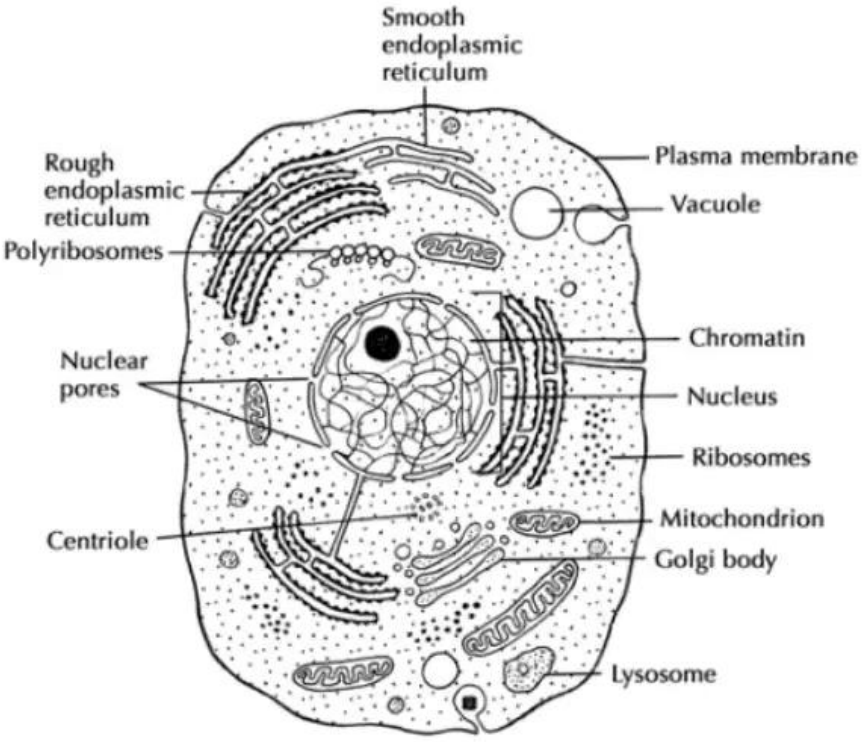


Fig. 1.3 Basic components of a cell

Cell Membrane

This surrounds each cell.

Functions of Cell Membranes

1. It forms a boundary to the cell or its constituents
2. It is involved in compartmentalization. It helps to keep substances together e.g. mitochondria and also keep substances apart e.g. granules (pyrolytic, hydrolytic) which are capable of destroying the cells if not kept apart.
3. It is involved in catalytic activities e.g. maltase (bounded to membrane eo f small intestine).
4. It is involved in locomotion e.g. leucocytes during amoeboid movement.
5. It is involved in tissue formation where flat sheets of tissues are shaped into solid blocks (modification of cell membrane structure).
6. It involved in self recognition. It allows cells to recognize equivalent cells (self from non- self). This is the major problem during blood or tissue transplant.\
7. It acts as receivers and transducers of information across the cell.
8. It is involved in transport and exchange of components across the cell.

9. It possesses a characteristic quality of contact inhibition. This is very important in the prevention of cancerous growth of cells and the prevention of keloid formation after wound healing.

Structure of Cell Membrane

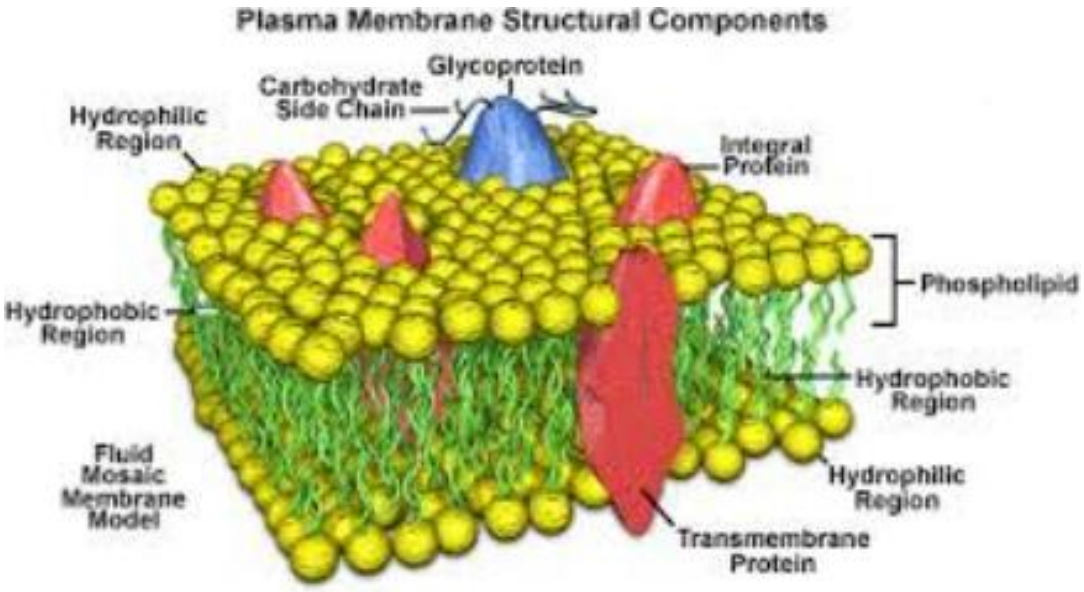


Fig. 1.4 The cell membrane showing the double layer lipid and proteins

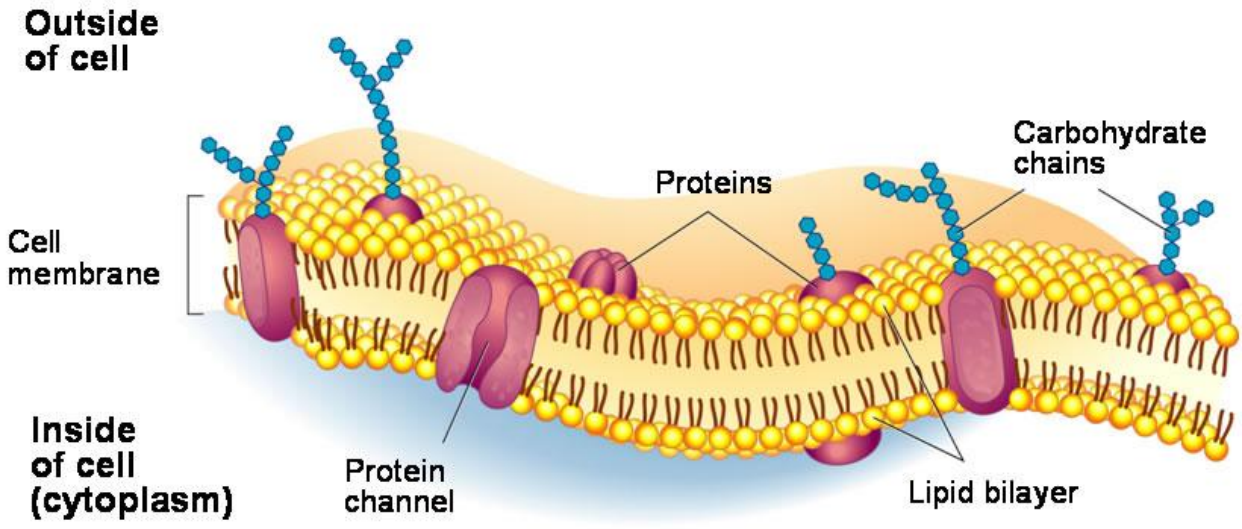


Fig. 1.5 The cell membrane showing the detailed components, essentially the proteins

Different tissues, different types of cells have different structures. Although they all have the basic structure but the chemical constituents may differ. Average thickness of cell membrane is 7- 10 nm. The most accepted model of cell membrane structure, the **FLUID MOZAIC MODEL** was popularized in 1972 by **Singer and Nicolson**. This model of cell membrane structure explains various observations regarding the structure of functional cell membranes. According to this biological model, there is a phospholipid molecules bilayer in which protein molecules are found on the surface and also embedded in it .The phospholipid bilayer gives fluidity and elasticity to the membrane. This Fluid mosaic model of cell membrane structure describes the cell membrane as a tapestry of several types of molecules (phospholipids, cholesterol, and proteins) that are constantly moving. This movement helps the cell membrane maintain its role as a barrier between the inside and outside of the cell.

All membranes are made up of primarily lipids, proteins and small amounts of carbohydrate found on the outside of most membranes. Lipids constitute about 50 percent of the mass and about 50 percent is protein with the carbohydrate portions of glycolipids and glycoproteins constituting 5 to 10 percent of the membrane mass; the actual proportion varies depending on the type of cell.

The protein and lipid that make up the cell membrane are of two types:

(a) Amphipatic/ hydrophilic which is water soluble
(b) Hydrophobic which is lipid soluble

The Lipid Bilayer: These are mainly phospholipids which are made up of – phosphatidylcholine, sphingomyelin, phosphatidylserine, and phosphatidyl- ethanolamine, glycolipids and cholesterol. Glycolipids are generally found in the outer layer. Membrane lipids are made of two parts;

(1) a polar head (hydrophilic or water-loving) and
(2) a non polar fatty acid tail (hydrophobic or water- hating), hence it is said to be amphipatic.

Normally the lipid bilayer of phospholipids when surrounded by water, arrange themselves in such a way that the fatty acid hydrophobic tails are hidden in the interior, facing each other, while the phospho lipid hydrophilic heads are exposed to the exterior and in contact with water. Cholesterol forms an integral part of the hydrophobic regions of the membrane and serves to reinforce the lipid permeability barrier. The cholesterol: phospholipid ratio determines the fluidity of the membrane and it is 1:1 in the nucleus of eukaryotes. The higher the level, the less the fluidity of the membrane.

The main function of the lipid bilayer of a cell membrane is to create permeability barrier between the interstitial fluid and the cytoplasm. The movement of any substance across the cell membrane depends on whether it is lipid soluble or not.

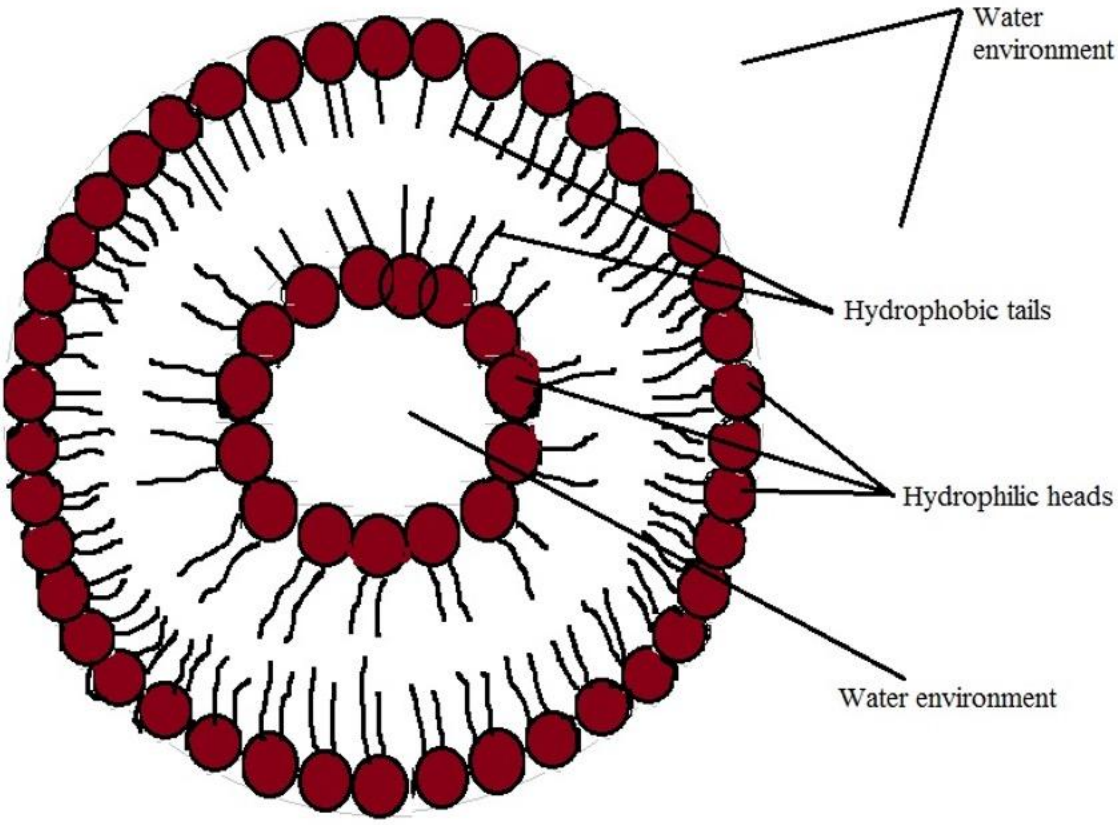


Fig. 1.6 Arrangement of cell membrane lipids

Membrane Proteins

The function of the cell membrane determines the protein content. There are three main types of cell membrane proteins:

(a) Transmembrane Proteins: This span through the entire thickness of the membrane. They are also called Integral or internal proteins. Their functions includes:
   (1) Channels or pores through which water- soluble substances can diffuse across the cell membrane.
   (2) Carriers which transport substances by facilitated diffusion.
   (3) Ion pumps which actively transport ions across the membrane.
   (4) Receptors which when activated initiate intracellular reactions.

(b) Peripheral proteins: These are inserted in the outer or inner leaflet, or bound to the cytoplasmic surface. They are also called external or extrinsic proteins. Many of them e.g. spectrin, bind with the hydrophilic heads of the lipids on the cytoplasmic side or to the integral proteins and connect the membrane intracellularly with the cytoskeleton of the actin and other microfilaments which maintains cell shape.

(c) Integral proteins on one side of the membrane: Those confined to the outer half of the membrane commonly acts as receptors, while those on the inner half serve as enzymes, or G-proteins that activate or inactivate various metabolic processes within the cell.

Fig. 1.5

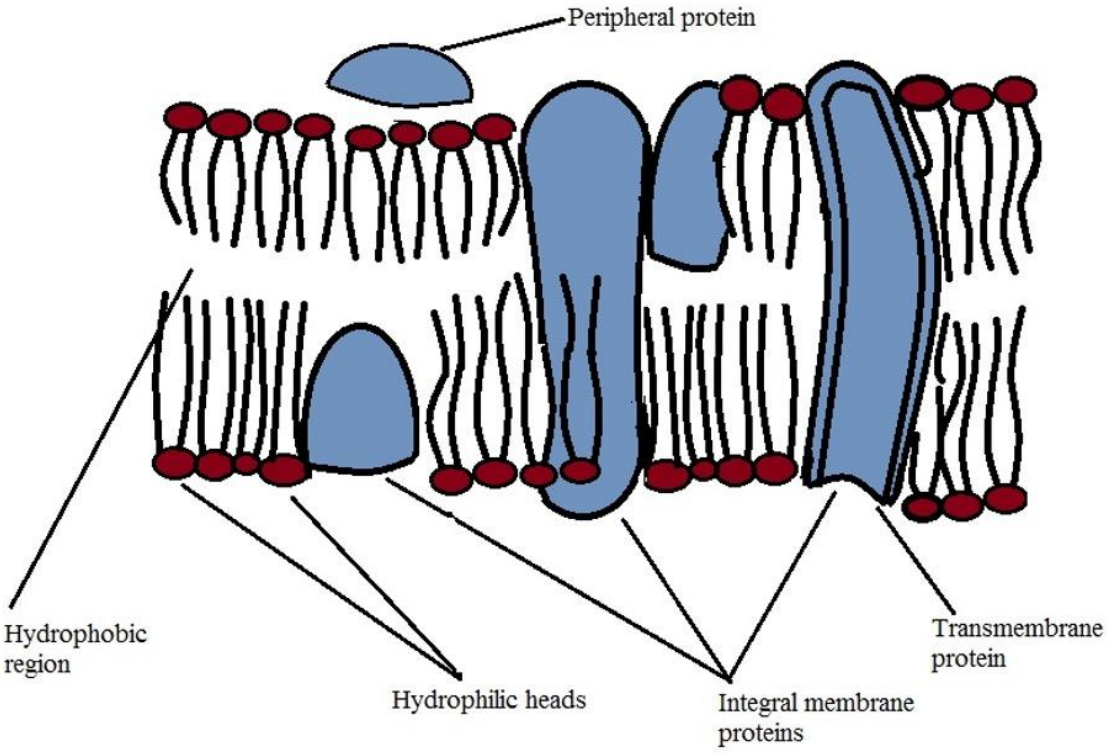


Figure 1.7: Arrangement of cell membrane proteins

Mitochondria

Their shape, size and numbers vary. They are the most abundant in cells and with high rate of metabolism. They are usually spherical shaped or cigar- shaped. They are mostly found in regions of the cytoplasm where metabolism is highest within each cell e.g. at the base or sides of ion- transferring cells of the kidney and intestine, or at the apices of ciliated cells.

Studies using electron microscopy shows that it has a bi-layer membrane- an outer and inner membranes. The outer membrane is a continuous enveloping membrane while the inner one is thrown into folds called cristae, projecting into the cavity of the organelle and contains the matrix.

It has a short life span and is constantly renewed. They contain DNA and are capable of self-replication and protein synthesis. The mitochondria are involved primarily in activities that lead to the production of energy- rich ATP.

Endoplasmic Reticulum

This is primarily a synthetic organelle, involved in the synthesis of transmembrane proteins, membrane lipids of the cell and organelles and secretory vesicles. It is made up of a network of anastomosing membrane tubules, vesicles and flattened cisternae. It is of two types:

(1) the rough and

(2) the smooth.

(1) Rough Endoplasmic Reticulum (RER)

It is called rough because the tubules and cisterns are filled with ribosomes on their external surfaces giving them a "rough" appearance. These ribosomes are essentially made up of RNA and protein and are synthesized in the nucleoli. The functions of RER are:

(1) Protein synthesis hence it is abundant in cells which synthesize proteins e.g. endocrine glands and in glands secreting digestive enzymes.
(2) It also involved in combination with the Golgi apparatus in the synthesis of glycoproteins from carbohydrates and proteins.

(2)Smooth Endoplasmic Reticulum (SER)

This has no ribosomes attached to its surface hence it is described as smooth. The function includes:

(1) Synthesis of lipids hence it is found in great quantities in cells that synthesize lipids (cholesterol, steroid hormones and phospholipids).
(2) It exists in the muscles as sarcoplasmic reticulum, and is specialized for the storage of calcium ion which is released during excitation- contraction coupling.
(3) It is involved in intracellular transport system as it is continuous with the RER and Golgi apparatus
(4) Also involved in detoxification or neutralization of noxious substances.

The Golgi Apparatus

It is generally located near the nucleus. The functions include:

(1) Packaging of secretory products into secretory granules.
(2) Formation of glycoproteins.

Lysosomes

It is involved mostly in intra cytoplasmic digestion. They are bound to the membranes and contain a variety of lytic enzymes. They are also called autophagosomes and are involved in the removal of worn out portions of the cell, so they can be replaced by new ones.

Microfilaments and Microtubules

The microfilament is made up of actin that contributes to the maintenance of the shape of the cell. The interactions of the actin and myosin within the cells is believed to be responsible for contractile phenomena within the cytoplasm e.g. during cell division, phagocytosis, transport and secretion of cellular materials.

Microtubules exist in the cells as long hollow structures consisting of subunits of a globular protein called tubulin, arranged in a closely packed helical manner. They help in forming a dynamic framework. They serve as "guide rails" for intracellular transport of molecules and secretory granules within the cytoplasm e.g. neurotransmitters. They are involved in the maintenance of cell shapes, the formation of centrioles in cell division, and the structure

and function of the cilia. All the microtubules are linked together by protein cross- linkages, forming a unit known as an axoneme.

Nucleus

This is contained in all the cells of the body except mature red blood cells hence the cells that contain it are called eucaryotic cells. Some cells e.g. bacteria cells do not contain nucleus hence are called prokaryotes. The nucleus is a central round, intensely staining structure, bounded by a bilayer membrane, and consisting of chromatin, the nucleolus, and nucleoplasm. It however varies in size, shape and location within the cells. It contains nuclear pores on its membrane and the membrane is continuous with the endoplasmic reticulum. The nuclear chromatin is made of coiled strands of DNA, bound to large quantities of basic proteins (histones). The DNA in turn contains the chromosomes inside which are the genes.

TRANSPORT OF SUBSTANCES ACROSS CELL MEMBRANES

As a result of the nature of cells, there exists a constant movement of ions, fluids etc across the membrane between the intra cellular compartment and the extracellular compartment. This is done in such a way as to maintain the constancy of the intracellular fluid. This is a primary role of the cell membrane through its selective permeability property to various substances and direct participation in the transport of specific substances across its walls.

The routes through which substances pass through the cell membrane can be classified as follows:

(1) Direct Passage through the Lipid Barrier.

This involves lipid- soluble substances e.g. respiratory gases, fatty acids, alcohol, ketones, aldehydes and many small uncharged molecules pass through the lipid barrier easily. Also water can easily pass through cell membranes.

(2) Passage through water - filled Channels or with the Aid of Protein Carriers.

This involves water- soluble substances e.g. electrolytes, charged particles, large uncharged polar molecules e.g. glucose and amino acids.

Transport of Substances across Cell Membranes can be divided into two mechanisms:

(1) active or
(2) passive.
    The passive mechanisms are as follows:
    (a) filtration and bulk flow
    (b) simple diffusion
    (c) Osmosis
    (d) carrier mediated processes (facilitated diffusion and active transport), and
    (e) associated solvent drag.

Their transport is downhill and does not require metabolic energy. e.g.

(a) **Filtration and Bulk flow**

This involves large scale movement over relatively large distance. It involves pressure gradient and non selective. Both liquids and gases are involved. e.g.

(i) Air moves from the atmosphere into the lungs by bulk flow as a result of pressure gradient between the atmosphere and alveoli of the lungs

(ii) Blood moves round the body by pressure gradient set up by the beating of the heart.

(iii) The glomerular filtration at the kidney is through bulk flow; however this is limited by the glomerular membrane pores.

(b) **Simple Diffusion**

This is a random molecular motion of substances through an opening in the cell membrane without necessarily binding with carrier proteins. It is a passive process because no metabolic energy is required. Factors affecting simple diffusion are the properties of the substance (concentration and permeability) and the properties of the membrane. They are as follows:

(i) Temperature: All particles of a fluid, whether liquid or gas, are in constant and random motion due to thermal energy. The motion increases with temperature and is only absent at absolute zero. Increase temperature will increase the rate of diffusion, however in humans the body temperature remains constant.

(ii) Surface Area. This is increased in some membranes e.g. alveoli and villi. The bigger the surface area, the higher the rate of diffusion.

(iii) Distance: The shorter the distance of the substance from the membrane, the faster the rate of diffusion.

(iv) Molecular weight. Diffusion of a substance across the cell membrane is inversely proportional to its molecular weight. Hence substances with smaller molecular weight diffuse faster.

(v) Lipid solubility. For the lipid- soluble substances, the permeability is proportional to their lipid solubility e.g. carbon dioxide, oxygen alcohols. Water soluble substances follow protein channels e.g. sodium and potassium ions.

(vi) Concentration difference. The gradients responsible for the direction of net transport may be chemical concentration, or electrical potential difference. The higher the concentration difference of a substance across the cell membrane; the higher its rate of diffusion. However blood flow prevents equilibration and maintains concentration difference e.g. between the alveolus and the capillaries.

(3) Osmosis

This is the net flux of water through a semi permeable membrane from a solution of lower solute concentration to that of higher solute concentration. Some substances that are not osmotically ineffective include urea and glucose while substances like plasma proteins, various complex polysaccharides e.g. dextran and sodium chloride are osmotically effective.

(4) Carrier Mediated Processes (facilitated diffusion and active transport)

Carrier mediated transport have a common feature of undergoing competitive inhibition and saturation kinetics.

There are two types:

(a) Facilitated Diffusion

This can be defined or explained as a random molecular motion of a substance through a membrane by the interaction of the molecular substance or ion with the carrier protein to aid it through the membrane. It enters, binds chemically with it and shuttling in through the membrane. Transport is from area of high concentration to low concentration. Energy is not required. It can also be explained as a "transport faster than predicted on lipid solubility and molecular size alone". It is analogous to enzyme kinetics and is known as "ping- pong hypothesis".(PING- into the cell interior and PONG- out of the cell).

The rate of transport of facilitated diffusion depends on:

(i) The concentration difference of substance across the cell membrane.

(ii) Number of carrier molecules involved.

(iii) Affinity of carrier molecule for the substrate.

Characteristics of Facilitated Diffusion:

(1) It uses a carrier protein which can carry two or three related substances initially

(2) It shows specificity. The implication is that there must be enough carrier molecules to transport many substances e.g. the carrier that carries glucose can only transport glucose- D and does not carry L – glucose at all.

(3) It displays saturation kinetics.

(4) It displays competitive inhibition e.g. in the presence of glucose and galactose in the intestine, there is more affinity for galactose that for glucose.

(c) Active Transport

There are two types: (i) Carrier- mediated active transport (primary or secondary)

(ii) Vesicular transport (endocytosis and exocytosis)

Common characteristics of active transport area as follows:

(1) Uphill transport: The transport is against the electrochemical gradient of the substance.

(2) Requires Metabolic Energy: It derives energy from the breakdown of ATP, and is , therefore , susceptible to metabolic poisons.

(3) Exhibits saturation kinetics: This is because of limitation in the rate of availability of carriers or supply of energy.

(i) Carrier- Mediated Active Transport

This is of two types:
(a) primary or
(b) secondary.

(a) **Primary:** In this case metabolic energy is directly linked to the transport process. e.g. Na^+- K^+ pump, Ca^{2+} pump, and H^+ pump. Here a cell membrane moves molecules uphill against a concentration gradient or uphill against an electrical or pressure gradient.

(b) **Secondary:** In this case, transport of one substance provides the energy for the transportation of another substance e.g. Na^+ and glucose. It depends on transportation of substances by carrier proteins that operate through the membrane. In his case, energy must now be imparted onto the substance by the carrier protein to move it against an electrochemical gradient for ions. It utilizes metabolic energy and takes place in all the cells of the body.

A system in which a carrier transports a substance in one direction, the carrier is called **Uniport carrier**.

A system in which a carrier transports two substances in opposite directions, the carrier is called **Antiport carrier**.

A system in which a carrier transports two substances in the same direction, the carrier is called **Symport carrier**.

(ii) Vesicular Transport
This is the mechanism by which large particles enter the cells. This involves membrane fusion and vesicle formation. It is a dynamic and energy consuming process. It involves two mechanisms:
(a) endocytosis and
(b) exocytosis.

(a) Endocytosis
This involves movement into the cell. It is a mechanism by which the membrane actually engulfs particulate matter or ECF and its contents and it requires energy from ATP and Ca^{2+}. It begins by the formation of small vesicles at the cell membrane, these vehicles then pinch off into the interior of the cell and float freely in the cytoplasm. It is receptor mediated mostly and occurs via special coated pits in the cell membrane.

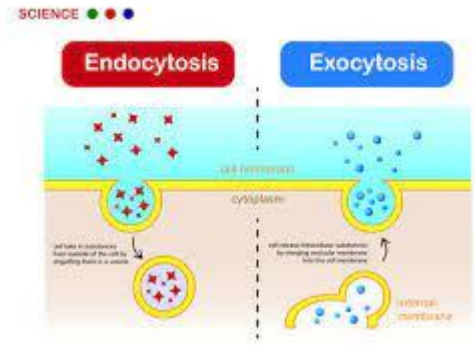


Fig. 1.8. Endocytosis and Exocytosis

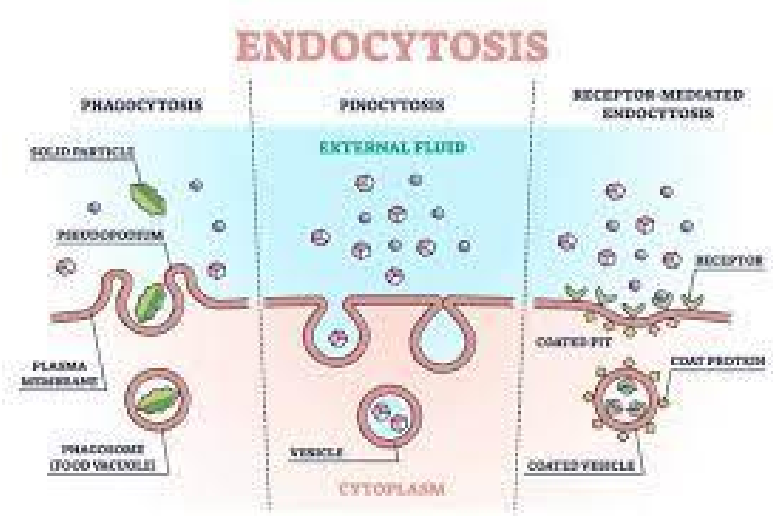


Fig. 1.9 Details of Exocytosis

It is of two types:

(i) Phagocytosis and

(ii) Pinocytosis.

(i)Phagocytosis: This involves ingestion of large particles of bacteria cells or portions of degenerating tissues. It has the same stages as phagocytosis.

(ii)Pinocytosis: It is also called “cell drinking” of substances in solution in extracellular fluid. It involves ingestion of large macromolecules such as proteins. It is a continuous process which occurs in most cells, but is particularly rapid in some cells such as macrophages.

The stages involved are as follows:

(a)The protein and other macromolecules attach to receptors on the membrane surface; these receptors are normally concentrated in small pits called “coated pits”, beneath which are located fibrillar proteins called clathrin, and contractile filaments of actin and myosin.

(b)The attachment of the proteins to the receptors stimulates the invagination of the entire pit, enclosing the proteins and a small portion of the ECF in a pinocytic vesicle.

(c)The vesicle detaches from the cell membrane.

(d)Fusion of the pinocytic vesicle with one or more lysosomes which empty their acid hydrolases into the vesicle leading to the digestion of the substances in the vesicle; the products of digestion diffuse through the membrane of the vesicle into the cytoplasm; and

(e)Undigested material is removed from the cell by exocytosis.

(b) Exocytosis

This is reverse endocytosis, cell vomiting or emeiocytosis. It involves removal of substances from the cell membrane without touching the cytoplasm e.g. enzymes, neurotransmitters. It adds to the total amount of cell membrane and if the cell membrane is not removed from elsewhere at an equivalent rate, the cell membrane would enlarge. However, removal of membrane occurs by endocytosis and such exocytosis- endocytosis coupling maintains the cell at its normal size and leads to continuous renewal of the membrane.

PHYSIOLOGY OF EXCITABLE TISSUES

Tissues that is capable of self-generation of electrochemical impulse at their membranes and in some instances, employment of these impulses to transmit signals along the membranes.

Excitability: Ability which certain cells have to respond in a predictable manner to a stimulus.

Tissues with these properties are said to be excitable .eg. nerves, muscles and some gut glands.

Stimulus: Disturbance of the environment of the cell by a change in energy status e.g. chemical, electrical. mechanical, thermal stimulus.

When you stimulate a nerve, it responds by generating and conducting an electrical signal called Action Potential which is the way information is transferred from tissues to CNS and back. When you stimulate a muscle, it does the same but the AP leads to production of force used for contraction. The general mechanism of response of excitable cell to stimuli always starts in increase permeability of the membrane of the cell to Na^+. Any factor that increases Na^+ permeability also increases excitability.

Factors that increase excitability	Factors that decrease excitability
1. Low level of Ca^{2+}	High levels of Ca^{2+}
2. Drugs such as veratrine	Anaesthetic drugs

The Resting Membrane Potential (RMP)

The existence of an electrical potential difference for all cells in the body across their membrane for excitable cells was established over a century ago. The potential difference has a high value and is basis of excitability. RMP is defined as the potential difference across the cell membrane during rest (not transmitting nerve signals). It ranges from -9mv to -100mv. For large nerves fibers: -90mV, skeletal muscle: -80Mv and smooth muscle -70mV.

Origin of RMP

It results from unequal distribution of ions across the cell membrane at rest. In a typical mammalian neuron (spinal motor neuron) it is – 90mV. R.M.P is brought about by an unequal distribution of ions across its cell membrane at rest, in such a manner that the inside of the cell has a little excess of negatively charged (- ve) ions while the outside has small excess of positively (+ ve) charged ions. The inside of the cell is thus negative with respect to the outside. This unequal distribution of ions across membranes results from:

(1)membrane permeability and particles sizes of these ions (diffusion of ions), a passive process.

(2) Na^+ - K^+ pump, an active process.

Degree of Permeability of ions etc across the cell membrane

Intracellular proteins + other organic anions - impermeable

Na^+ - moderately permeable

K^+ - CL^- - freely permeable

K^+ - 50 – 100 times more than Na^+

Ca^{2+} - 50 – 100 times less than Na^+

e.g mammalian neuron [conc. –ml mols./liter)

Ions	**inside**	**outside**	**equilibrium potential (E)**	
Na+	14	142	+61mv	(0:1)
K+	140	4.0	-94mv	(35:1)
Cl-	3.5	103	-90mv	
$Prtn^-$ and other Organic anions (A^-)-	155			

Measured RMP = -90mV

These ions are unequally distributed across the cell membrane as expected with Na^+ more outside as inside, more K^+ inside than outside and more Cl- outside than inside. This unequal distribution of ions arises mainly because the cell membrane is selectively permeable. The membrane may be regarded as an insulator with pores which allows diffusion of some ions but not of others. Membrane is very readily permeable to K+ and Cl- ions, only slightly permeable to Na^+, totally impermeable to organic anions (A-).

In a resting state, the nerve cell membrane is 50 – 100 times more permeable to K+ than Na+.

N.B: This membrane is about 100 times less permeable to Ca^{2+} than it is to Na+

For all practical purposes Na+ may be regarded as being impermeable because the Na+ pumps which are active pump out the little Na+ that comes into the cell.

In a selectively permeable membrane the distribution of ions across it is detected by the **"GIBBS – DONNAN equilibrium effect"**. This is explained thus: presence of a non – diffusible ion on one side each, the non-

diffusible anion will tend to facilitate the diffusion of diffusible anions (A-) but inhibits the diffusion of diffusible cations (A+). Thus in the nerve cell, diffusion of K+ is inhibited. Consequently there is more K+ inside the cell and because of the principle of electro neutrality there are more Na+ on the outside.

RMP is also made possible and maintained by the operation of an electrogenic (rheogenic) Na- K+ pump that creates electrical gradient. It transports 3 Na^+ out of the cell for every $2k^+$ brought into the cell. With a combination of these two the inside is maintained slightly negative in respect to the outside.

NB- Diffusion alone - 86Mv

- Na/K+ pump -4mV

Ionic equilibrium potential

Definition: This is **t**he membrane potential at which equilibrium exists between the ions inside and outside the cell. The tendency for each ion to diffuse down its concentration gradient across a membrane is opposed by an electrical force driving the same ion down its electrical gradient. The magnitude of this electrical force when equilibrium is established is called the equilibrium potential for that ion. This magnitude is calculated by the **Nernst Equation**

Emf (mV) = -61 $\log\frac{[Conc]}{[Conc.]}$ and the value obtained is the **Nernst potential**

Factors which affect the RMP

This is essentially the concentration of ions (K^+, Ca^{2+}) in the external medium-

Decrease $[K^+]o$ leads to increase RMP.

Increase $[Ca^{2+}]o$ leads to increase RMP.

K^+ and Ca^{2+} are called membrane stabilizers and errors in K^+ metabolism leads to a disease condition called "**Periodic familial Paralysis**". As K^+ concentration increases, equilibrium potential decreases.

EXCITABLE FEATURES USING NERVE CELLS

Nerve cell (neuron) is the functional unit of the nervous system (NS). NS contains about 100 billion neurons of which about ¼ (25 billion) are found inside the brain while the others are found in the spinal cord and peripheral nerves. Neurons are more diverse in size and shape than cells in any other tissues of the body. However they have certain features in common. It varies considerably in structure, in higher animals; specialized function of nerves is transmission of nerve impulses while muscles are specialized for contraction.

Specialized functions of the neurons:

1. Reception of information from the internal and external environment.
2. Transmission of signals to other neurons and effector organs.
3. To process information (integration).

4. To determine or modulate the differentiation of sensory receptor cells and effector organs (trophic functions).

Morphology of nerve cells

e.g. Spinal motor nerve (SMN) which takes messages from the CNS to muscles (effectors).

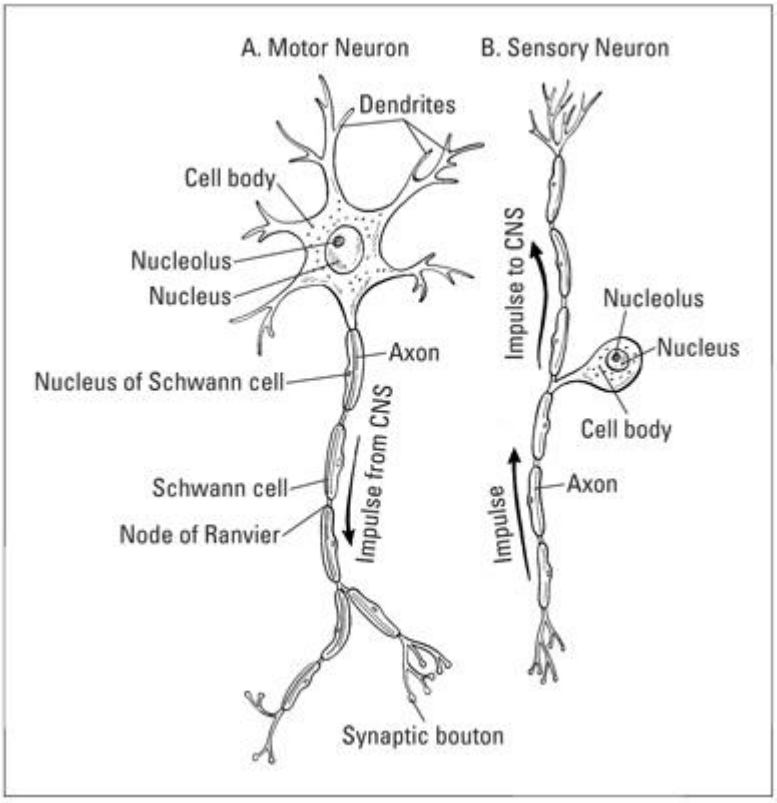


Fig.1.10: A nerve cell

Various types of neurons

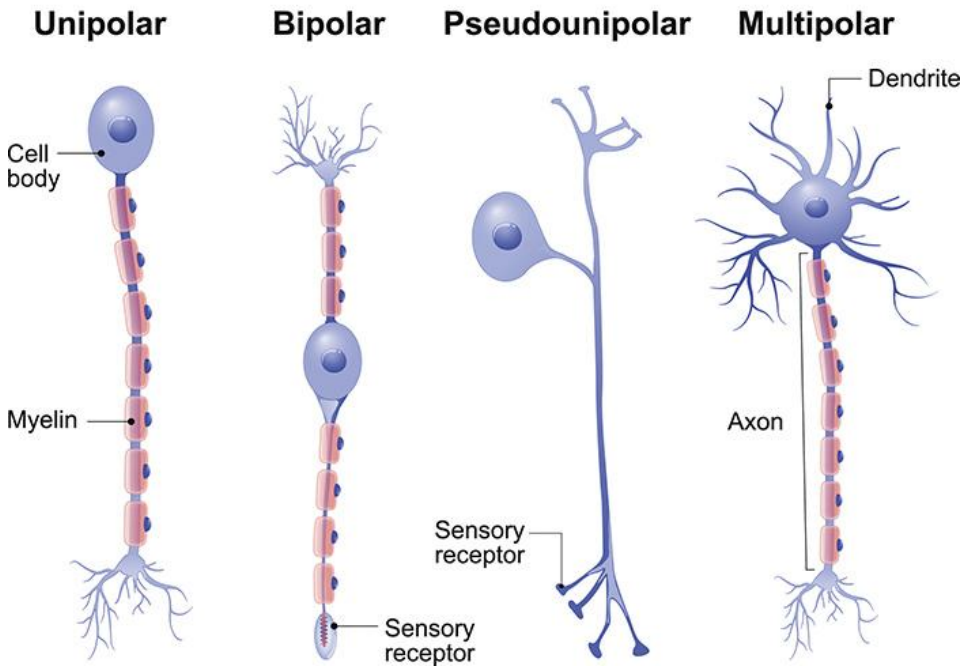


Fig. 1.11 Types of neurons

The parts include:

(1) **Axon**

This is a one extremely long process that originates from the axon hillock. It functions to propagate or conduct the impulse (AP) away from the cell body. It ends in a number of synaptic knobs also called terminal buttons or axon telodendria which contains granules or vesicles in which the synaptic transmitter secreted by the nerve is stored. The length ranges from few hundred microns to more than one meter. Inside it are microtubules through which substances are transported down the axon via a mechanism called axoplasmic transport. There are two main types:

(a)The fast component which takes about 400mm/day, and requires ATP.

(b) The slow component which carries substances at about 1mm/day.

Certain substances are transported in the opposite direction (reverse) to the cell body which is called **retrograde axoplasmic flow** at a rate of 220mm/day. The Axon reciprocally supports the cell body. There are two types of axons:

(a)myelinated (covered by myelin sheath) and

(b)non-myelinated (not covered by myelin sheath).

(2) Cell body (Soma, Perikaryon)

It contains the nucleus and other inclusions responsible for maintaining the axon, protein synthesis; synthesis of neurotransmitter substances and other materials takes place here.

(3) Schwann Cells/sheath

It causes myelination of the nerves involved in conduction. It is mostly found in the peripheral nervous system (PNS), while in the CNS we have Oligodendrocytes

(4) **Node of Ranvier**

It is a periodic constriction of the myelin sheath which is about 1mm in diameter or points where the myelin sheath does not cover the axon. It is also involved in conduction of impulses in the neuron.

(5) The dendrites

These act as receptors of the neuron

(6) **Axon Hillock**

It is the origin of the axon. It has the lowest threshold for excitation i.e. the most excitable region. Combination of the cell body and the axon hillock makes up the receptive zone of the neuron, usually a site for reception of stimuli and generation of AP.

(7) Myelin sheath

This is a protein-lipid insulating material, the presence improves impulse propagation. Most spinal motor nerves (SMN) are myelinated, while invertebrates are mostly non-myelinated. A pathology of the myelin sheath called **Multiple sclerosis**, a crippling (paralyzing) disease causes the distortion of the myelin sheath leading to poor or no conduction of the impulse.

(8) **Telodendritic area**

This functions for transmission of impulses across the synapse (synaptic transmission).

THE ACTION POTENTIAL

This the response of an excitable cell to an adequate stimulus, consisting of series of rapid changes in the electrical potential difference of the membrane from the resting negative value to a more positive value and back to the resting negative value. A cathode ray oscilloscope (CRO) is usually used to record these changes.

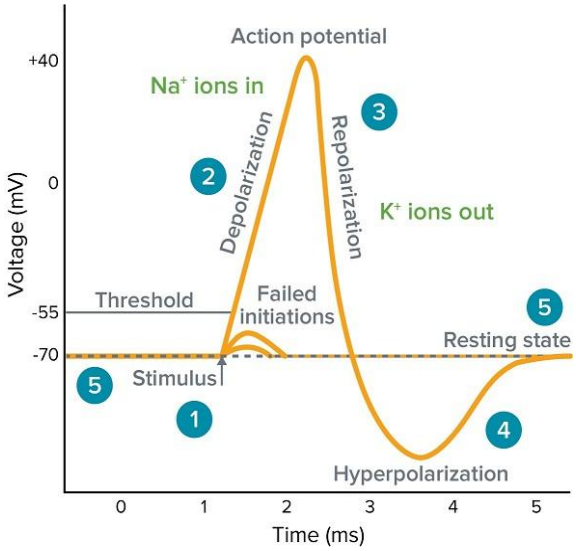


Fig. 1. 12. Action Potential and its stages

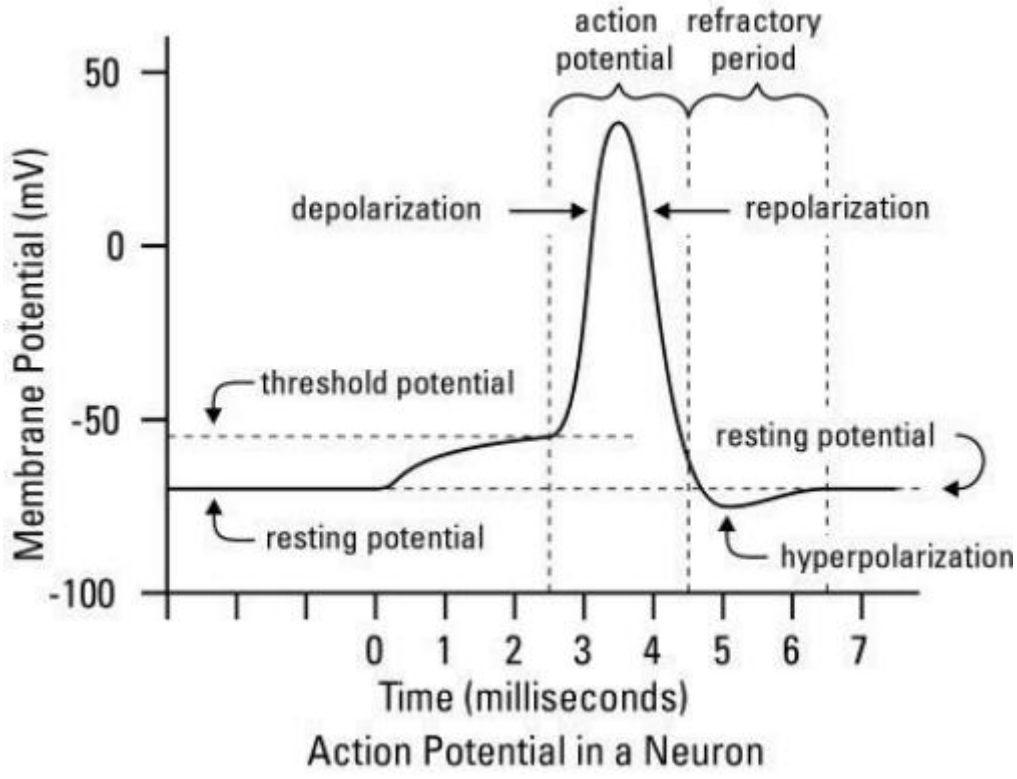


Figure 1.13: Electrical Events of Action Potential

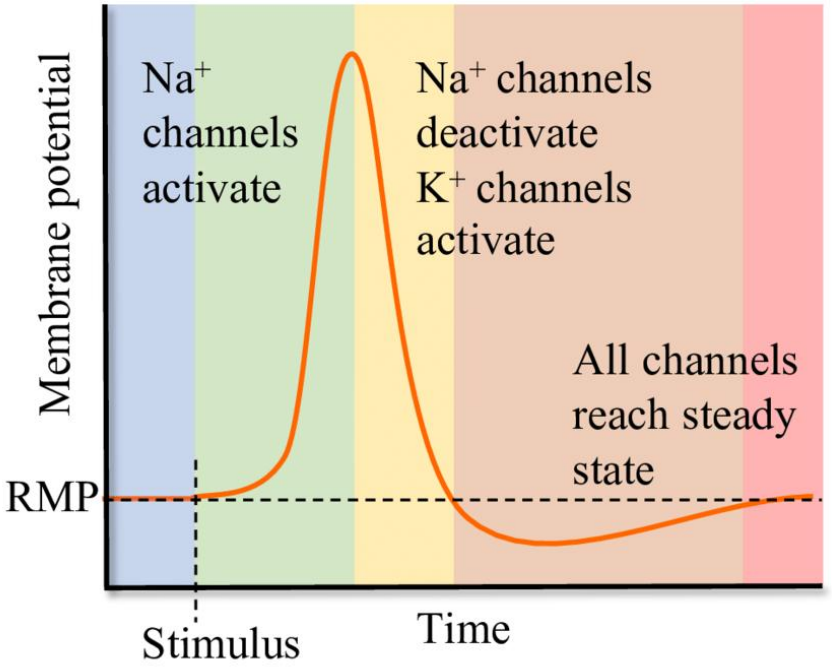


Fig 1.14. Role of ions in establishment of Action Potential

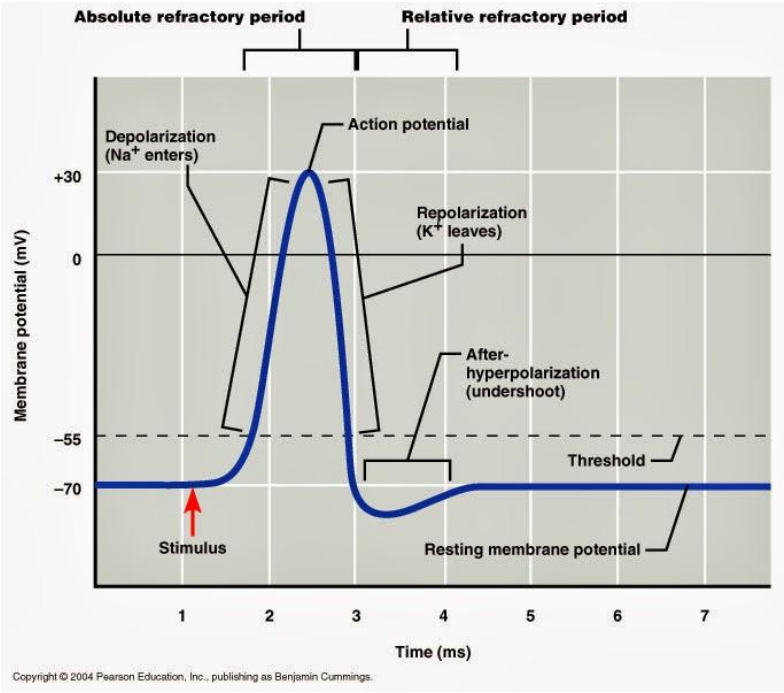


Fig. 1.15: Detailed Stages of Action Potential

There are two types of AP:

(1) **Monophasic**

This is when the wave movement is in one direction. This is measured or recorded by placing one of the recording electrodes inside the nerve and the other outside the nerve.

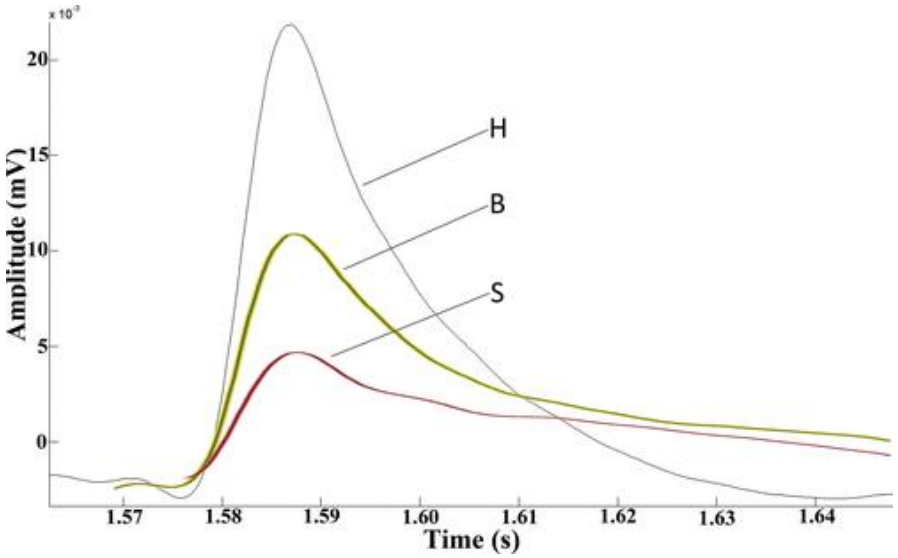


Fig. 1.16: Monophasic Actin Potential

Biphasic

It occurs when the wave movement is in two directions.

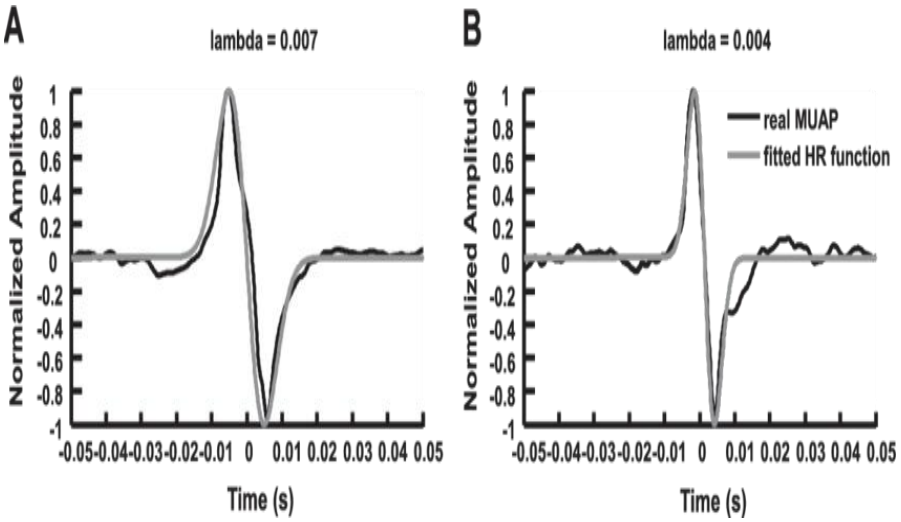


Fig 1.17 Bi- Phasic Action Potential

ELECTRICAL EVENTS OF THE AP

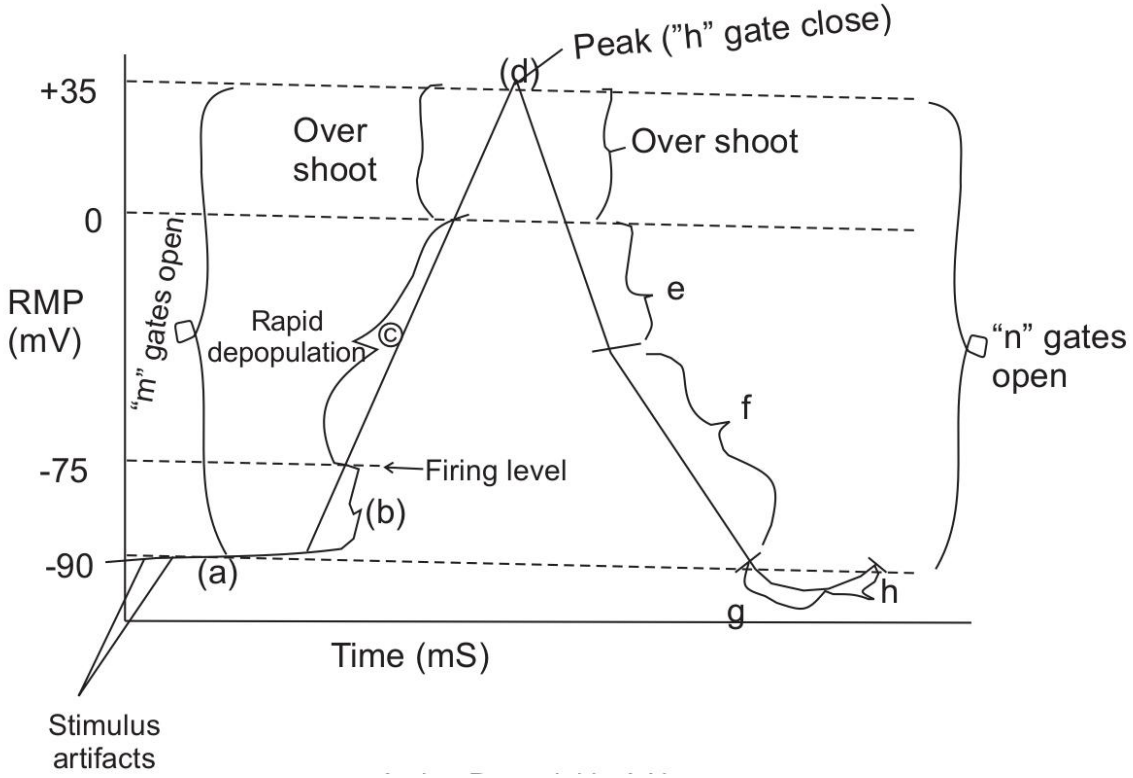


Fig. 1.18 Electrical Activities of Action Potential showing the ionic gates

The beginning of the AP recording is marked by a stimulus artifact, a slight deflection caused by leakage of the stimulating current from the stimulating electrode to the recording electrode. Latent period (P) follows the stimulus artifact. This is the time it takes for the changes in the membrane that bring about AP to occur. In practice most of it represent the time for the AP to travel from the stimulating electrodes to recording electrodes. The first manifestation of the approaching impulse is the commencement of depolarization of the membrane. After an initial +15mV of depolarization the rate of depolarization increases. The point at which this change in rate occurs is called the **firing level**. This gives rise to the upstroke.

THE UPSTROKE

The first part of the electrical potential changes consists of an upward deflection towards zero potential and above the zero line. This upward deflection (upstroke) indicates that the membrane potential is progressively becoming less negative and later it is reversed and becomes positive. It is called depolarization and it consists of three segments:

(a) slow depolarization phase.

(b) rapid depolarization phase.

(c)an overshoot

THE DOWNSTROKE

After the membrane potential reaches a peak, the membrane potential changes occur in the opposite to the upstroke. This is the downstroke which is also called repolarization. Here the membrane potential is becoming more negative and proceeding towards the resting value. It consists of four parts:

(a) Part of the overshoot

(b) The normal repolarization

(c) The after depolarization (negative after potential)

(d) The after hyperpolarization (positive after potential)

a and b are steep decline, c is a slower decline, d (after hyperpolarization) represents the part of the AP that is more negative than the RMP. Electrical changes that make up an AP are caused by changes in the permeability of the membrane to Na^+ and K^+.

NB- The sharp rise and rapid fall are the SPIKE POTENTIAL of the neuron

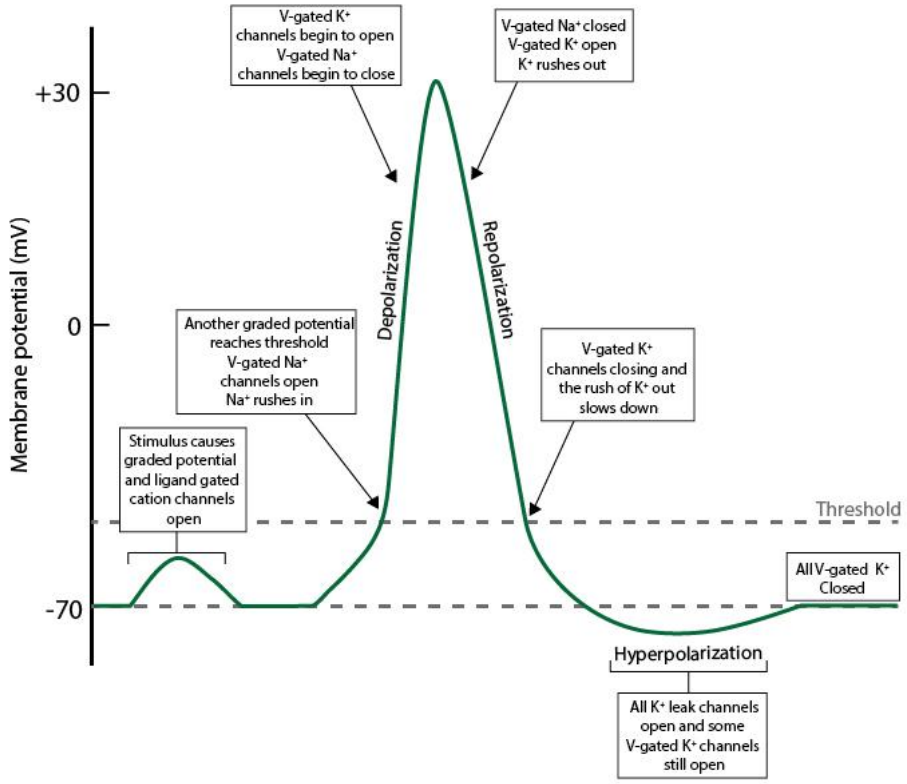


Fig. 1.19 Role of gates in the ionic basis of Action Potential

Ionic basis of the AP

1. **Latent period (LP)**: During the L.P membrane permeability changes resulting from the arrival of the stimulus, starts to occur. It takes some time before the membrane potential changes results in a response. This time taken represents the Latent period.
2. **Slow depolarization**: Application of an electrical stimulus results in addition/subtraction of charges to the membrane. A cathode current results in reduction of the positivity on the outside and negativity inside i.e. a decreased in the membrane potential. A slight depolarization so carried makes the membrane to become slightly more permeable to Na^+. If a sub threshold depolarization was produced, i.e. if it is unable to depolarize the membrane to the firing level the response dies away because the depolarizing effect of Na^+ entry is countered by the repolarizing effect of K^+ efflux. If the stimulus is of threshold or greater than the threshold the membrane is depolarized by up to +15mV to about – 75mV. If it can increase to – 75mV, the response proceeds to an A.P.-Slow depolarization phase is a local response given by all stimuli whether they are up to threshold or not.

3. Rapid Depolarization: If the depolarization of the membrane is up to a firing level (threshold voltage) a series of unstable events now occur:

(a) The depolarization causes the Na^+ gates to open; Na^+ enters the cell and further causes the membrane potential to decrease.

(b) A viscous cycle occurs at a very rapid rate and the membrane potential quickly decreases to zero **(called Hodgkin Cycle).**

(c) As more Na^+ move into the cell, the membrane potential reverses and becomes positive. This depolarization is caused by Na^+ influx.

This phase lasts for about 0.2 – 0.5 mS. After this period the gNa^+ (permeability) suddenly falls and the Na^+ gates closes, at the same time K^+ permeability increases above normal. The point at which gNa^+ permeability drops to zero represents the peak and we refer to it as **Na^+ gate inactivation.**

4. Rapid Repolarization (Overshoot and Normal Repolarization)

With the increase in K^+ conductance, K^+ quickly moves out of the cell making the membrane potential to become once again negative.

5. After Depolarization: This last 30% of K^+ efflux is slower than the earlier 70% and constitutes the after depolarization.

6. After Hyperpolarization: K^+ efflux continues beyond the amount required to balance the Na^+ influx because the K^+ gate close rather slowly. Membrane potential therefore falls below the RMP and this phase is called the after hyperpolarization.

7. RECOVERY: An A.P displaces some K^+ and Na^+ to bring the situation to normal (re-equilibration). The Na^+ that came in has to be taken out and K^+ that went out has to be brought back into the cell.

NB- During AP Na^+-K^+ exchange rate is insignificant. It's about 1 in 3000 of K^+.

Plateau in Some Action Potential

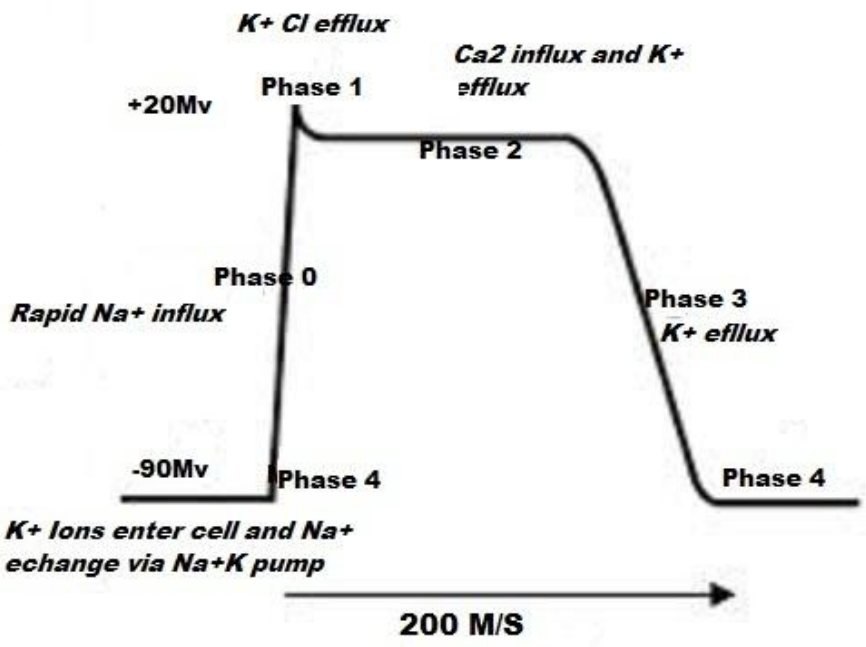


Fig. 1.20 Action potential showing a plateau

This is caused by:

a)usual voltage activated Na^+ channels (fast channels).

b)voltage activated Ca^+ - Na^+ channels (slow channels)

a and b are found in the heart muscles

c)slow activation of voltage gated K^+ channels in some excitable tissues

Initiation of A.P

Any event that can cause enough initial rise in the membrane potential from – 90mv to 0 (zero) directly affects the voltage – gated Na^+ channels leading to a vicious cycle.

Membrane channel blockers

1. Tetrodotoxin: It blocks voltage- dependent Na^+ channels leading to increase gNa+ (permeability) e.g. fish neurotoxin.
2. Scorpion/ snake venom: This prevents Na^+ inactivation. As a result the cell remains in a depolarized condition after initiation of an A.P resulting to jerky movement e.g. after snake bite.
3. Tetraethyl ammonium (TEA):This blocks K^+ channels leading to delayed recovery of the A.P

4. Local anaesthetics: This prevents the generation of the AP by inhibiting the voltage dependent opening of the Na^+ channels.

The Ionic Gates

This was first studied with **Voltage Clamp Technique**

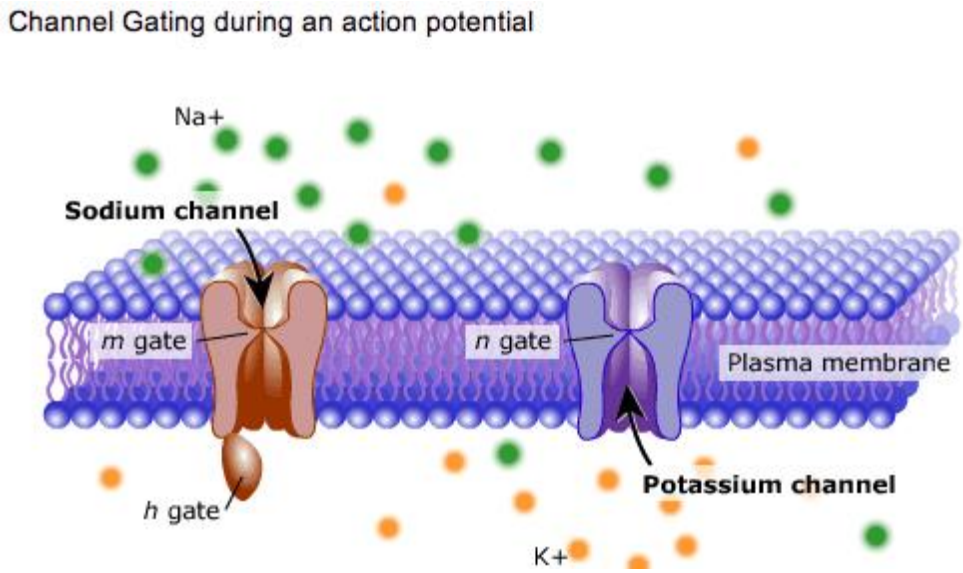


Fig.1.21 Membrane ionic channel gates

All or None Law

At rest the RMP of a nerve cell is constant but if an electrical stimulus is applied it leads to excitation of the nerve due to disturbance of the nerve membrane. The membrane potential at a depolarization which gives rise to AP is called a threshold potential. The minimum stimulus strength which depolarizes the membrane to threshold level is called stimulus of threshold intensity. A stimulus below threshold intensity (sub-threshold) does not elicit an AP rather it produces a local effect known as **electrotonus** which decreases with time and distance. A stimulus of threshold intensity or greater (supra threshold) always gives an A.P of constant amplitude.

Threshold intensity varies with the experimental conditions and the type of axon, but once reached, a full-fledged A.P is produced. Further increase in the intensity of the stimulus will not result to any further increment in A.P. Therefore we can see that the A.P fails to occur during sub-threshold stimulus and occurs with constant amplitude and form regardless of the strength of the stimulus if it is at or above threshold intensity. A.P is therefore all or none in character hence is said to **obey the "All or none law".**

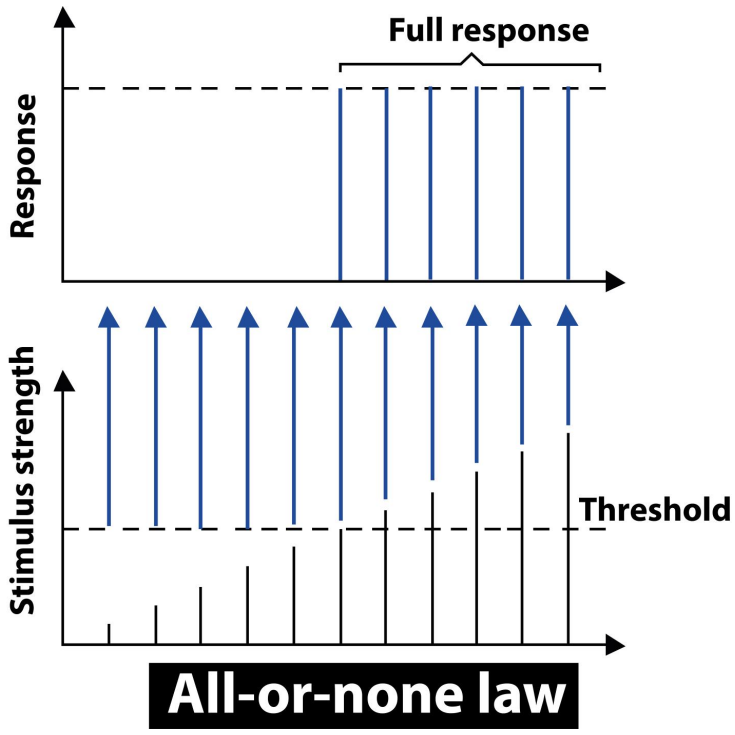


Fig. 1.22. Tracing of All or Non law in a nerve cell

Strength- Duration Relationship

The strength – duration curve shows the relationship between the strength of the stimulus and the minimum duration it must act to elicit a response. No matter how great is the strength of the stimulus a minimum time is required for that stimulus to be able to elicit a response. Thus if a very strong stimulus does not act long enough it will not elicit a response. It has the following terms:

Rheobase: This is the minimum strength of stimulus just sufficient to excite a given nerve or muscle. The unit is volt.

Utilization time: This is the minimum time required by stimulus of rheobase strength to give a response. The unit is milliseconds.

Chronaxie: This is the minimum time a current of twice rheobase intensity must be applied to produce a response. The unit is milliseconds.

The clinical value of the chronaxie is that it may be used to compare the excitability of different tissues. The longer the chronaxie, the less excitable is the tissue.

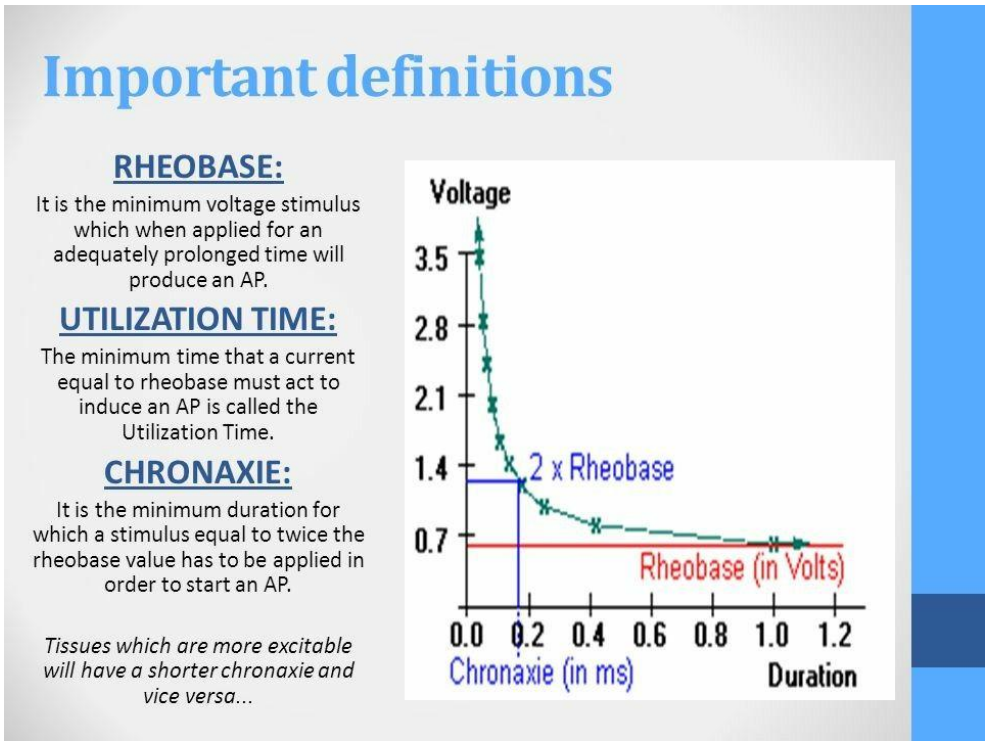


Fig. 1.23 Graph of Strength- Duration Relationship

Conduction (propagation) of the A.P

At the point where a nerve is stimulated, depolarization causes the polarity there to change in respect to the neighboring parts. This causes a viscous cycle of depolarization along the nerve and the AP is conducted from the point of the stimulus to the end of the nerve.

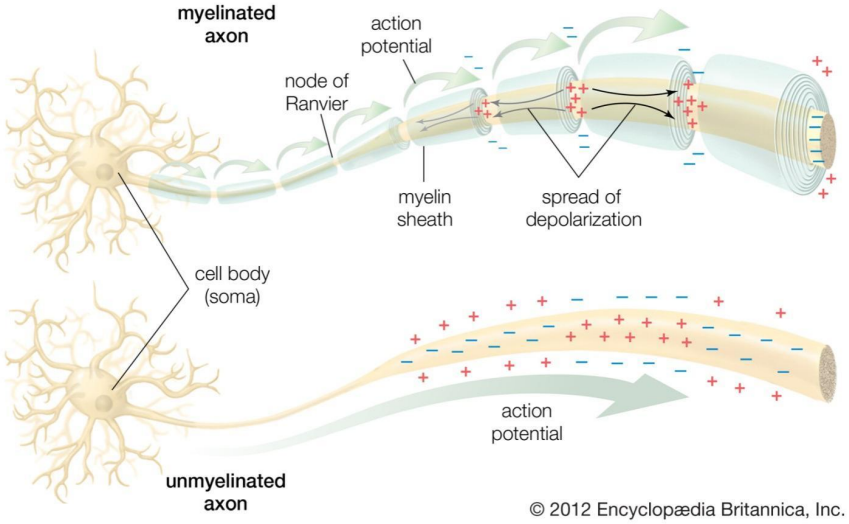


Fig. 1.24 Conduction (propagation) of Action potential in a neurone

There are two types of conduction:

(1)**Streamlined (unmyelinated nerves)**

Here depolarization occurs generally along the length of the nerve fiber membrane. It is also called local circuit. It is slow and consumes lots of energy. It is also called local circuit.

(2)Saltatory (Jumping) (myelinated nerves)

This involves the jumping of depolarization from one node of ranvier to another. It is much faster (about 50 x) than local circuit, uses metabolic energy and is more economical i.e. more efficient.

Direction of propagation of A.P

An excitable membrane has no single direction of propagation, but the A.P can travel in both directions away from the stimulus and even along all branches of a nerve fiber until the entire membrane has become depolarized. In life however, impulse is conducted only in one direction i.e. away from the cell body due to the presence of the synapse.

Types of conduction

There are two types:

(a)Orthodromic conduction: This is conduction from the synapse or receptors along axons to their termination. This is found in real life.

(b)Antidromic conduction – This is conduction in the opposite direction.

Advantages of myelination

(a)Higher conduction velocities for rapid signaling.

(b)Smaller diameters for conserving space.

(c)Higher metabolic efficiency because of the decreased flux of ions and hence the decreased expenditure of energy required to restore ionic composition.

Velocity of conduction of AP

This is primarily determined by the nerve diameter. In myelinated fibers, the velocity (V) is directly proportional to the diameter (D) of the fiber. In non myelinated fibers, velocity is directly proportional to the square root of the diameter. Nerve fibers maybe classified on the basis of their diameters and hence their conduction velocities. It varies from as little as 0.5m/s in very small unmyelinated fibers to as high as 100m/s (the length of a football field) in very large myelinated fibers.

Other factors affecting conduction

↓ $[Na+]_o$	↑$[K+]_o$
↓RMP	local anaesthetics

All of the above leads to a decrease conduction velocity.

Classification of nerves

There are four (4) major methods of classifying nerves.

a. **Generally accepted classification was by Erlanger and Gasser using diameter and conduction speed.**

Fiber Type	Function	Fiber Diameter (µm)	Conducting Velocity (mS)	Spike Duration (mS)	Absolute refractory period (mS)
A α(alpha)	Proprioception, somatic motor	12 – 20	90 – 120	04 – 0.5	0.4 – 1
$A_{\beta\ (beta)}$	Touch, pressure	5 – 12	30 – 90		
AY (gamma)	Motor to mzl spindles	3 – 6	15 – 30		
Aδ(delta)	Pain, temp, touch	2 – 5	12 – 30		
B	Preganglionic autonomic	<3	3 – 15	1.2	1.2
C(Dorsal root sympathetic)	Pain, reflex responses	0.4 – 1.2	0.5 – 2.0	2	2
	Post ganglionic sympathetic	0.3 – 1.3	0.7 – 2.3	2	2

b. **Some physiologists have classified sensory nerves numerically as I, divided into IA and IB, II, III and IV. This type of classification was popularized as LLOYD/ HUNT classification.**

NUMBER	ORIGIN	FIBRE TYPE
I (a)	Muscle spindle, annulo-spiral ending	A α
(b)	Golgi tendon organ	A α
II	Muscle spindle, flower spray ending; touch,	A β

	pressure	
III	Pain and temperature receptors, some touch receptors	A α
IV	Pain and other receptors	Dorsal root C

c. **Also peripheral nerves have been classified according to their sensitivity to hypoxia, anaesthetics and pressure.** This classification is very important physiologically in that local anaesthetics affect or decrease transmission in C fibers before affecting A fibers (touch fibers).

Also when pressure is applied on a nerve, it will lead to loss of conduction in motor, touch and pressure fibers while pain fibers remain intact.
This pattern is seen in a phenomenon called **Saturday Night Paralysis or Early Sunday Morning Paralysis**. This can be explained to happen to individuals when they get drunk commonly on saturday nights and on coming home easily sleep off on the sofa usually with the hand supporting the head. Later in the midnight of saturday or on waking up on sunday morning, the hand feels paralyzed and painful.

Relative susceptibility of mammalian A,B,C nerves to conduction block produced by various agents.

	Most susceptible	**Intermediate**	**Least**
Sensitivity to hypoxia	B	A	C
Sensitivity to pressure	A	B	C
Sensitivity to cocaine and local anesthesia	C	B	A

d. Human peripheral nerves are also classified on a physio-anatomical basis into afferent and efferent categories. These are further classified according to whether they are somatic or visceral, having either general or special functions.

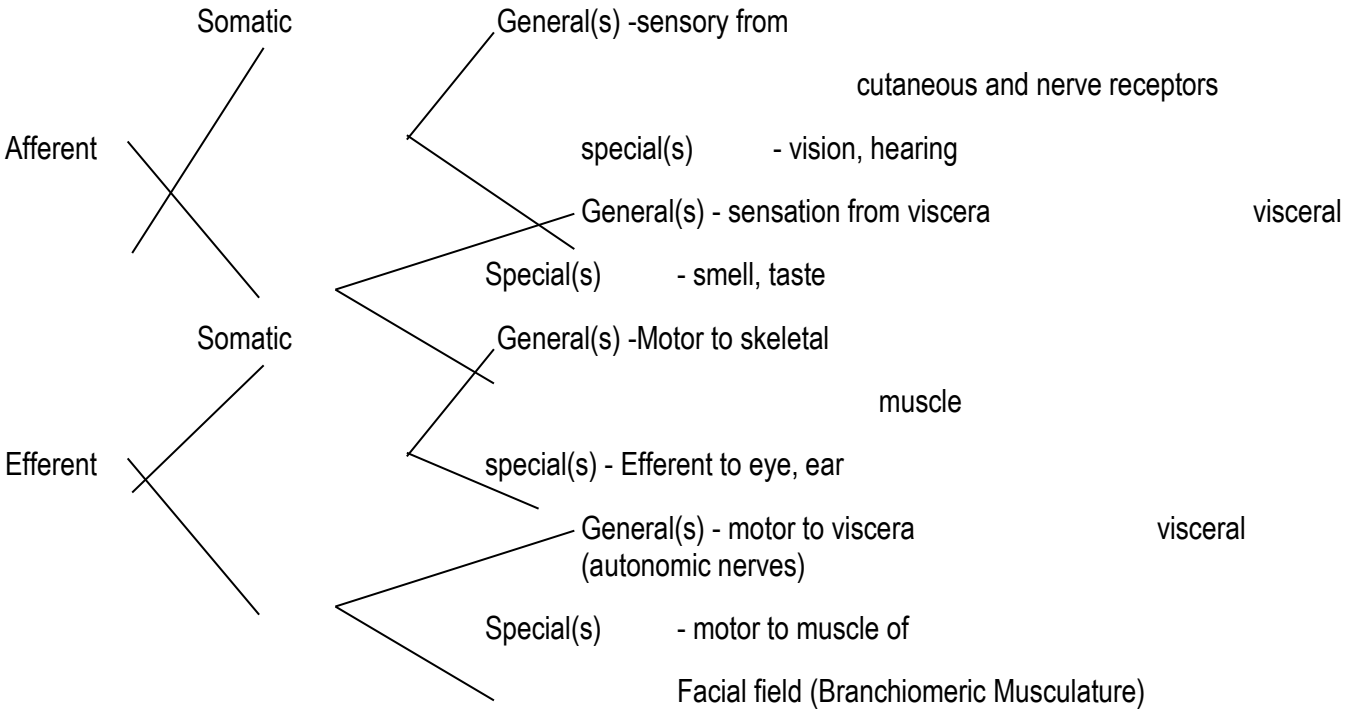


Fig. 1.25: Type of fibers in peripheral and cranial nerves

Thus we have

GVA = General visceral afferent

SVE = Special visceral efferent etc

Compound AP

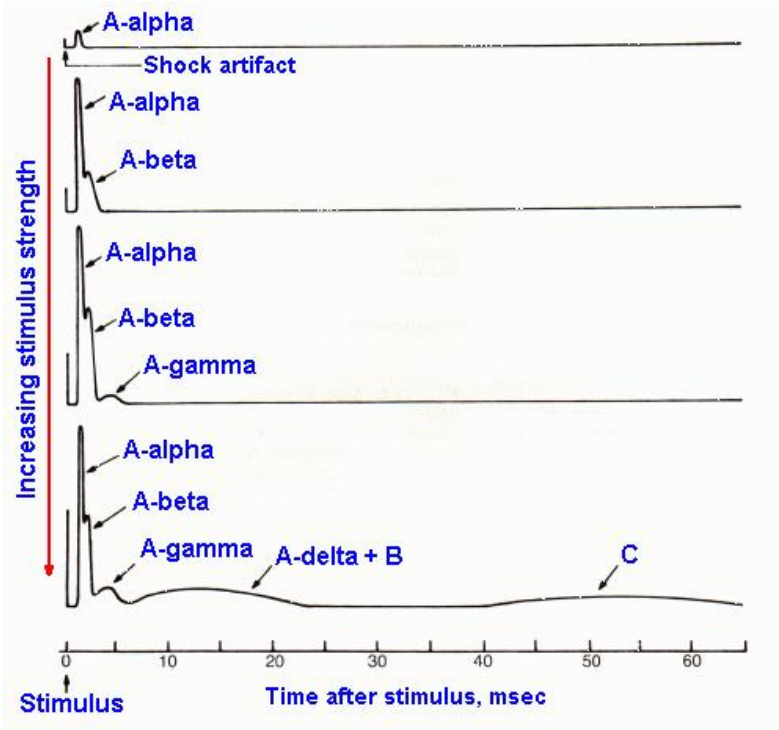


Fig. 1.26. Action potential tracing in a mixed nerve

Property of mixed nerves:

In mammals, peripheral nerves are made up of many axons bound together in a fibrous envelops called epineurium. The potential changes recorded for such nerves therefore represent a summation of the all or none action potential of many axons. A variation in threshold and distance from the stimulating electrodes exists for the different axons. If it is a sub-threshold stimulus, none of the axons will be stimulated and no response occurs. If the stimulus is of threshold intensity, axons with low thresholds will fire and small potential changes will be observed. If we increase stimulus intensity, axons with higher thresholds are discharged. This continues until the stimulus is strong enough to excite all of the axons in the nerve.

Maximal stimulus

This is the stimulus that produces excitation of all the axons. Further application of greater or supra maximal stimulus will lead to no further increase in the size of the observed potential. When a mixed nerve or nerve bundle is stimulated it produces a **compound AP.**

"All or None Law" for Nerve Bundle

Different threshold exist for different fibers found in a nerve bundle. Generally large fibers are more excitable than smaller ones. Thus with increased stimulus strength the AP of a nerve bundle increases as less excitable fibers are being excited. This phenomenon of addition of AP results from spatial summation.

Refractory period

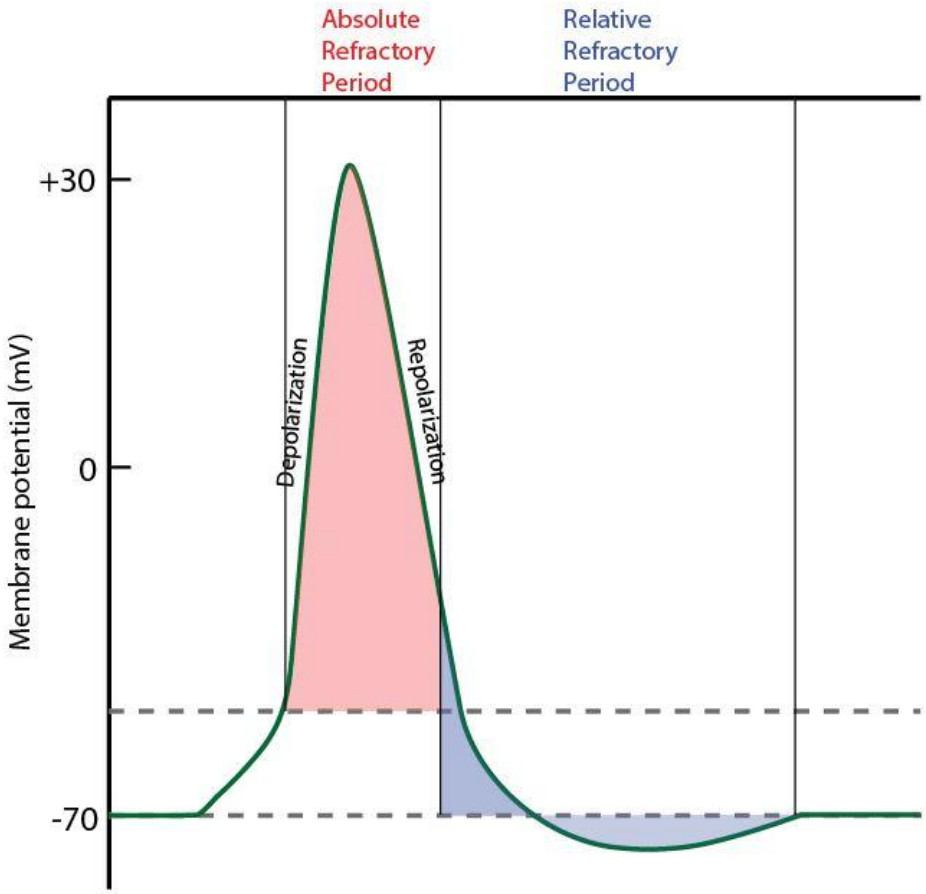


Fig. 1.27 Types of Refractory Periods

These are the periods during an action potential when the nerve cannot respond to another stimulus. A second AP cannot occur in an excitable fiber as long as the membrane is still depolarized from the preceding AP. The reason is

Reason: After the inactivation of the Na^+ gate shortly after the initiation of AP, no amount of excitatory stimulus applied to the nerves can open it except the membrane potential returns to either or almost to the original RMP level. It is divided into two types:

R period → absolute R.P
R period → Relative R.P

(a) Absolute R.P

This is the period of time during which a second A.P cannot be elicited, even with a very string stimulus i.e. no stimulus, no matter how strong will excite the nerve. It corresponds to the period from the time the firing level is reached until repolarization is about 1/3 complete.

(b) Relative R.P

This is the period of time when only stimuli stronger than normal can excite the nerve fiber. It lasts from the end of absolute R.P to the start of after depolarization.

Causes of relative refractoriness

(1) Delayed rectification by K^+ efflux. The K^+ channels are usually wide open at this time.

(2) Residual Na^+ inactivation. During this time some of the Na^+ channels still have not been reversed from their inactivation state.

1 and 2 causes a state of hyperpolarization that makes it more difficult to stimulate the fiber.

Reason for the name positive after potential

Historically the first potential measurements were made on the outside of the nerve fiber membrane rather than inside, hence the potential caused a positive record on the meter rather than a negative one.

Central Nervous System (CNS) Synapses

Information is transmitted in the CNS in the form of action potentials (nerve impulses). These occur through a succession of neurons across a synapse. A synapse can be defined simply as a junction between two excitable tissues i.e. it is a functional membrane to membrane contact of the nerve cell with another nerve cell, an effector (muscle or gland) or a sensory receptor cell. The synapse sub serves the transmission of nerve impulse commonly from a variable large (1-12 μm), generally knob-shaped or club-shaped axon terminal (the pre-synaptic element) to the circumscript patch of the receiving cell's plasma membrane (post-synaptic element) on which the synapse occurs. In most cases, the impulse is transmitted by means of chemical substances called neurotransmitters (NT) e.g. adrenalin, acetylcholine, gamma amino butyric acid (GABA), glycine, serotonin, substance P, histamine, glutamate, encephalin, endorphins, released into the synaptic cleft (about 15-50 nm wide). The cleft separates the pre from the post synaptic element. The NT is stored in quanta forms at the pre-synaptic vesicles which are round ellipsoid membrane bound vacuoles (10-50nm in diameter) found in the pre-synaptic element.

In other synapses, transmission takes place by direct propagation of the bioelectrical potential from the pre to the post-synaptic membrane. These are called electrical/electronic synapses e.g. gap junctions. In electrical synapses, the synaptic cleft is just about 2nm wide, e.g. in smooth muscles, cardiac muscles. In most cases transmission takes place in only one direction (dynamic polarity of the synapses). However in some synapses, synaptic vesicles occur on both sides of the synaptic cleft suggesting the possibility of reciprocal chemical transmission. In humans the chemical synapse pre-dominates.

Synapse Terminologies

Synapse is broadly classified into electrical/chemical. Types of chemical synapse include:

1. Neuron- neuron synapse (N -N)
2. Neuro-muscular synapse (N – M)

3. Neuro-glandular synapse (N –G)

2 and 3 make up neuro-effector synapses

Types of Neuron-Neuron Synapse

a. Axo-axonic Synapse: This is between an axon terminal of one neuron and either the initial axon segment or an axon terminal of another neuron or nerve cell.

b. Axo-dendritic Synapse: This is between the axon of one neuron and the dendrite of another neuron.

c. Axo-somatic: This between the axonal terminal of a nerve cell and the soma of another nerve cell.

Functions of a Synapse

1. Reception of information (major function): either directly from outside world through specialized dendrites or from receptor cells.
2. Valve function: By permitting unidirectional flow of impulse, they permit orderly activities in the CNS.
3. Amplification: An impulse may be amplified at the synapse i.e. changed from a single impulse into repetitive impulse, allowing a greater area of the brain to be excited.
4. Inhibition: An impulse can be completely or selectively inhibited at the synapse.
5. Integrative function: At the synapse, an impulse may be integrated with impulses from other neurons to cause highly intricate pattern of impulses in successive neurons.
6. Site of Action of drugs and other chemical agents: Chemical agents are more sensitive at the synapse than they are at the nerves thus neural function is most easily manipulated pharmacologically at the synapse.
7. Aid to Anaesthesia: Blocking of information or impulses at the synapses, allows clinicians to use local or light anesthesia. Local anesthesia is better than general one because it can be easily managed or controlled.
8. Learning and memory: Each time a given sensory signal passes through a sequence of synapses, it makes it easier for the same information to pass through that same sequence or synapse on another occasion. This is called facilitation. When this process takes place repeatedly for some time, it becomes possible for a signal within the brain to go through the same sequence of signal without a sensory input. Synapses transmit better when frequently used.

Physiologic -Anatomy of a Neuron-Neuron Synapse

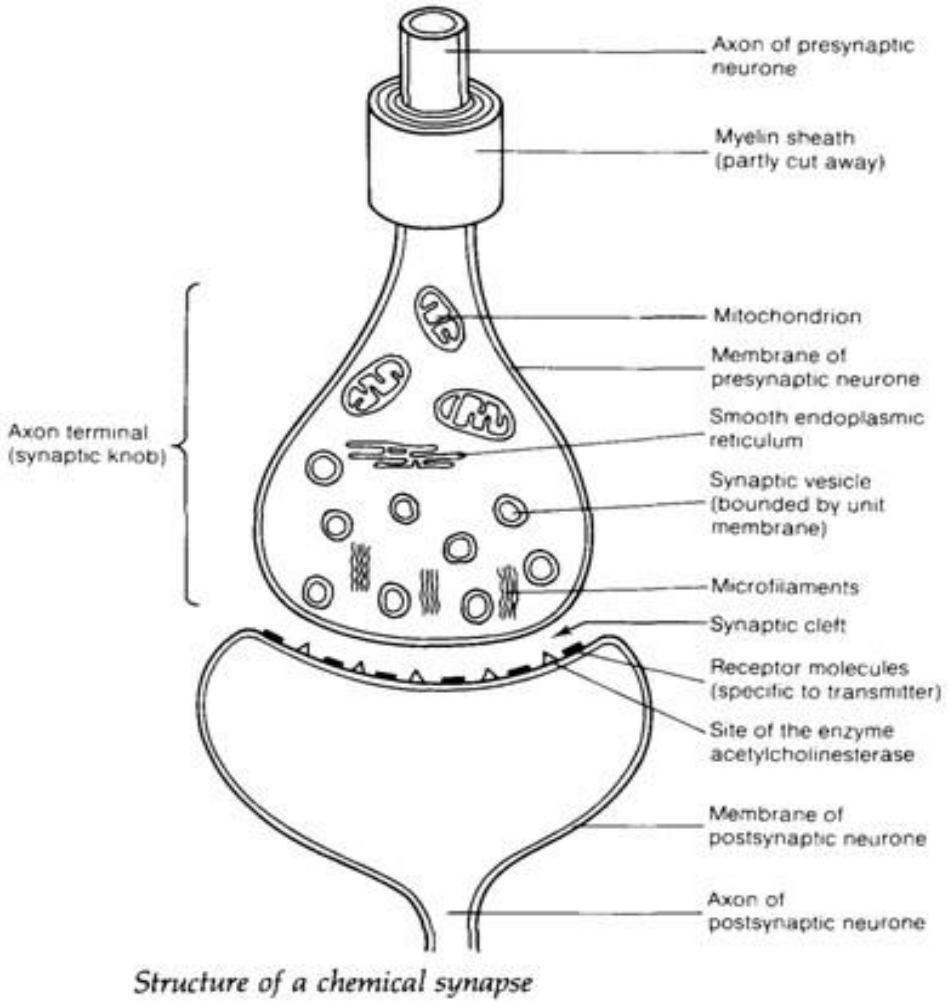


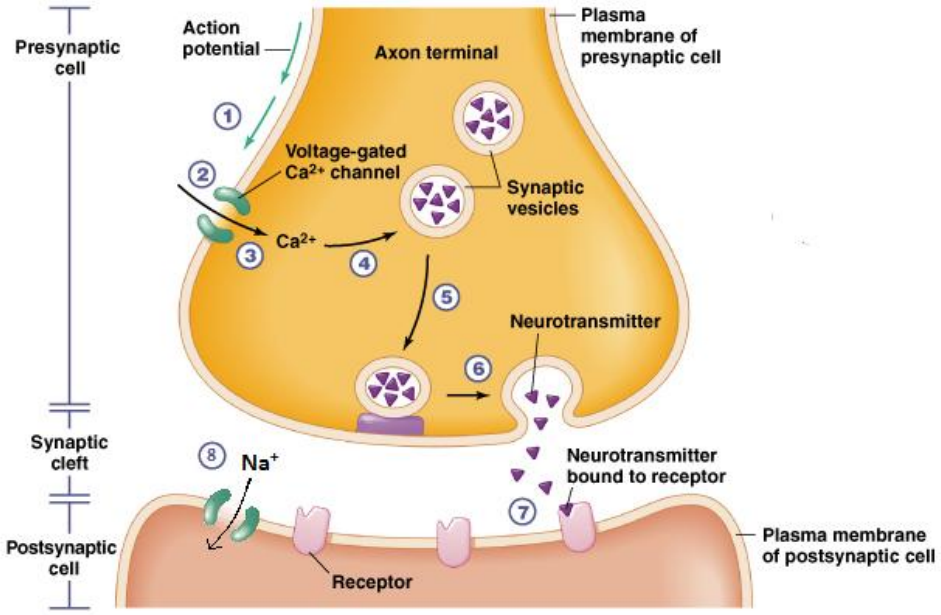
Fig. 1.28. A chemical synapse

Neuron-Neuron Synaptic Transmission

This involves transmission of information from a neuron to another neuron across a synapse. Information in form of AP arise in pre-synaptic neuron terminal and gets to the terminal buttons. On reaching the terminal button, the AP causes conformational changes across the membrane of the pre-synaptic neuron.

This conformational change causes the voltage-gated Ca^{2+} channels found on the pre-synaptic membrane to open and Ca^{2+} moves into the synaptic vesicles to coalesce and become bigger and less in number, and bind with protein molecules on the inner surfaces or the pre-synaptic membrane.

Fig.



1.29 Chemical Synaptic Transmission

By a process of exocytosis, the pre-synaptic membrane opens and liberates its contents (NT substances) into the synaptic cleft. The NT binds with post-synaptic receptor proteins which have 2 components:

a) Binding component-protrudes into the cleft and binds to neurotransmitter

b) Ionophore component which passes all the way through the membrane and:

i) Stimulate ionic channels which allows passage of specific ions
ii) Activate 2nd messenger activator

The ion channels are of 2 types:

1. The cation channels which are positively charged
2. The anion channels which are negatively charged.

The cation channels allow mostly Na^+ and sometimes K^+

and Ca^{2+}. However it repels Cl^- and other anions while

the anion channel allows mostly Cl^- because of its small size.

The 2nd messenger activator

It is not an ion channel. It protrudes into the cell cytoplasm and stimulates one or more substances inside the post synaptic neuron which then act as 2nd messengers. It has many types: commonest is the G-protein made of 3 components: the $\propto$, β and γ components. The $\propto$ component is called the activator portion while the β and γ

attach the G-protein to the inside of the cell membrane adjacent to the receptor protein. On activation of the G protein by a nerve impulse:

-∝ separates and moves within the cytoplasm of cell freely and activates:

a) opening of specific ion channels through post synaptic cell membrane.

b) activation of c Amp/ c Gmp in the neural cell which initiates chemical results.

c) activation of one or more intracellular enzymes e.g. protein kinases.

d) activation of gene transcription (most important function).

Resulting from the above activities, Na^+ and K^+ channels are opened simultaneously. This allows influx of Na^+ into the post synaptic neuron and exit or efflux of K^+. The entry of Na^+ sets up a depolarization called **post synaptic potential (PSP)** at the post-synaptic neuron. One PSP is not usually enough to set up an AP hence it has to be summated spatially or temporarily. This summation enables the PSP to transform into the excitatory PSP (EPSP) which now leads to AP.

However, if the body does not want the information to continue in the post-synaptic neuron, the PSP is transformed into inhibitory PSP (IPSP) by the action of increased exit of K^+ leading to repolarization or influx of Cl^- leading to hyperpolarization of the post synaptic neuron.

Both conditions will not cause the generation of AP at the axon Hillock or (initial segment of axon) of the post-synaptic neuron. Therefore formation of AP at the axon hillock allows the initial information to continue at the post synaptic neuron.

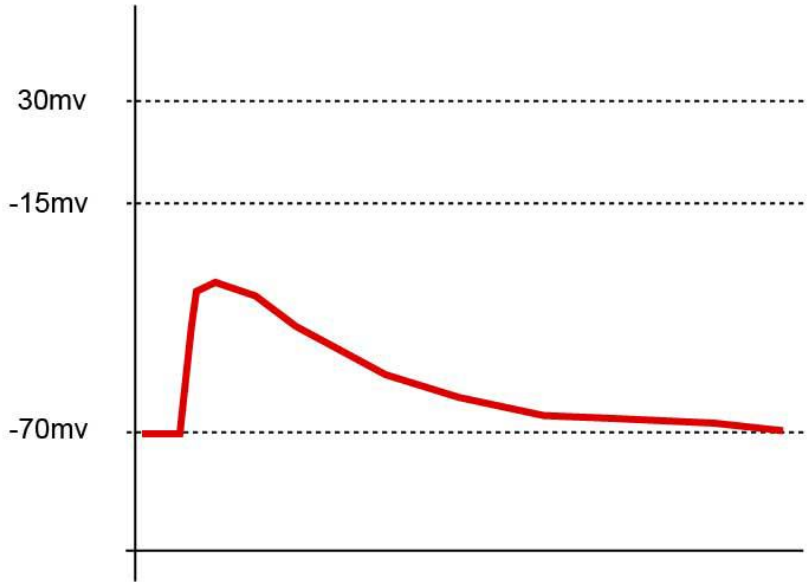


Fig. 1.30 Diagram of Slow Depolarization

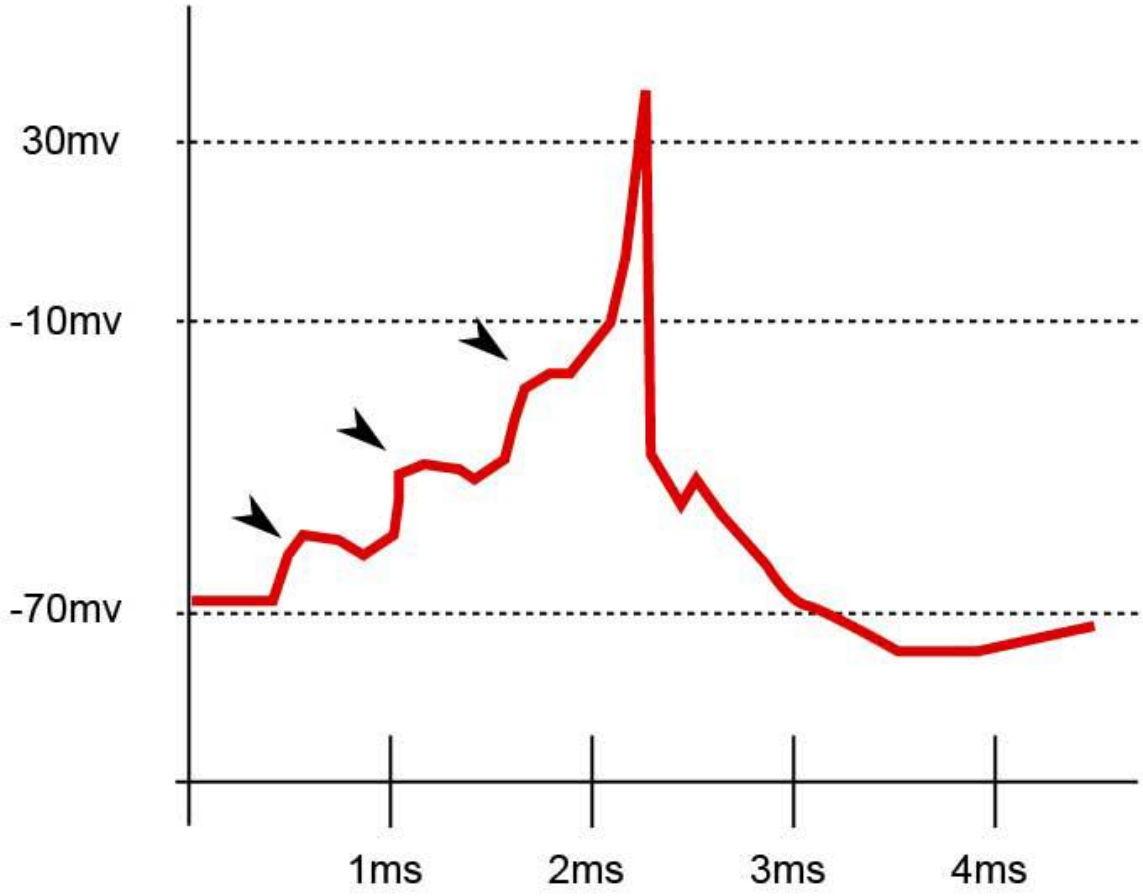


Fig. 1.31 Diagram of Development of Action Potential from Slow Depolarization

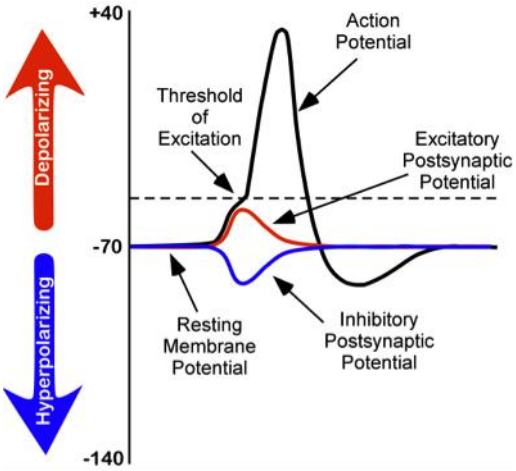
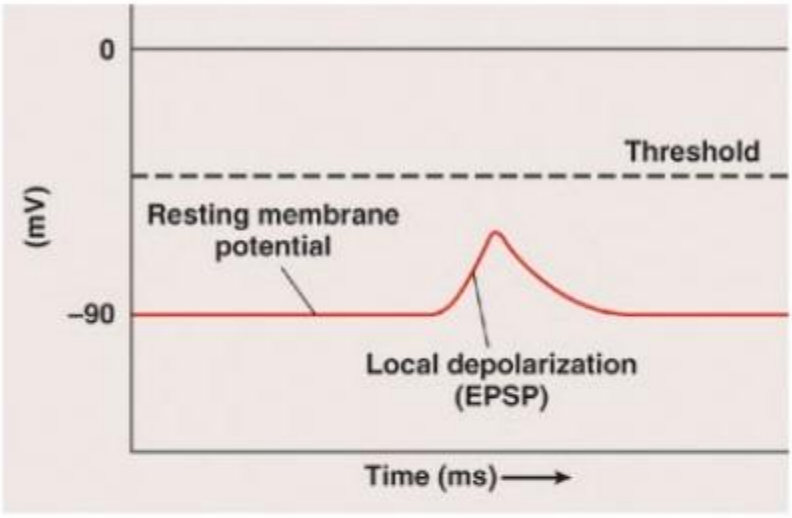

+40
-70
-140
Depolarizing
Hyperpolarizing
Action Potential
Threshold of Excitation
Excitatory Postsynaptic Potential
Resting Membrane Potential
Inhibitory Postsynaptic Potential

Fig. 1.32a



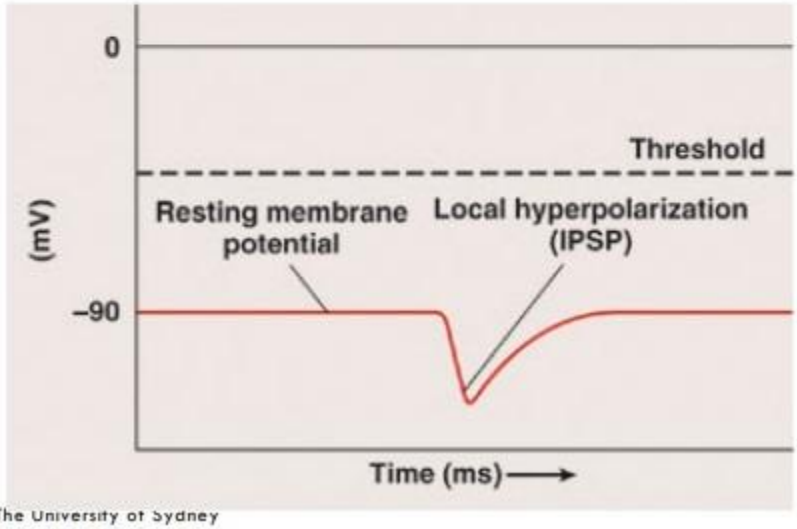


Fig. 1.32b

Figs 1.32 a and b showing types of Post Synaptic Potentials

Excitatory and Inhibitory Receptors in the Post-

Synaptic Membrane

(1)Excitation

This involves opening of Na^+ channels, decrease in conduction through Cl^- or k^+ or both channels and various changes in the internal metabolism of the cells. These will lead to excitation of cell activities, increase in number of excitatory membrane receptors and reduction in number of inhibitory membrane receptors.

(2)Inhibition

This involves opening of the Cl^- channels, increase conductance of K^+ through the membrane out of the cell and activation of receptor enzymes that;

a. Inhibits cellular metabolic functions
b. Increases the number of inhibitory synaptic receptors.
c. Decreases the number of stimulatory synaptic receptors.

Removal of NT Substance after It's Action

This involves diffusion out of synaptic cleft, enzymatic destruction within the cleft e.g. for ACH by acetylcholinestarese and NT re-uptake into pre-synaptic neuron.

Electrical Events during Neuronal Excitation

This involves the RMP of neuronal soma (-65mv). In this case, K^+ efflux contributes most. The RMP is less than that of a large peripheral nerve (-90mV). Also the origin of RMP of neuronal soma contributes. All these contribute to the effect of synaptic excitation on the postsynaptic membrane leading to formation of EPSP leading to formation of AP.

Electrical Events in Neuronal Inhibition

This results from the effect of inhibitory synapses and post synaptic membrane leading to IPSP from hyperpolarization of post synaptic membrane. It also occurs via short circuiting of the membrane.

There are two types of inhibition:

A. Presynaptic Inhibition: This can occur as a result of
1. Repeated activity of pre-synaptic fiber leading to exhaustion progressively of the neurotransmitters. This leads to a condition called **Synaptic fatigue** hence EPSP cannot cause AP.
2. Decreased amplitude of AP: This results from inadequate neurotransmitter release which can be cause by an inhibiting NT e.g. GABA (gamma amino butyric acid).

B. POST-SYNAPTIC INHIBITION:
This can occur as a result of:
1. Setting up of IPSP at the post synaptic neuron by the release of an inhibitory NT or glycine. Two poisons which block IPSP usually leads to convulsion i.e. strychnine and tetanus toxin. These poisons prevent release of inhibiting NT at receptor site.
2. Previous activity in the neuron such that it is refractory to arriving excitation.

Synaptic Delay

There is a small delay between the arrival of an impulse at the pre-synaptic terminal and the AP in the post synaptic neuron. This delay represents the time taken for discharge of chemical transmitter substance, its diffusion across the cleft and influx of Na^+ into post synaptic cell. In excitatory situations it lasts for about 0.5ms while in inhibitory situation it may last 10- 15ms or more. This time is called **Synaptic Delay or latency of the EPSP.** Transmission across a synapse is unidirectional because the chemical transmission substance is located only on the pre-synaptic membrane.

Chemical transmitter substances

Various substances have been identified as neurotransmitter substances which include:

1. Acetylcholine
2. Noradrenalin
3. Adrenaline
4. Dopamine
5. Serotonin
6. Substance P
7. Glycine
8. GABA
9. Glutamic acid
10. Encephalins and
11. Endorphins

Acetylcholine act on:

(1) Neuromuscular joints.

(2) All pre ganglionic endings in the autonomic nervous systems.

(3) All post ganglionic parasympathetic endings.

(4) All sympathetic synapse in the adrenal medulla.

(5) Post ganglionic sympathetic endings in the sweat glands.

(6) Some parts of the brain's pre-synaptic endings on Renshaw cells.

Nor-adrenalin act on:

(a) all post ganglionic sympathetic endings except sweat glands.

(2) some parts of the CNS.

Adrenalin act on:

(1) the adrenal medullar.
(2) some parts of the CNS.

Termination of neurotransmitter action

Shortly after acetylcholine has caused depolarization of the post synaptic membrane. It is hydrolyzed in a reaction characterized by the enzyme acetyl cholinesterase.

NB: that the same neuro transmitter substance does not always produce the same permeability changes, instead the properties of postsynaptic receptors determine whether neurotransmitter is excitatory or inhibitory.

Example of an electrical synapse is **gap junctions.** It is found in visceral smooth muscles and cardiac muscles. It mostly consists of small protein tubular structures that allow free movement of ions from the interior of one cell to the next.

Inhibition of Impulse at the synapse

In some cases the arrival of an A.P at the pre-synaptic terminal leads to inhibition instead of excitation of the post synaptic membrane. Here the pre synaptic vesicles release an inhibitory neurotransmitter which hyperpolarizes instead of depolarizes the membrane. The mechanism is as follows:

An inhibitory neurotransmitter selectively increase post synaptic membrane permeability to chloride and potassium ions. Chloride influx increase negativity inside thereby increasing R.M.P. This hyperpolarizing potential is called an **inhibitory post synaptic potential (IPSP).** Like EPSP, IPSPs can be summated spatially or temporarily. Glycine is known to be an inhibitory neurotransmitter. Poisons which block inhibitory neuro transmitter may cause convulsion.

MUSCLE

Found all over the body, adapted for converting chemical energy into force

On hierarchy, the components of the muscles of the body are as follows:

Human body

↓

Muscle (myo) bundles

↓

Muscle (myo) fibers

↓

Muscle (myo) fibrils

↓

Muscle (myo) filaments

↓

Muscle (myo) Proteins

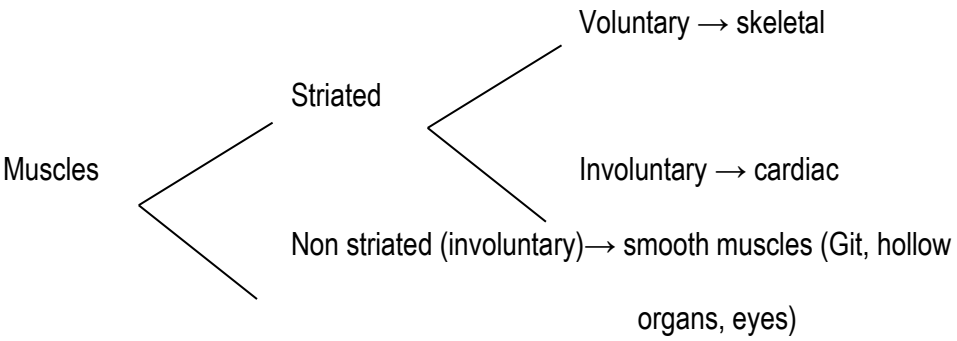
Classification of types of muscles

They can be classified based on:

(a) **Anatomy (structure)**:

This involves the presence or absence of lines (striations) on the fibers. It is called **striated** if lines are present and **non striated** if lines are absent.

(b) **Physiology (function)**:
This refers to the pattern of stimulation/ response. It is called **voluntary** if it needs external stimulation before responding and **involuntary** if it can initiate the stimulation of itself and does not require external stimulation before responding. Combination of both is called **physio- anatomic classifications.**



Skeletal muscles makes up 40% of the body while the smooth and cardiac muscles make up 10% of the body. Striated muscles are characterized by alternating Light and dark bands called **Cross Striations**. Many of the same principle of contraction apply to all these different types of muscles.

Skeletal Muscle

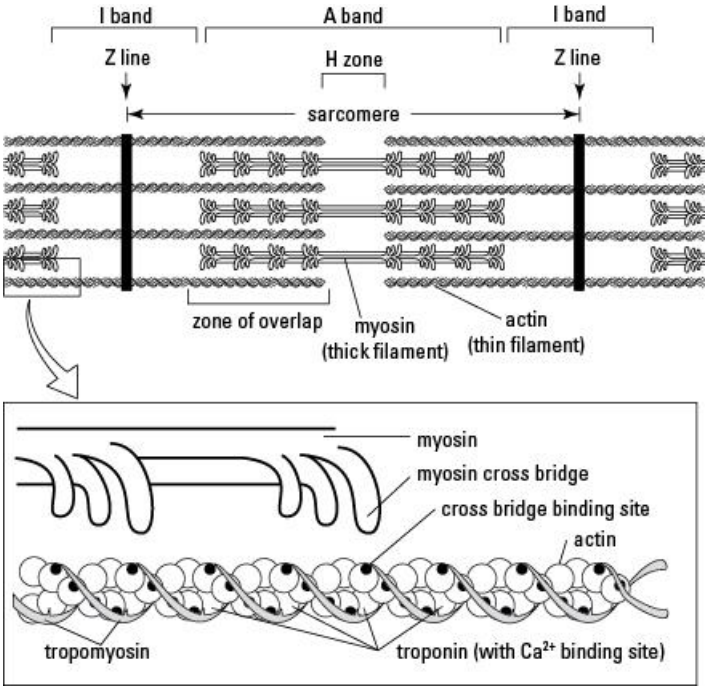


Fig. 1.33: Sjeletal muscle fiber

Skeletal muscle has numerous fibers or cells called myofibers which are about 10 – 18μm in diameter. It constitutes the building blocks of the muscular system and varies with the length of the muscle bundle. Most of them begin and end in tendons and the muscles fibers are arranged in parallel between the tendinous ends running from one end of the tendons to another. Most of the fibers are innervated by only one nerve ending, located near the middle of the fiber. Each fiber is a single cell, multinucleated, long and cylindrical in shape and there are on syncitial bridges between cells. The sarcolemma (cell membrane) bounds the muscle fibers.

Inside the fiber are found numerous myofibrils which make them up. They are cylindrical rods running from one end of the fiber to the other. The fibrils are divisible into individual myofilaments made up of contractile proteins. There are two types of filaments: thick filament (myosin) and thin filament (actin). They are both involved in the development of tension in muscles.

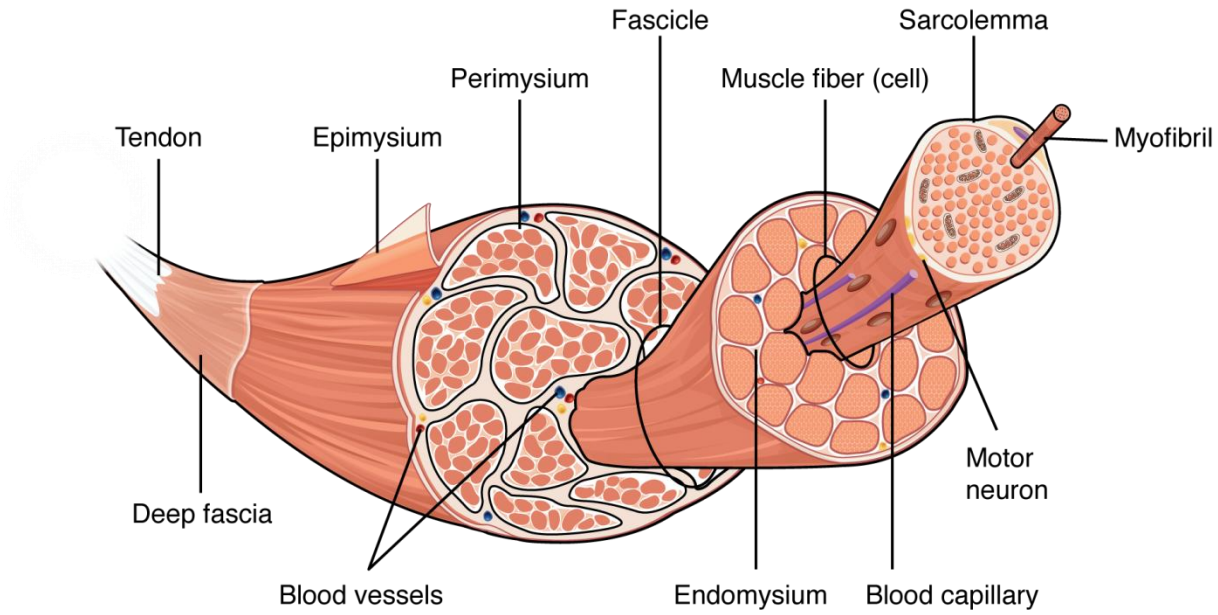


Fig. 1.34 Components of a skeletal muscle

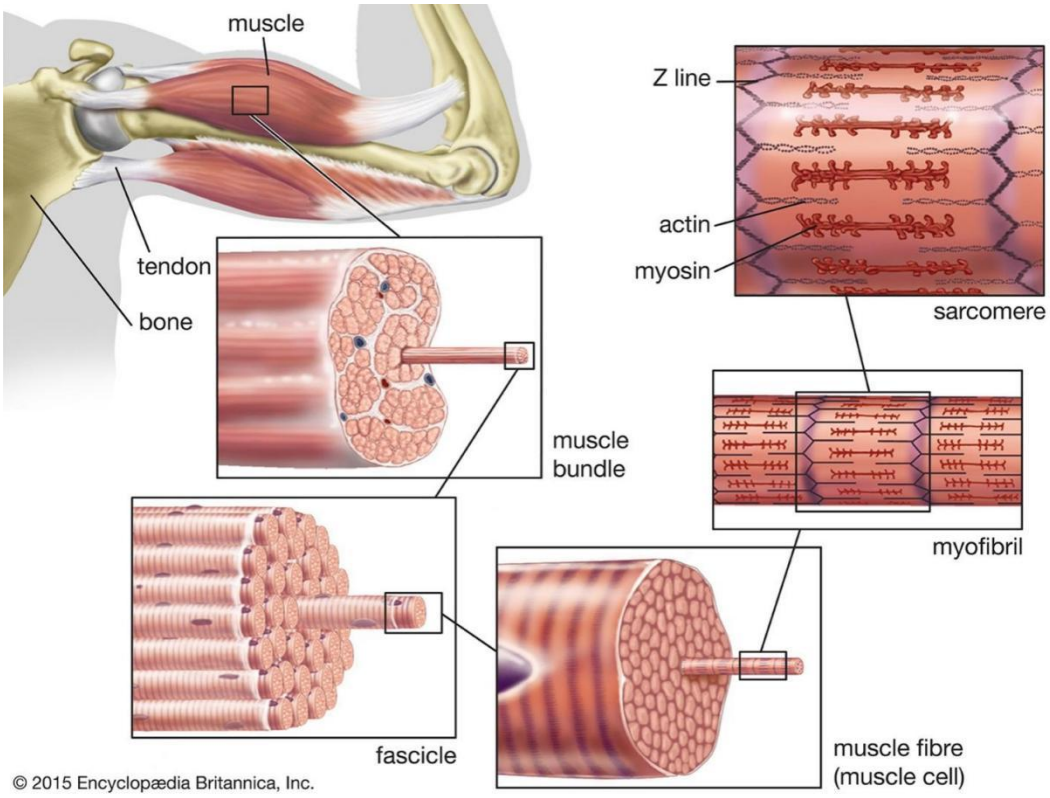


Fig. 1.35: Building blocks of skeletal muscle

Muscle Fiber Morphology

Skeletal muscle fiber is an elongated cell with several nuclei located on the periphery. Each cell contains many specialized endoplasmic tubes called sarcoplasmic reticulum (S.R) that surrounds the myofibrils. Each muscle fiber contains several hundred to several thousand myofibrils which in turn has lying side by-side about 1500 **myosin filaments (thick filament)** and 3000 **actin filaments (thin filament)** which are large polymerized proteins responsible for muscle contraction.

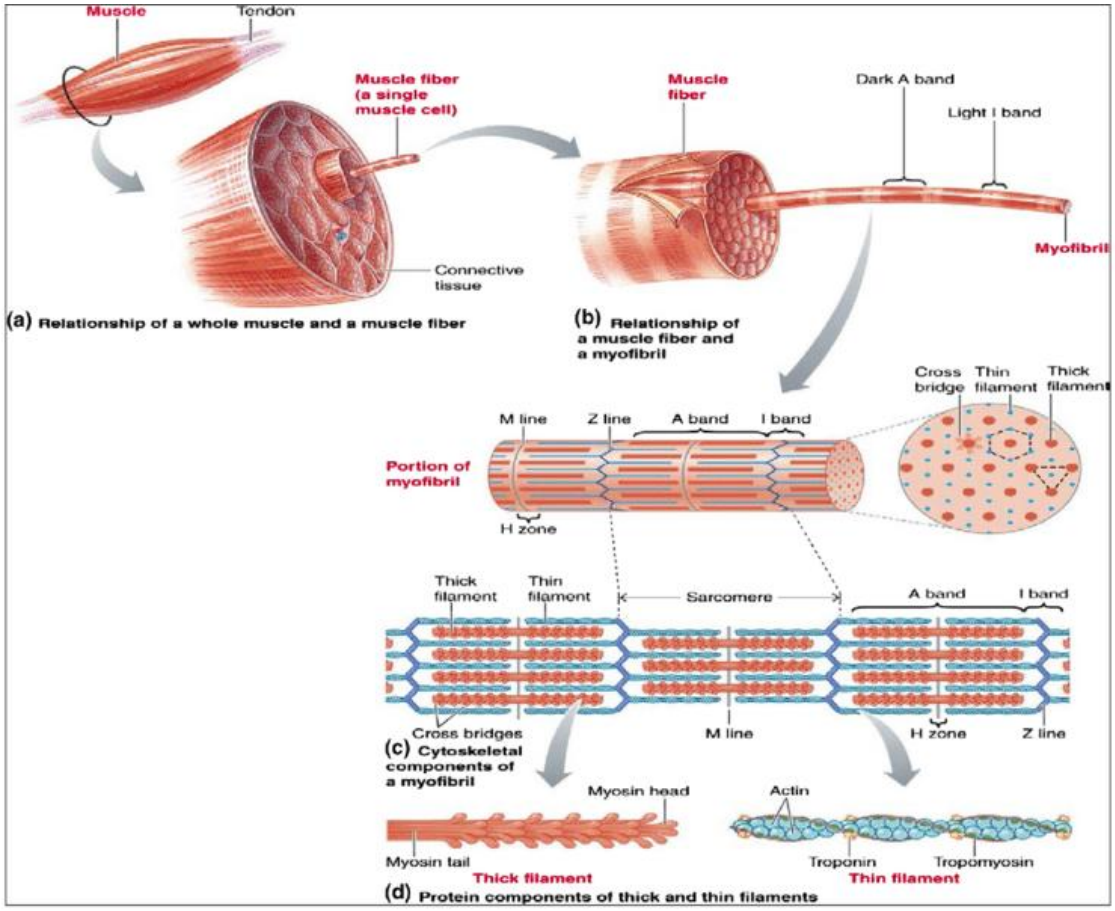


Fig. 1.36 Structure of a muscle fibril

Fig. 1. Structure of a sarcomere ???

Election microscopy reveals fine structure of the myofibril and the arrangement of its components, part of which is responsible for the cross striations. Cross section of the myofibril reveals that each thick filament is surrounded by six thin filaments to give a hexagonal arrangement. Myofibrils are made up of longitudinal segments called **sarcomeres** and these are the functional unit for muscle contraction.

The sarcomeres are made up of one A band and 2 units of ½ I bands at each end of the A band. In humans the length varies from 2- 2.6 μm. The myosin and actin filaments partially overlap (interdigitate) making the myofibrils to have alternate light and dark bands. The light bands contains only action filaments and are called **I bands** because they are mainly **isotropic** to polarized light. The dark bands contains only myosin filaments as well as the ends of the actin filaments where they overlap the myosin and are called **A bands** because they are **anisotropic** to polarized light.

There are small projections from the sides of the myosin filaments called **cross bridges** which project from the surfaces of the myosin filaments along the entire extent of the filament, except in the very centre. Interaction between the cross bridges and actin causes contraction. Z disc is the attachment of the actin filaments and they extend on either side of the z disc to interdigitate with the myosin filaments. The Z disc or band of each myofibril aligns with that of other myofibrils so that the entire fiber and indeed the entire muscle also show cross-striations.

The sarcomere is the portion of the myofibril (or of whole muscle fiber) that lies between two successive Z discs. The H zone is the light area in the middle of the A band. It rarely occurs in the normal functioning muscle but can occur when the muscle fiber is over stretched and hence the ends of the action filaments pull apart.

Myosin (thick filament)

It is about 15 nm wide and 1.6μm long. They are about 1500 in number in a muscle fiber. It is a fairly large protein with M.W 480,000, about 10 – 14 nm wide and 1.6 μm long. It is made up of 2 main subunits:

(a) **Heavy Mero Myosin** which is made up of two heavy chains, each with MW 200,000 which wraps spirally round each other to form a **double helix** with one end protruding to form two free heads. Also called the **heavy chain.**

(b) **Light Mero Myosin.** This is made up of four light chains, each with MW of 20,000. They also form part of the myosin head, two to each head. They are involved in controlling the functions of the head during muscle contraction.

There are two free heads in a myosin lying side by side, protruding from the end of the tail, while the tail section is coiled in the form of a double helix. The tails of the myosin molecules bundles together to form the **body** of the filament, while many heads of the molecules hang outwards to the side of the body. Also part of the helix portion of each myosin molecule extends to the side along with the head forming the **arm** that extends the head outward from the body. The protruding arms and head are called the **cross bridges**, each is flexible at two points called **hinges:**

(a) where the arm leaves the body of the myosin filament

(b) where the heads attach to the arms

The hinges allow the head to extend forward or backwards during contraction. The myosin head can function as ATPase enzyme.

The actin filament (thin filament)

It consists of two chains of globular protein or submits arranged in the form of a double helix. They are about 7nm wide and 1.0 μm long. It has polarity: an active positive end and an inert negative end. It is made up of three different components: F Actin (MW 42,000), made up of two G actins each (total of four G actins), Tropomyosin (MW 70,000) and Troponin. (13,000 – 120,000 depending on the type). The above 3 exists in a ratio of 7: 1 : 1.

Tropomyosin is a long thin rod which lies in the groove between the two double stranded F-actin chains (two α helical chains). Troponin is a globular protein which is located at intervals on the tropomyosin filament as it winds round the actin double helix. It has three subunits:

(a) **Troponin T** that binds the other Troponin components to tropomyosin. In a resting muscle it covers myosin binding site on actin.
(b) **Troponin I** which inhibits the interaction of myosin with actin. It also binds troponin complex to actin.
(c) **Troponin C** which contains the biding sites for Ca^{2+} that initiates contraction.

Other Proteins includes: Z disc, α actinin, titin, nebulin and dystrophin.

The bases of the actin filament are inserted strongly into the 'Z' discs, while the other ends protrude in both directions into the adjacent sarcomeres to lie in the spaces between the myosin molecules. Classification of skeletal muscle proteins are of three functional types:

(1) Contractile – myosin and actin
(2) Regulatory – troponin and tropomyosin
(3) Attachment – titin, nebulin, dystrophin

Excitation in muscles

The RMP is of the order of – 90mv. The A.P has a longer duration than nerve by 10 – 15ms (nerve 1 – 5ms). Refractory periods and Chronaxie lasts longer.

Muscle Contraction

Muscle contraction brings about movement. The basis for this movement is a biologic energy transformation called **Chemo-Mechanical Transduction**. In this process most of the body's metabolic production of ATP is converted into force or movement by muscle cells. Muscle contraction or force production takes place in 2 major forms:

1. **Isotonic contraction**. Here muscles shorten and work is usually done e.g. when lifting weight the biceps shortens but the tension is the same.
2. **Isometric contraction** – Here muscle does not change length and so no work is done. It generally includes maintenance of posture e.g. the quadriceps muscles and gastrocnemius muscle.

Sliding Filament Mechanism of Skeletal Muscle Contraction

This was popularized by Huxley in 1969 using cross bridge theory. Other theories includes the viscoelastic or new elastic body (1840), and continuous filament theory. Muscle contraction occurs when two sides of interdigitating thin actin filaments and thick myosin filaments slide past each other with the length of each set of filament remaining constant. This is called **sliding filament mechanism.**

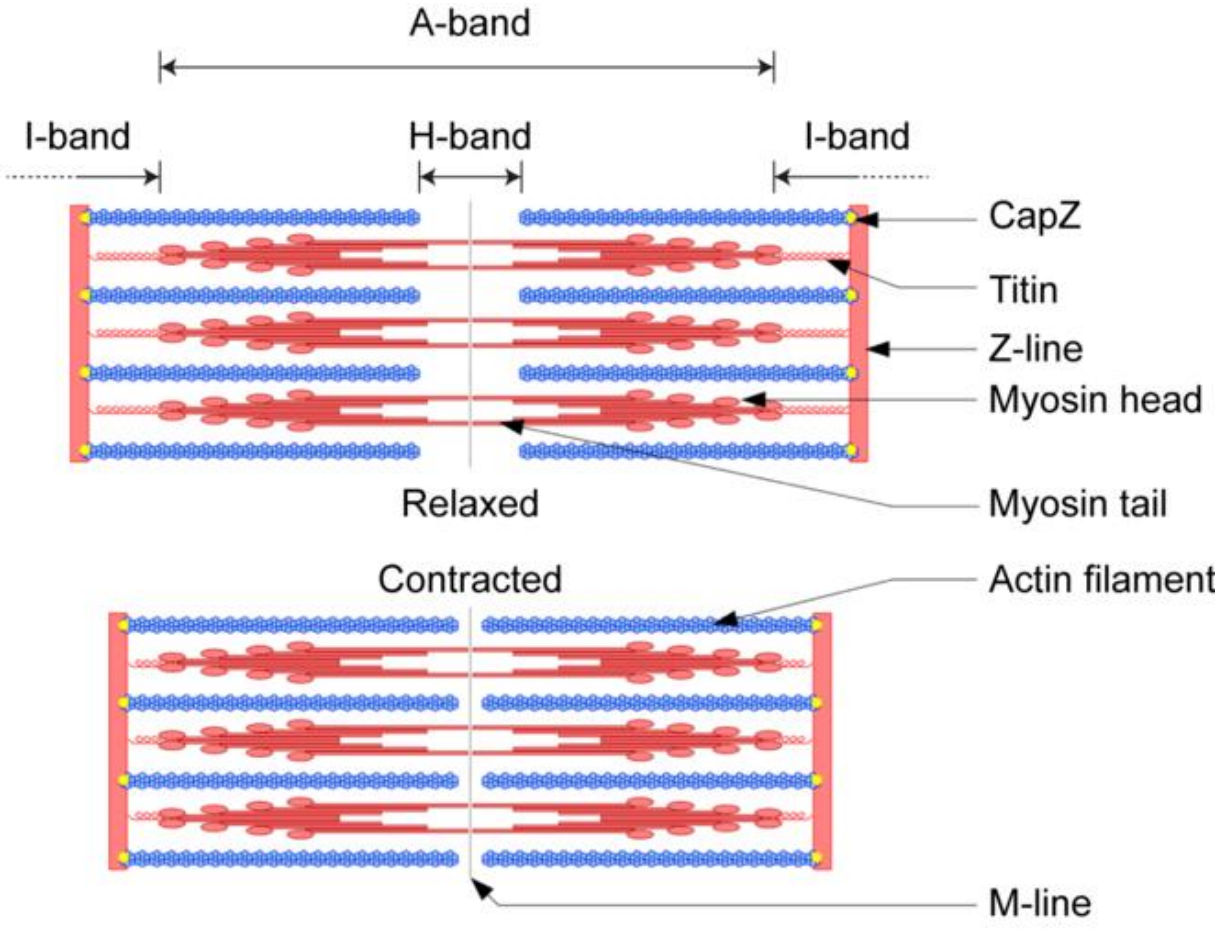


Fig. 1.37 Structure of the actin filament

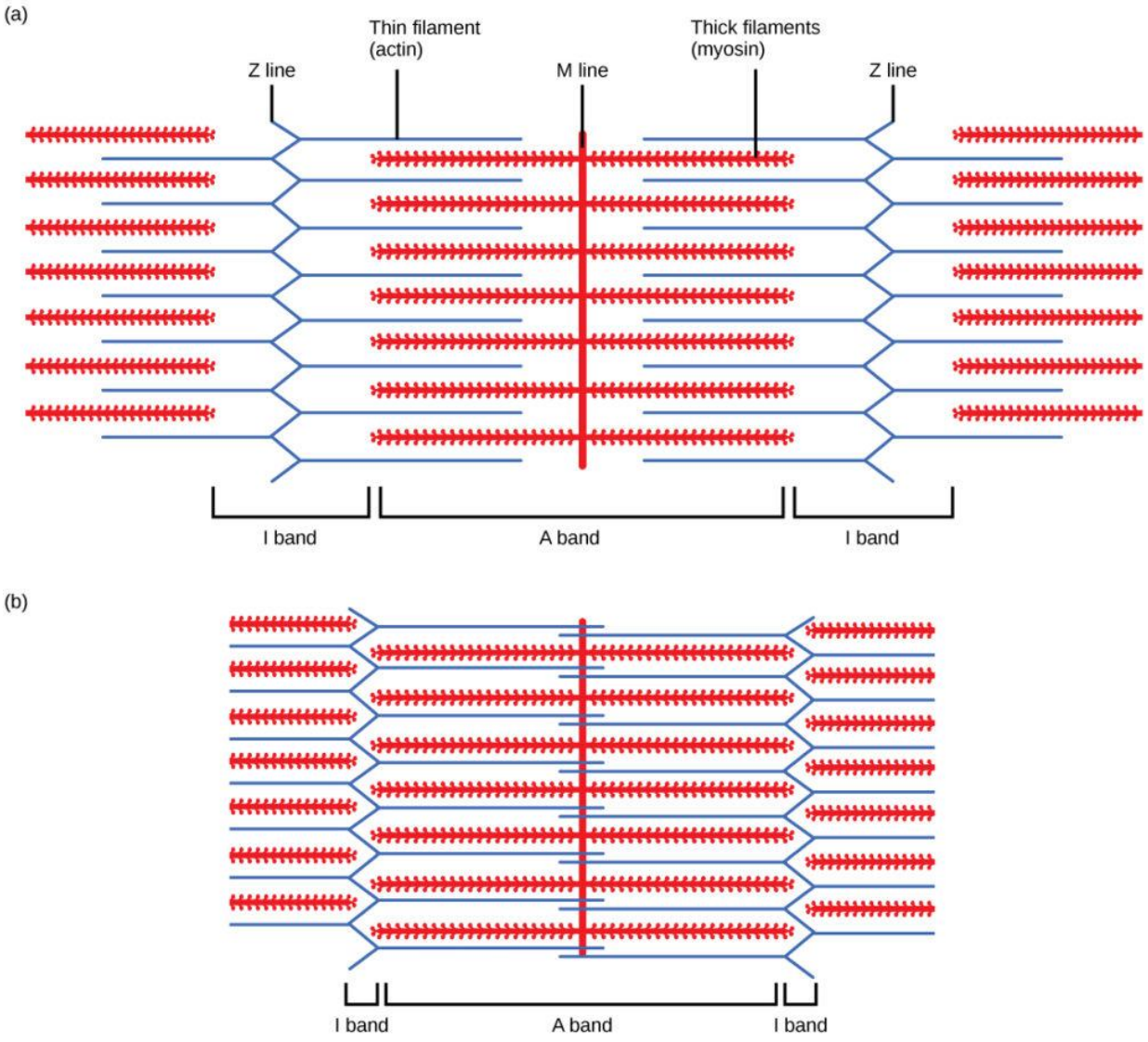


Fig. 1.38: Title ?????

According to the mechanism, when muscle shortens during contraction, A band remains constant in length while theI and H zones shortens.

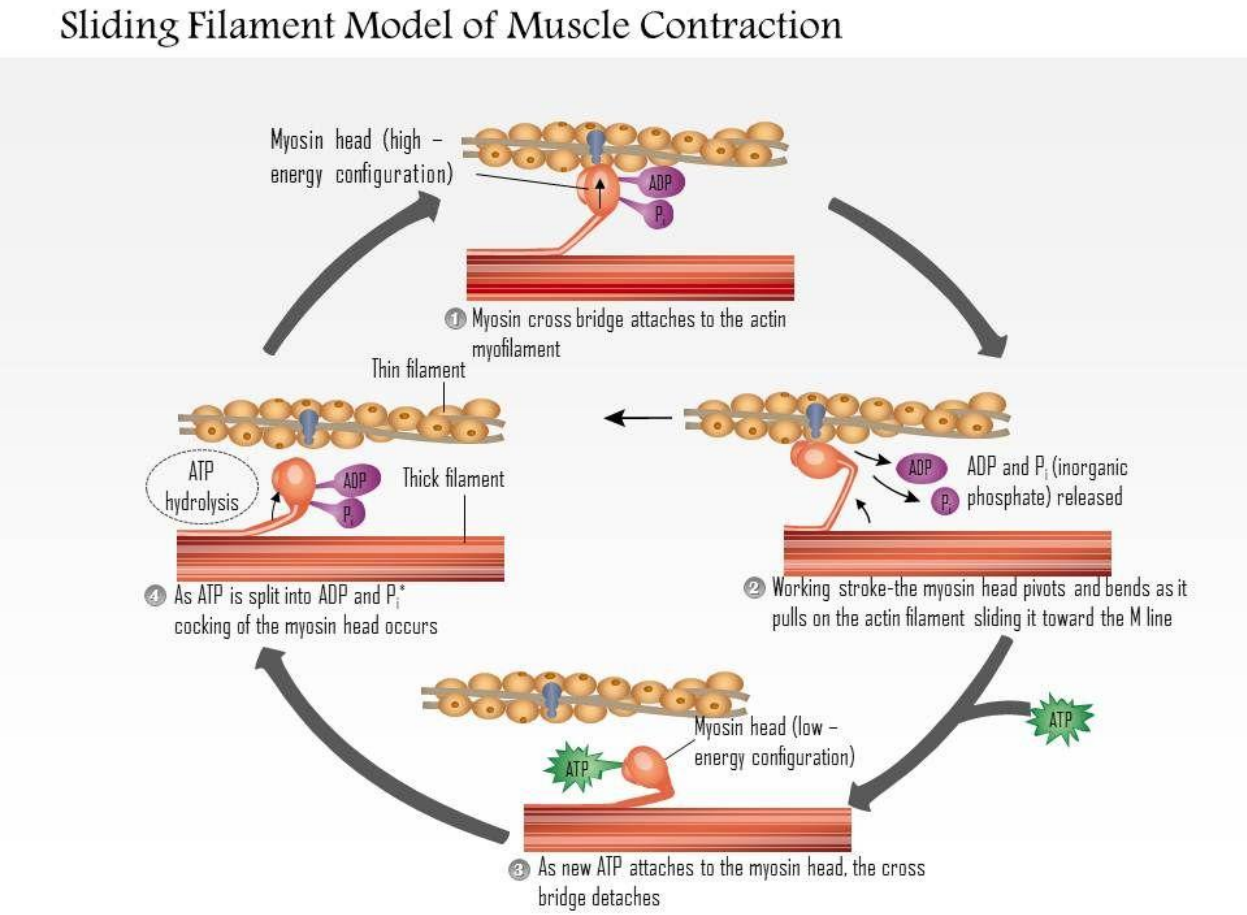


Fig. 1.39: Sliding filament model of contraction

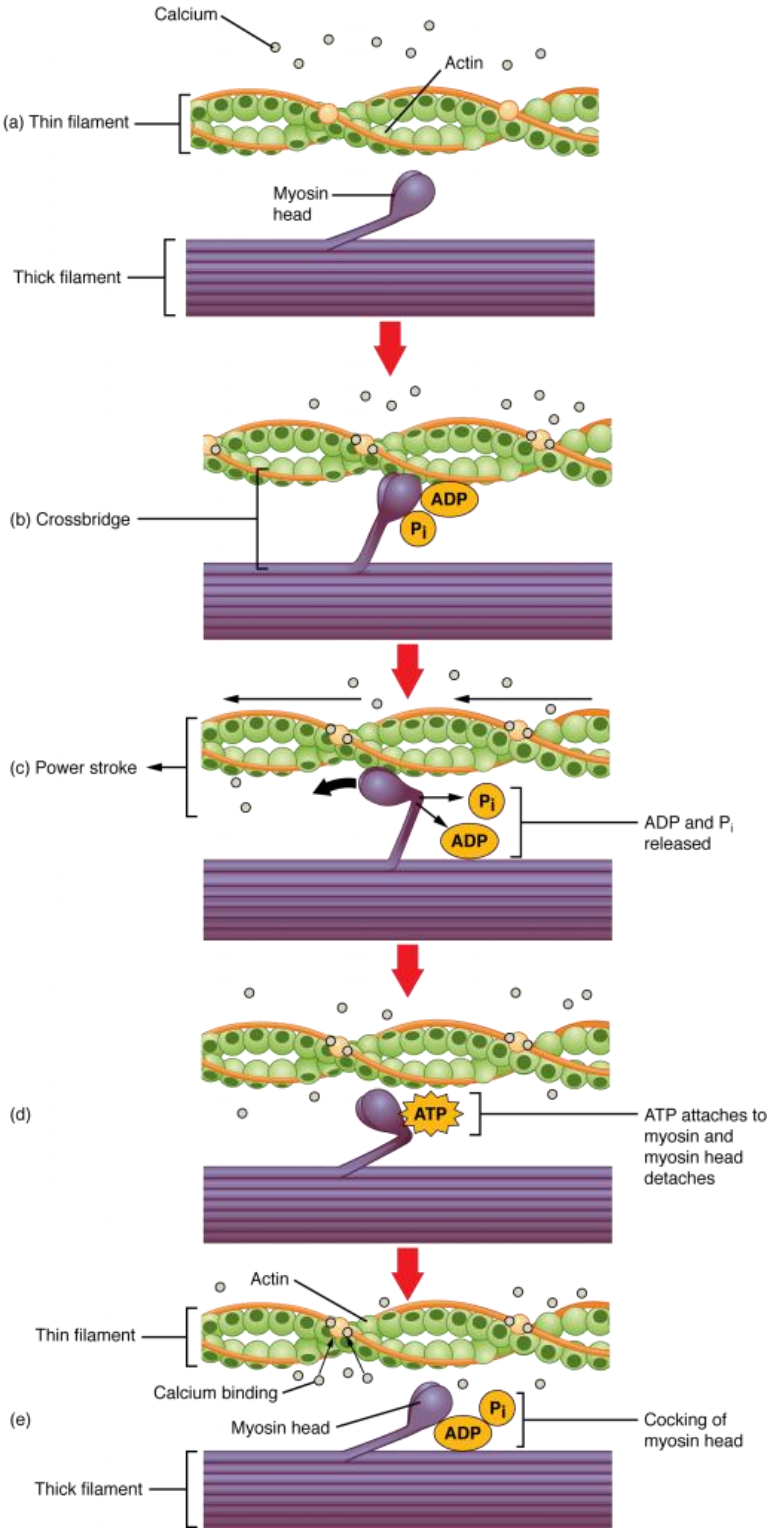


Fig. 1.40: Crossbridge Model of Contraction

Cross Bridge (Walk- Along) Theory of Muscle Contraction -

The widely accepted theory that explains this sliding filament mechanism process is the cross bridge theory of muscle contraction, also called **Ratchet's theory of muscle contraction**. The theory explains that the sliding process is driven by cross bridges which extend from the myosin filament and cyclically interact with active sites on the actin filament. ATP is hydrolyzed by ATPase enzyme during each cycle by every cross bridge. In relaxed muscles the cross bridges are in a high energy state and they extend from myosin filament at an angle of about 90^o. They lie close to but remain detached from the actin filament.

When a muscle becomes excited (arrival of muscle action potential), an ATP binding site located on the head of the crossbridge is exposed and a molecule of ATP binds and is broken down to provide the energy with which the cross bridges attaches to the active sites on the actin filament at an angle of 90^o and then is moved (rotates) to 45^o thereby pushing the actin filament towards the H zone. Once the crossbridge rotates, another ATP binding site on the head of the crossbridge is exposed and crossbridges now binds to a second ATP molecule immediately hydrolyzing it. This provides the energy with which the crossbridges detach from the actin filaments, are re-charged (brought back) to 90^o and the cross bridge is now ready for another cycle. Cycles of interaction and detachment are repeated hundreds of times per second.

In an isotonic contraction, each attachment at an active site takes place further along the actin filament while in isometric contraction, interaction occurs repeatedly at the same actin active site. The tilt of the head of the cross-bridge is called Power Stroke. Force generation at multiple sites in numerous cycles contributes to the total force produced by the muscle. Therefore total force produced is a function of the area of overlap between thick and thin filament. The cross bridge theory can be illustrated by the action of a paddle used for rowing canoe.

Energy for contraction

A total of two molecules of ATP are used for a complete contraction:

(1) Activation of crossbridge head, binding to the actin active site at 90^O and movement to 45^o.
(2) Disengagement from actin active site at 45^o and recharge to 90^o.

ATP is involved in all aspects of muscular activity. ATP splitting makes possible the cyclic activity of crossbridges during contractions. If ATP splitting is inhibited i.e. myosin ATPase is inactivated, the crossbridge cannot re-attach and the muscle relaxes. If the muscle is completely depleted of ATP, the crossbridge becomes permanently attached to actin in an abnormal rigid manner; this is known as Rigor and occurs after death as Rigor Mortis (Plasticizing effect of ATP).

Neuromuscular (N-M) transmission

The junction where a motor nerve terminates on a skeletal muscle in a vertebrate is called myoneural or neuromuscular junction or motor end plate. Neuromuscular transmission is similar in many respects to chemical transmission at neuron - neuron synapse. The following are however the following peculiarities of neuromuscular transmission:

(1)The depolarization of the muscle membrane (motor end plate) is called End Plate Potential (EPP). The EPP generated by arrival of an AP on one sole foot is usually several times greater than the threshold for generating muscle AP. There is therefore a safety factor so that in every case the muscle is excited, and temporal summation is unnecessary.

(2)There is no convergence at N-M junction since only one nerve branch terminates at the endplates therefore spatial summation cannot occur.

(3)In the absence of a nerve AP i.e. at rest some acetylcholine is spontaneously released. These give rise to tiny depolarization of about 1 to 2mv. These are known as **Miniature End Plate Potential (MEPP).** Thus the arrival of an AP simply causes release of large quanta of Ach as with neuron – neuron synapse. Ach release here is facilitated by Ca^{2+} but inhibited by $Mg^{+}$and Mn^{+}.

(4)The action of Ach on the muscle membrane receptors is quickly terminated by hydrolysis catalyzed by acetylcholinestarese (Achase).

Summary of Events Occurring During N-M Transmission

A.P in preganglionic motor neuron terminal

↓

Opening of Ca^{2+} channels and entry of Ca^{2+} into axonal terminal

↓

Release of Ach from synaptic vesicles into synaptic cleft

↓

Diffusion of Ach into post junctional membrane

↓

Combination of Ach with specific receptor proteins of post junctional membrane

↓

↑ in conductance of post junctional membrane to Na+ and K+ causes EPP

↓

Depolarization of muscle membrane adjacent to endplate initiates A.P

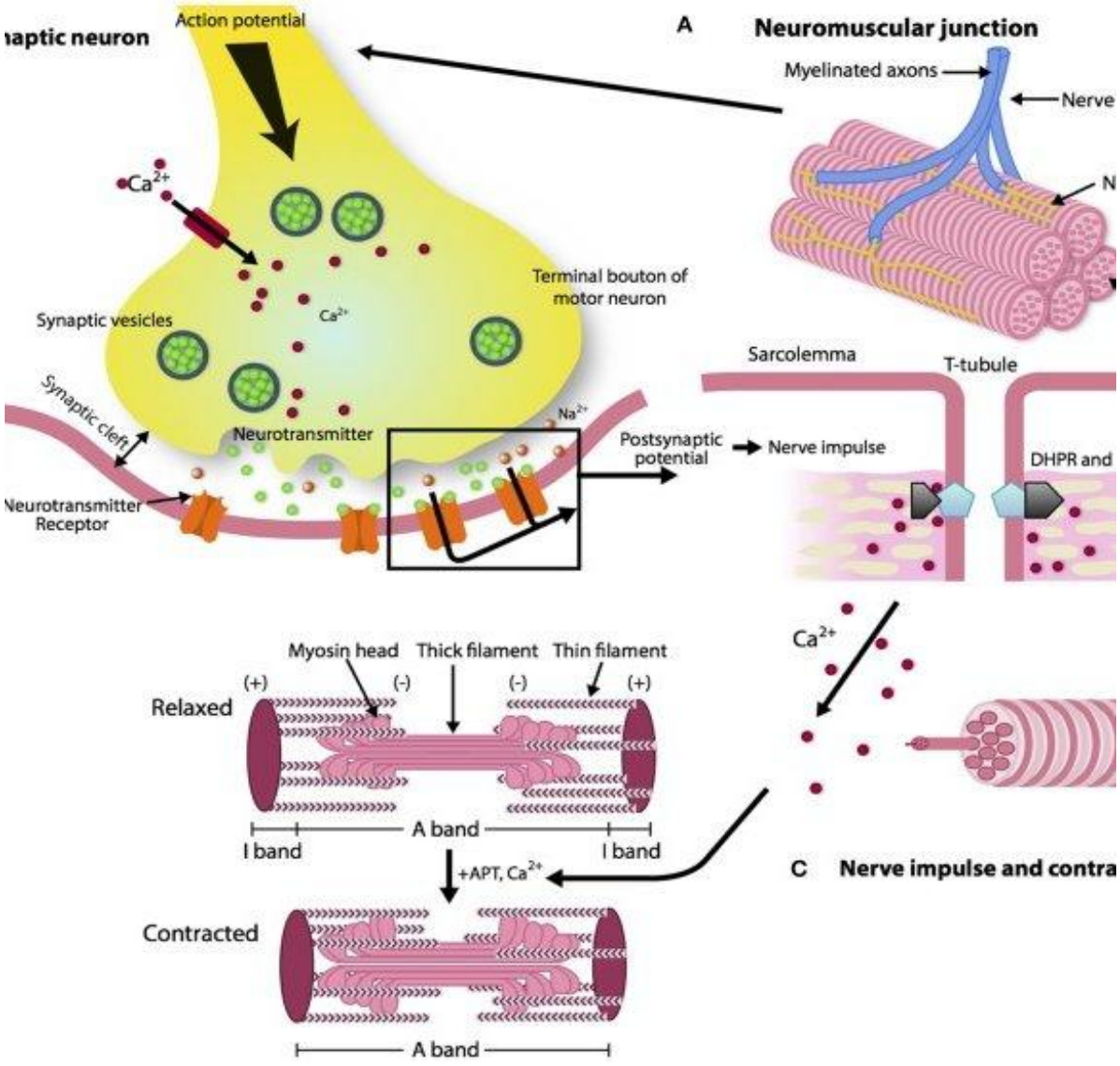


Figure 1.41: Title ????

Physiologic Mechanisms for Blocking Of Neuro- Muscular Transmission (NMT)

NMT may be blocked by interfering with any one of the several process involved:

A. Pre-synaptic block

(1) Blocking of acetylcholine release.

Factors that affects it :

(a) Low Ca^{2+} in ECF
(b) High mg^{+} in ECF
(c) High mn^{+} in ECF
(d) Botulinus toxin

(e) Antibiotics e.g. gentamicin
(f) Tetanus and botulinus toxins (found in spoiled foods) causes' respiratory muscle paralyses.
(g) β – bungarotoxin

(2) By inhibiting syntheses of acetylcholine e.g. using the drug hemicholinium

B. Post synaptic block

(1) By irreversible binding of substance to acetylcholine receptors e.g. using some substance from snake venom- ∝ bungarotoxin and ∝ cobrotoxin (from the venom of the cobra, formosa krait).

(2) Competitive binding to Ach receptions

These substances are not destroyed by acetylcholinestarese

(Achase) so they occupy the receptor site more permanently

than does Ach e.g. tubocurare (curare) a skeletal muscle

relaxant.

(3) By mimicking Ach, these substance or drugs behave like Ach but not hydrolyzed by Achase. They therefore cause prolonged depolarization leading to paralysis e.g. nicotine, decamethonium
(4) By inhibition of Achase by anticholinesterase they also cause prolonged depolarization e.g. neostigmine (causes muscle spasm).
(5) Also hypothermia (temperatures > 30 – 32^{o}C)

Myasthenia Gravis

This is a disease which illustrates the neuromuscular block. It is also called **Goldflam or Hoppe's** disease. This is a disease in which the neuromuscular transmission is chronically disturbed. It is characterized by:

(1)chronic progressive muscle weakness which usually begins in the face and throat and can lead to paralysis especially of the respiratory muscles leading to death.

(2)abnormal fatigability

(3)increase width of the synaptic cleft and decrease number of sole foot and palisades.

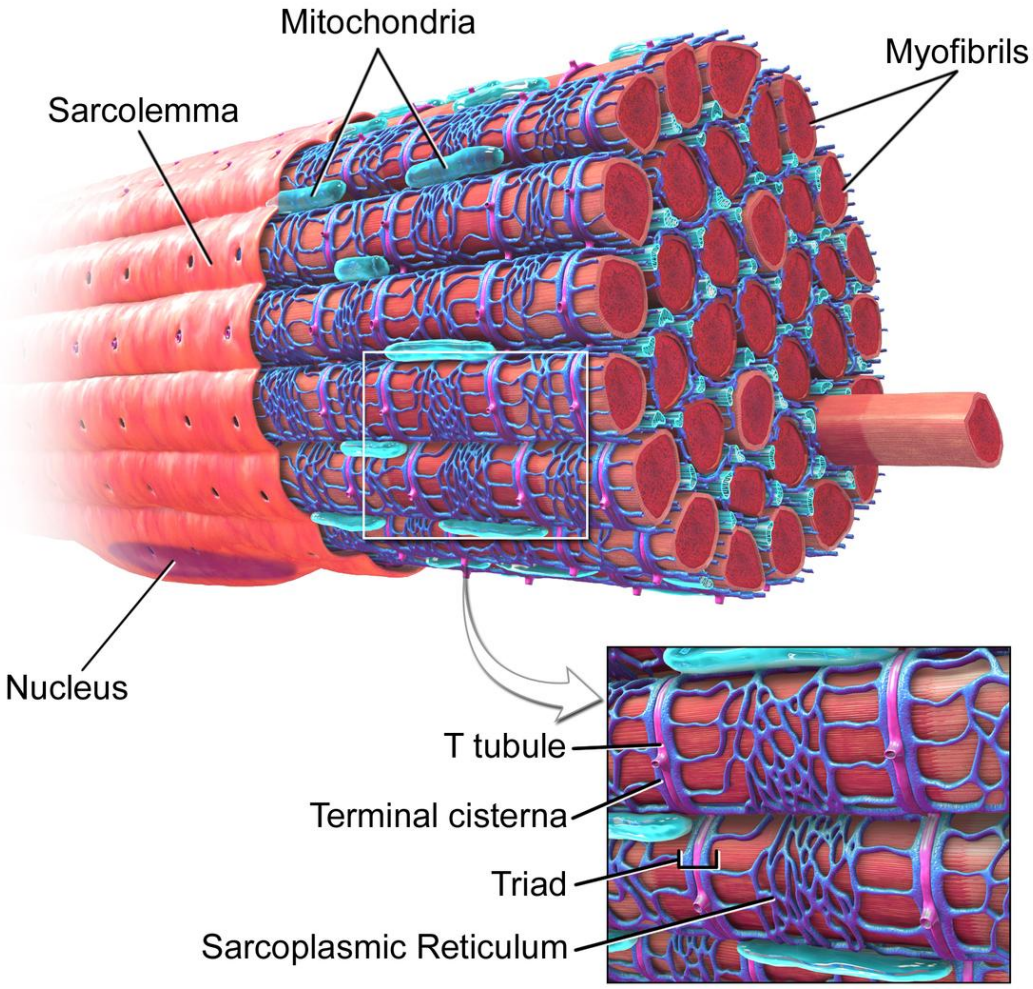
It is recently found to be due to an auto-immune response (where the antibodies do not recognize their antigens). There is no known treatment but the condition may be relieved with anticholinesterase such as neostigmine. Also thymectomy, steroids and plasma exchange are used to treat this condition. The basic problem is the retardation of ACH synthesis in the pre-synaptic neuron so that when the synapse is activated repeatedly, progressively less transmitter subs is released and N.M transport is eventually blocked. It is typical of these patients that their NMT is good in the morning and deteriorates during the day (an early symptom is drooping eyelids).

THE REGULATION OF MUSCULAR CONTRACTION

This explains how the contraction of a muscle is switched on and off i.e regulated. This involves the mechanism of excitation- contraction coupling (E-C. Coupling).

Excitation- Contraction Coupling (E. C. Coupling)

Muscular contraction is regulated by a process known as excitation- contraction (E – C) coupling.



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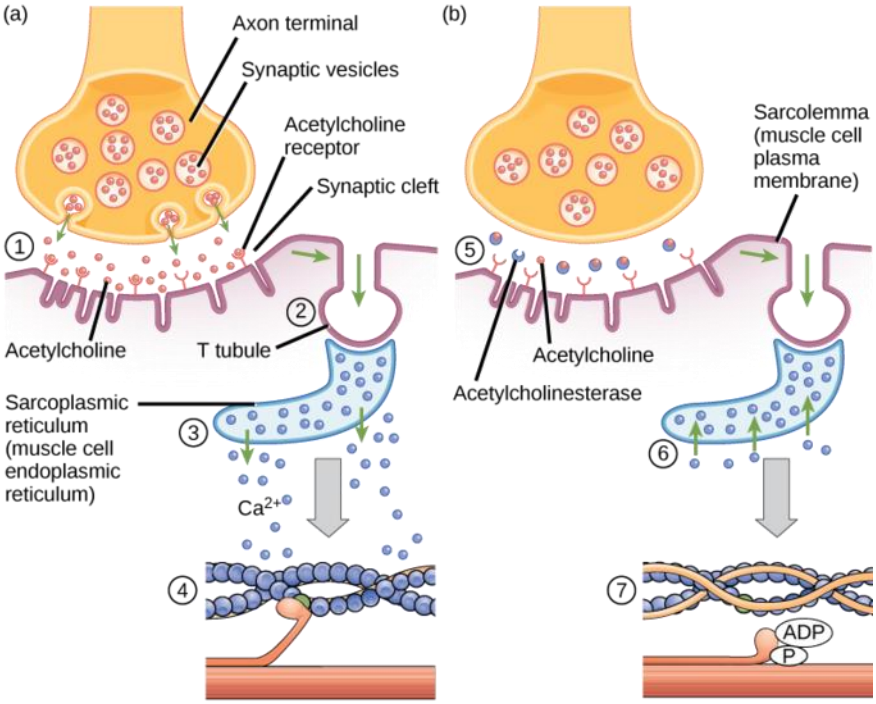


1. Acetylcholine released from the axon terminal binds to receptors on the sarcolemma.
2. An action potential is generated and travels down the T tubule.
3. Ca^{2+} is released from the sarcoplasmic reticulum in response to the change in voltage.
4. Ca^{2+} binds troponin; Cross-bridges form between actin and myosin.
5. Acetylcholinesterase removes acetylcholine from the synaptic cleft.
6. Ca^{2+} is transported back into the sarcoplasmic reticulum.
7. Tropomyosin binds active sites on actin causing the cross-bridge to detach.

Fig. 1.43 Title ???

A muscle AP travel along the sarcolemma continues down the membrane of the Terminal (T) tubule**.** The T tubule is surrounded by two enlarged ends of the longitudinal sarcoplasmic reticulum (S.R) called terminal cisternae (TC). The structure formed by T tubule and TC is called TRIAD**.**

When an AP arrives in the region of triad and the membrane of T.C is depolarized, that membrane becomes more permeable to Ca^{2+}. Ca^{2+} are stored in the T.C and with increased permeability they diffuse out of the T.C.

into the sarcoplasm (cytoplasm of muscle). At rest the level of Ca^{2+} in the sarcoplasm is low about 10^{-7} molar or 10^{-8} molar. With the arrival of the AP, the Ca^{2+} level in the sarcoplasm rises and when it reaches a level of 2×10^{-5} molar, Ca^{2+} binds to one sub unit of troponin C. This reaction causes a conformational change in the tropomyosin such that troponin I is displaced from its resting position on the action filament. By this movement, the actin active site which previously was covered by troponin I become uncovered. Thus the inhibition of actin and myosin is removed and the muscle is now switched on. Myosin interacts with actin and force productions of the cross bridge can now occur. Immediately after, if no other AP comes along, Ca^{2+} is actively pumped out of the sarcoplasm and back into the tissue and Ca^{2+} level falls back to the resting value. Tropomyosin and troponin return to their resting position and the muscle relaxes. The pumping of Ca^{2+} into the tissue consumes energy in the form of ATP. This entire process by which troponin inhibition which normally prevents actin - myosin interaction is removed is known as excitation contraction (EC) coupling (link). In addition to removing troponin-tropomyosin inhibition Ca^{2+} performs another function: it activates myosin ATPase. Calcium is known as the agent of E.C. coupling.

Sequence of Events In Contraction And Relaxation Of Skeletal Muscles

Steps in contraction

1. Discharge of motor neuron
2. Release of neurotransmitter (ACH) at motor end plate
3. Generation of end plate potential
4. Generation of AP in muscle fibers.
5. Inward spread of depolarization along T tubules.
6. Release of Ca^{2+} from lateral sacs of sarcoplasmic reticulum and diffusion to thick and thin filaments.
7. Binding of Ca^{2+} to troponin C, uncovering myosin binding sites on action.
8. Formation of cross-linkages between actin and myosin and sliding of thin on thick filaments, producing shortening.

Steps in relaxation

1. Ca^{2+} is pumped back into sarcoplasmic reticulum.
2. Release of Ca^{2+} from troponin.
3. Cessation of interaction between actin and myosin.

FUNCTIONAL ADAPTATION OF SKELETAL MUSCLES

(FAST AND SLOW TWITCH MUSCLES)

Although the basic properties of all skeletal muscles as already discussed are generally similar, there are certain differences related to function of difference muscle types. Based on these differences skeletal muscle fibers are classified into 2 main types:

1. **Fast twitch fibers (white muscles)**
2. **Slow twitch fibers (red muscles)**

In humans every muscle contains some of each type but one fiber type pre-dominates in each muscle.

GENERAL APPEARANCE

Slow twitch fibers have smaller diameter than fast twitch fibers. They are commonly reddish in colour. This is due to an abundance of myoglobin and high degree of vascularization. Fast twitch are the opposite i.e. larger and pale.

ELECTRICAL – PROPERTIES

In fast twitch fibers the muscle A.P is shorter and propagates faster than a slow twitch fiber. The motor end plates differ in their sensitivity to neuromuscular blockers. The end plate in fast twitch muscle is more sensitive to competitive blockers e.g. tubocurarine and lens sensitive to depolarizing blockers e.g. decamethonium. However the respiratory muscles diaphragm may not have the same sensitivity for neuromuscular blockers with other muscles.

MECHANICAL PROPERTIES

Slow twitch fibers contract more slowly than fast twitch fibers e.g. the time from onset to the peak of isometric twitch is about a 120ml sec in the slow twitch muscle such as the soleus muscle but only about 50 – 60 ml sec in the fast twitch muscle in the hand of foot. Relaxation time is also shorter in fast twitch. This is because fast twitch fibers have more SR and therefore can sequester (pump back) Ca^{2+} faster. Fast twitch muscles generates more power but it is less efficient in doing work or maintaining tension.

The mechanical response of the two muscle types are affected differently by a number of factors:

1. **Temperature factor**: increased temperature decreases the height of contraction in fast twitch fibers.
2. **Response to adrenalin**: physiological levels of adrenalin depress slow twitch fiber but potentiate fast twitch fiber. The concentration required to have an effect on fast twitch muscle is about 5 X higher.
3. **Post tetanic potentiation**: following a tetany the twitch amplitude is potentiated.
4. **Metabolism**: slow twitch muscle has a greater concentration of lipids and oxidative enzymes whereas fast twitch muscle has a greater concentration of glycogen and glycolytic enzymes. Consequently fast twitch muscles fatigue faster. In addition slow twitch muscle has greater capillary density and higher resting blood flow than fast muscle.
   Because of all this, slow twitch muscle are adapted for prolonged activity (postural) **actonic- isometric (long bursts)** while fast twitch muscle are adapted for short bursts of activity **acphasic- isotonic (short bursts)**.

CARDIAC MUSCLE

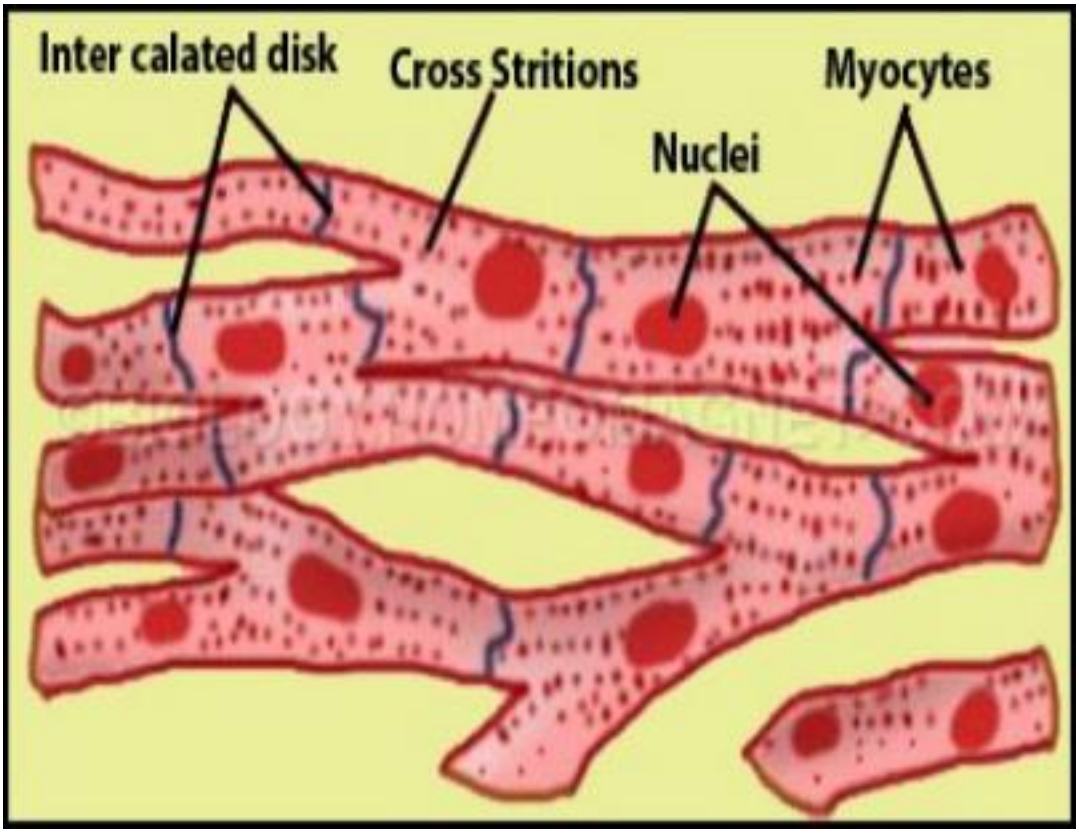


Fig. 1.44: Title ????

The normal muscles of the heart called the functional myocardium are similar in structure to skeletal muscle by also having cross striations. They have the same arrangement of contractile proteins and mechanism of contraction. However in cardiac muscle the individual fibers are in close contact with one another to form a sheath of branched processes. At the junction between the ends of two adjoining fibers the membranes are folded and very close together forming an intercalated disc. The fibers also make contact along their membranes that form tight junctions. These two junctions are areas of low electrical resistance across which impulses move unhindered. Cardiac muscle is therefore said to be a functional syncytium.

SIMILARITIES AND DIFFERENCES BETWEEN CARDIAC AND SKELETAL MUSCLES

(1) STRUCTURE

Both have the same arrangement of contractile and the same contraction mechanism. Both are striated, cardiac muscle has one centrally placed nucleus per cell while skeletal muscle has several peripherally located nuclei per cell. Cardiac muscle has modified cell membrane called functional syncytium

(2) Cardiac muscle obeys **All or None Law** strictly while in skeletal muscle there is first spatial summation

(3) Some fibers within the heart are specially modified for automatic excitation (**Pace maker cells**) and for rapid conduction (**Purkinje bundle fires**).

(4) The AP of skeletal muscle is very brief while that of cardiac muscle is extremely long and displays a plateau. Because the AP in cardiac muscle is very long, the Absolute Refractory Period (ARP) is also very long. Due to this long ARP temporal summation is not possible in cardiac muscle and so it is not possible to have Tetanus. This is a safety factor of the heart because tetanus will interfere with the rhythmic contraction and relaxation of the heart which pumps blood through the body.

(5)E-C Coupling in cardiac muscle

Long tubules of the SR are poorly developed so that calcium store is inadequate for repeated contraction. For E-C Coupling, the AP in cardiac muscle mobilizes some Ca^{2+} from the calcium stores in the ECF. Unlike skeletal muscle, cardiac muscle does not show fatigue easily. It is well adapted for aerobic energy metabolism by having abundant blood supply, high concentration of mitochondria and myoglobin and ability to metabolize lactate. Consequently cardiac muscle does not incur an O_2debt.

(6) Cardiac muscle is sensitive to the direct action of chemical agents and drugs e.g. NA, Ach.

(7) Cardiac muscle is innervated by autonomic nervous system (ANS) (both facilitatory and inhibitory) while skeletal is innervated by somatic nervous system (SNS) (only facilitatory).

(8) Cardiac muscle is similar to skeletal muscle in the stair case effect.

(9) Length – tension relationship also applies to cardiac muscle.

(10) Some modified cells in the heart are capable of generating rhythmic or spontaneous impulses. This is responsible for intrinsic rhythmicity of the heart.

SMOOTH MUSCLE

It differs from both skeletal and cardiac muscles structurally in that cross striations are absent. Contractile filaments are present but not arranged in an orderly fashion seen in striated muscle. The SR is poorly developed and E-C Coupling is a very slow process thus contraction and relaxations are very slow. The regulatory proteins which participate in E- C Coupling are different. Smooth muscle is divisible into 2 main types:

A. Visceral smooth muscles (single unit)
B. Multi unit

(A) Visceral smooth muscle is found in the walls of internal hollow organs such as the bladder, uterus, and gastrointestinal tract. The muscle fibers are arranged in sheaths with modified cell membrane and function as a syncytium. Visceral smooth muscle undergoes 2 types of contraction:

(i) Tonus – prolonged sustained partial state of contraction. This consumes little energy and hardly ever shows fatigue. It usually occurs spontaneously without external nervous stimulation. Therefore we say it is a myogenic type of contraction. It is a form of rhythmic contraction but differs from that of cardiac muscle in that there is no fixed pace maker (location of origin of impulses). Cell depolarization of smooth muscles is due to low (-50 – -55mv) and an unstable RMP.

(ii) Vigorous contraction - these are superimposed on the basal

tonic contraction e.g. peristalsis of the gut.

Other Properties of Visceral Smooth Muscles.

1. They extend very easily and respond to stretch by contraction. Mechanical stimulus is important in the function of smooth muscles.
2. They are innervated by A.N.S which is both facilitating and inhibitory.
3. They have very low critical frequency.
4. Their contractions and relaxation are very slow.
5. They consume very little energy for contraction.
6. They respond readily to the direct action of drugs and chemical substances e.g. many smooth muscles are inhibited by AD and NA and facilitated by ACH.
7. Uterine smooth muscle is affected by hormones such as oestrogen, progesterone etc.
8. Visceral smooth muscle exhibits plasticity**.** When stretched, the resting tension produced at a given length is not constant rather it drops with time. Thus in hollow organs their volume can increase without the expected increase in their wall tension and internal pressure. The phenomenon is known by various names including receptive relaxation, stress, relaxation and it occurs in the bladder, blood vessels and stomach etc.

(B)Multi-Unit. These are smooth muscles found in the Iris of the eye and the walls of large blood vessels. Unlike visceral smooth muscle this type occurs as individual cells with no syncitial function. Their contraction though involuntary is neurogenic rather than myogenic. The multi-unit smooth muscle is also responsive to the direct action of chemical agents and drugs.

FUNCTIONAL ORGANIZATION OF THE AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system is divided into two functional systems: sympathetic nervous system and parasympathetic nervous system. The sympathetic system is associated with the fight-or-flight response, the parasympathetic system is associated with the rest and digest response.

Functional anatomy of the Sympathetic nervous system

The sympathetic nervous system is also called the thoracolumbar outflow because the preganglionic neurons are located in the intermediolateral horn of the spinal cord from level T-1 to L-2. It supplies the smooth muscles of all visceral organs of the body such as blood vessels, heart, lungs, glands, etc.

The sympathetic system has three groups of ganglia:

i. Paravertebral or sympathetic chain ganglia
ii. Prevertebral or Collateral ganglia and
iii. Terminal or peripheral ganglia

Paravertebral or Sympathetic chain ganglia

The sympathetic chain ganglia are arranged on the anterolateral surface of the vertebral column and they form majority of ganglia of the sympathetic system. There are 23 ganglia in the chain on either side of the spinal column. The cervical region has 3, thoracic region has 12, lumbar region has 4, and sacral region has 4.

Cervical ganglia has 8 ganglia arranged in three groups

a. Superior cervical ganglia
This is formed by fusion of the upper 4 cervical ganglia, it is the largest ganglia in the ANS, receives preganglionic fibres from T-1 via the white rami. Their postganglionic fibres supply blood vessels, glands, etc. Also supplies the heart via the superior sympathetic nerve and cardiac plexus.

b. **Middle cervical ganglia**: formed by the 5th and 6th cervical ganglia, its preganglionic fibres begin from T-1, its postganglionic fibres supply sweat glands, thyroid glands and parathyroid glands. It also supplies the heart via the middle sympathetic nerve and cardiac plexus.
c. **Inferior cervical ganglia**: formed by fusion of 7th and 8th cervical ganglia, its preganglionic fibres also arise from T-1, postganglionic fibres supply the heart via the inferior cervical sympathetic nerve and cardiac plexus.
Thoracic ganglia

There are 12 thoracic ganglia and all are evenly spaced. The preganglionic fibres arise from the thoracic segments of the spinal cord. The postganglionic fibres supply the visceral organs in the thorax and abdomen.

Lumbar ganglia

The lumbar region has 5 ganglia. Their preganglionic fibres arise from L-1 to L-2 of the lumbar segments of the spinal cord, reach the lumbar ganglia and extend to sacral ganglia. Their postganglionic fibres supply the abdomen and pelvic organs.

Sacral ganglia

The sacral region has 5 ganglia, they receive preganglionic fibres from L-1 and L-2 segments. Their postganglionic fibres supply the blood vessels and sweat glands in the lower limbs.

B. Prevertebral or Collateral Ganglia.
Colleral or Prevertebral ganglia are located in the thorax, abdomen, pelvis and are situated anterior to the vertebral column and receive inputs from splanchnic nerves as well as central sympathetic neurones. The three collateral ganglia are the celiac ganglion, superior mesenteric ganglion and inferior mesenteric ganglion. They control organs in the abdominal cavity and are also considered part of the enteric nervous system.

C. Terminal or Peripheral ganglia
The terminal ganglia are usually located within or close to structures innervated by them. The supply the heart, bronchi, pancreas and urinary bladder.

Functional Anatomy of the Parasympathetic Division

This division of the autonomic nervous system is named because its central neurons are situated on either side of the thoracolumbar region of the spinal cord. (para-=" beside" or "near"). The parasympathetic system is also called **craniosacral system or outflow** because the preganglionic fibres are located in nuclei of the brainstem and the lateral horn of sacral spinal cord.

The preganglionic neurons from the cranial region travel in cranial nerves, whereas preganglionic fibres from the sacral region travel in spinal nerves. The terminal ganglia are the targets of these fibres and are located near—or even within—the target effector.

Their postganglionic fibres projects from the terminal ganglia a short distance to the target effector, or to the specific target tissue within the organ. Comparatively, the preganglionic fibres are long and the postganglionic fibres are short because the ganglia are close to—and sometimes within—the target effectors.

The cranial part of the system in the brain stem innervates the blood vessels of the head, neck, and many thoracoabdominal visceral organs. The sacral part innervates smooth muscles in the walls of viscera and glands such as large intestine, liver, spleen, kidneys, bladder, genitalia, etc.

The cranial nerves transmitting preganglionic parasympathetic neurons are cranial nerve 111(oculomotor), VII (facial), IX (glossopharyngeal) and X(Vagus). The sacral outflow arises from the 2nd to the 4th (S-2 -S-4). The preganglionic fibres of the parasympathetic division arise from fibres located at three different levels:

a. Tectal or midbrain level (111 cranial nerve)
b. Bulbar level or bulbar outflow (VII, IX, and X cranial nerves)
c. Sacral outflow.

1. Tectal or Midbrain level

The tectal fibres arise from the group of nuclei forming the Edinger-Westphal nucleus of the 111 cranial nerve and they terminate in the ciliary ganglion. Their postganglionic fibres supply the sphincter papillae and ciliary muscles and help to control pupillary size.

2. Bulbar level or Bulbar outflow

These are the preganglionic fibres of cranial nerves VII, IX, and X and they arise from the following nuclei: superior salivary nucleus for the VII, inferior salivary nucleus for the IX and the dorsal motor nucleus for the X in the medulla oblongata.

The neurons of the VII cranial nerve supply the lacrimal, nasal submaxillary and sublingual glands. The preganglionic fibres terminate in the sphenopalatine ganglion and submaxillary ganglion. The postganglionic fibres from the sphenopalatine ganglion supply the lacrimal and nasal glands while the postganglionic fibres from the submaxillary ganglion, supply the sublingual and submaxillary glands.

The preganglionic fibres of the IX cranial nerve synapse with neurons of the Optic ganglion and the postganglionic fibres from the Optic ganglion, supply the parotid gland.

The X cranial nerve fibres supply most of the visceral organs in the body. About 75 per cent of all parasympathetic nerve fibres are in the Vigus nerve, passing on to the entire thoracic and abdominal regions of the body. The preganglionic fibres terminate in the ganglia, usually located on or close to the organs. The postganglionic neurons from the ganglia supply various organs such as heart, lungs, oesophagus, entire small intestine, proximal half of the colon, liver, gall bladder, kidneys, etc. However, Vagus nerves do not supply the pelvic organs.

3. Sacral outflow

The preganglionic fibres from the sacral components of the parasympathetic outflow arise from the anterior horn cells of the S-2 to S-4, sometimes from the first also, of the spinal cord. They form pelvic nerves (nervi erigens). Their postganglionic fibres supply the descending colon, rectum, and bladder, and the lower portions of the ureters and external genitalia.

Comparism of Sympathetic and Parasympathetic Systems

The sympathetic and parasympathetic divisions have clear anatomical and functional differences. This is summarized in Fig….

Features	Sympathetic system	Parasympathetic system
Location of preganglionic neuron	Thoracolumbar segments of spinal cord, T-1to L-2	Nuclei of III, VII, IX, and X cranial nerves and S1 to S4 segments of spinal cord
Location of postganglionic neuron	Ganglia located in the paravertebral sympathetic ganglion chain or collateral ganglia, away from target organ	Terminal ganglia located near or embedded within target tissue
Length of preganglionic fibres	Relatively short	Relatively long
Length of postganglionic fibres	Relatively long	Relatively short
Preganglionic neurotransmitter	Acetylcholine	Acetylcholine
Postganglionic neurotransmitter	Noradrenaline	Acetylcholine
	Short cholinergic preganglionic fibres; long adrenergic postganglionic fibres	Long cholinergic preganglionic fibres; short cholinergic postganglionic fibres
Ratio of preganglionic to postganglionic fibres	1:20	1:3
Divergence	Great divergence coordinates activity of neurons at multiple levels of spinal cord	Limited divergence
Activity	Often involves mass discharge of the entire system	Activity normally to discrete organs
Response	Predominates during emergency “fight-or-flight” reactions	Predominates during quiet resting condition

Basic characteristics of sympathetic and parasympathetic divisions

1. Cholinergic and adrenergic fibres-secretion of acetylcholine or norepinephrine

In terms of release of chemical mediators, the autonomic nervous system is divided into two: **cholinergic** and **noradrenergic divisions**. The fibres that secrete acetylcholine are called cholinergic fibres; those that secrete norepinephrine are called adrenergic fibres. Cholinergic fibres include all preganglionic fibres in both sympathetic and parasympathetic systems of the ANS; all postganglionic fibres of the parasympathetic system; and sympathetic postganglionic fibres innervating sweat glands, piloerector muscles of the hairs, and to a very few blood vessels are cholinergic. Most sympathetic postganglionic fibres are adrenergic. Therefore, all the terminal nerve endings of the parasympathetic system secrete acetylcholine. Majority of the sympathetic nerve endings secrete norepinephrine, but a few secrete acetylcholine. These hormones then act on the different organs to cause respective parasympathetic or sympathetic effects. Thus, acetylcholine is called a parasympathetic transmitter and norepinephrine, a sympathetic transmitter. The main distinguishing features of the neurotransmitters are summarized in Table below.

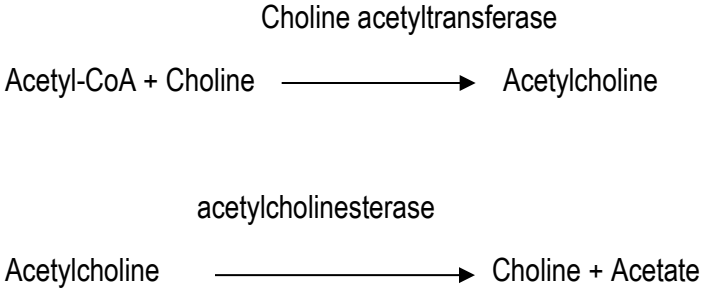
Table: Main differences between the ANS neurotransmitters.

Feature	Acetylcholine	Norepinephrine	Epinephrine
Site of release	All preganglionic neurons of ANS, all postganglionic neurons of parasympathetic system, some sympathetic postganglionic fibers to sweat glands, piloerector muscles of hairs, few blood vessels.	Most sympathetic postganglionic neurons; adrenal medulla (20% of secretion)	Adrenal medulla (80% of secretion)
Receptor	Nicotinic, muscarinic(cholinergic)	a1, a2, b1(adrenergic)	a1, a2, b1, b2(adrenergic)
Termination of activity	Enzymatic degradation by cholinesterase	Reuptake into nerve terminals; diffusion out of synaptic cleft, metabolic transformation by monoamine oxidase (within nerve terminals) or catechol-o-methyl-transferase within liver	Metabolic transformation by catechol-o-methyl-transferase within liver

2. Mechanisms of transmitter secretion and subsequent removal of the transmitter at the postganglionic endings.

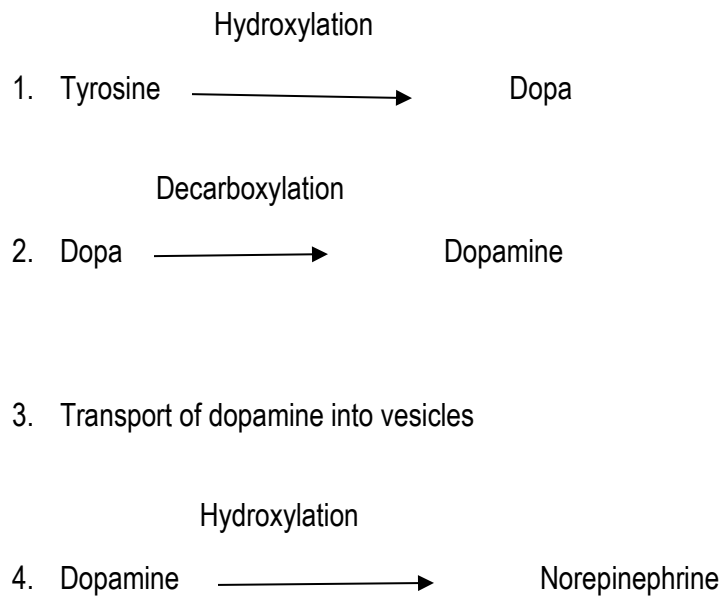
A. Secretion of Acetylcholine and norepinephrine by postganglionic nerve endings

Acetylcholine is synthesized in the terminal endings and varicosities of the cholinergic nerve fibres through the combination of acetyl-CoA with choline. The reaction is catalysed by choline acetyltransferase. Acetylcholine once released, persists in the tissues for a few seconds while performing its nerve transmitter function. It is then rapidly degraded by the enzyme, acetylcholinesterase. The choline formed is then transported back into the terminal nerve ending, where it is used and again for the synthesis of new acetylcholine.



B, **Synthesis of Norepinephrine, its removal and its duration of action**

Norepinephrine and epinephrine are synthesized from the amino acid, tyrosine. Its synthesis starts in the axoplasm of the terminal nerve endings and usually completed inside the secretory vesicles. The basic steps are:



Tyrosine is converted to DOPA, which is then converted to dopamine. Thereafter, dopamine is converted to norepinephrine.

In the adrenal medulla, the formation of norepinephrine goes one step further, transforming about 80% of the norepinephrine into epinephrine.

5. Norepinephrine —Methylation→ Epinephrine

After secretion, action of norepinephrine can be terminated in three ways:

(1) Reuptake into the adrenergic nerve endings by an active process- accounting for removal of 50-80 per cent of the secreted norepinephrine;
(2) diffusion away from the nerve endings into the surrounding body fluids and then into the blood, this accounts removal of most of the remaining norepinephrine; and
(3) destruction of small amounts by tissue enzymes such as monoamine oxidase, and catechol-O-methyl transferase. Note that:
(1) norepinephrine secreted directly into a tissue remains active for only a few seconds, that is, its uptake and diffusion away from tissues is rapid;

(2) norepinephrine and epinephrine secreted into the blood by adrenal medullae remain active until they diffuse into some tissues, where they are destroyed by catechol-o-methyl transferase in the liver, this can last for 10-30 seconds; thereafter, it declines exponentially for up to some minutes.

Receptors for Autonomic Neurotransmitters

All the effects of the ANS in tissues and organs throughout the body are done by neurotransmitters: acetylcholine, norepinephrine, and epinephrine. Each of the substances may stimulate activity in some tissues or organs and inhibit activity in others. The effect(s) of any of the substances is determined by the receptor distribution in the particular tissue and the biochemical properties of the cells in that tissue, especially, the second messenger and enzyme systems present within the cell.

Acetylcholine activates two main types of receptors: **muscarinic** and **nicotinic** receptors. Muscarinic receptors are found on all effector cells stimulated by the postganglionic cholinergic neurons of both divisions of the ANS. Muscarinic receptors are linked to G-proteins and second messenger systems which carry out the intracellular effects. Acetylcholine released from all parasympathetic postganglionic neurons and some sympathetic postganglionic fibres that travel to sweat glands binds to these receptors. Furthermore, muscarinic receptors may be either excitatory or inhibitory, depending on the tissues they are situated. In the myocardium, muscarinic receptor stimulation is inhibitory and decreases the heart rate while stimulation of these receptors in the lungs is excitatory, leading to contraction of airway smooth muscles and bronchoconstriction.

Nicotinic receptors are found in the autonomic ganglia at the synapses between the preganglionic and postganglionic neurons of both the sympathetic and parasympathetic systems. Nicotinic receptors are also found in some non-autonomic nerve endings such as neuromuscular junctions in skeletal muscles. Acetylcholine released from the preganglionic fibres binds to these nicotinic receptors and causes a rapid increase in the cellular permeability to Na ions and Ca ions. The influx of these cations causes depolarization and excitation of the postganglionic neurons in the ANS pathways.

Adrenergic receptors have two classes for norepinephrine and epinephrine: alpha(a) and beta(b). Each class has at least 2 subtypes of receptors: a1, a2, b1 and b2. All these receptors are linked to G-proteins and second messenger systems which carry out the intracellular effects.

Among the adrenergic receptors, the alpha receptors are more abundant. Furthermore, a1 receptors are more widely distributed on the effector tissues.

Norepinephrine and epinephrine usually secreted into the blood by adrenal medulla, have slightly different effects in exciting the alpha and beta receptors. Norepinephrine excites mainly alpha receptors but also excites the beta receptors to a lesser extent.

Conversely, epinephrine excites both types of receptors almost equally.

Table -----is a summary distribution of alpha and beta receptors in some organs and system controlled by the sympathetic. Certain alpha receptor functions are excitatory, whereas others are inhibitory. In the same vein, certain beta receptor functions are excitatory and others are inhibitory.

Table Adrenergic receptors and functions

Alpha receptor	**Beta receptor**
Vasoconstriction	Vasodilation(b2)
Irish dilation	Cardio acceleration(b1)
Intestinal relaxation	Increased myocardial strength(b1)
Intestinal sphincter contraction	Intestinal relaxation(b2)
Pilomotor contraction	Uterus relaxation(b2)
Bladder sphincter contraction	Bronchodilation(b2)
	Calorigenesis(b2)
	Glycogenolysis(b2)
	Lipolysis(b1)
	Bladder wall relaxation(b2)

Autonomic Effects on some 0rgans of the Body.

Table ------ shows the autonomic effects on Callogenesis different visceral functions of the body caused by stimulating either the parasympathetic nerves or the sympathetic nerves.

Table: Autonomic effects on some organs of the body

Effector Organ	Effect of sympathetic stimulation	Effect of parasympathetic stimulation
1. Eye		
a. Pupil	Dilatation	Constriction
b. Ciliary muscle	Relaxation	Constriction
2. Heart		
a. Rate and force	Increase	Decrease
b. Atria c. Ventricles	Decrease in contractility and increase in conduction velocity. Decrease in contractility	Increase in contractility and conduction velocity. Increase in contractility
3. Blood vessels	Constriction of all blood vessels except those in the heart and skeletal muscles	Dilatation
4. Glands (Nasal, lacrimal, parotid, submandibular, gastric, pancreatic)	Vasoconstriction and slight secretion	Stimulates copious secretion
5. Sweat glands	Copious sweating(cholinergic)	Sweating on palms of hands
6. Apocrine glands	Thick odoriferous secretion	None
7. Lungs(bronchioles)	Dilatation	Constriction
8. GIT		
a. Motility	Inhibition	Acceleration
b. Secretion	Decreases	increases
c. Sphincter	Constriction	relaxation
d. Gall bladder	Relaxed	contracted
e. Liver	Glucose release	Slight glycogen synthesis

9. Urinary bladder		
a. Detrusor	Relaxation	Contraction
b. Trigone	Contraction	Relaxation
10. Skin	Constriction	None
11. Penis	Ejaculation	Erection
12. Blood		
a. Coagulation	Increased	None
b. Glucose	Increased	None
c. Lipids	Increased	None

Introduction to Human Genetics

Introduction

Genetics is the study of genes and attempts to examine hereditary and variations of inherited characteristics. Gregor Johann Mendel (1822-1884) an Australian biologist, mathematician and catholic priest is a regarded as the father of modern genetics. His pioneering studies on the inheritance pattern in pea plants laid the scientific foundations for modern genetics and established many of the rules of hereditary known today as the laws of Mendelian inheritance.

Chromosomes

The genetic information of an individual is contained in 23 pairs of chromosomes with every human cell containing these 23 pairs of chromosomes. These 23 pairs of chromosomes are divided into two separate types: autosomal chromosomes and the sex chromosomes.

Autosomal chromosomes: There are a pair of 22 homologous chromosomes called autosomes. Each pair of autosomal chromosome pairs are called a homologous pair. The two chromosomes in the same pair are referred to as homologous chromosomes. One member of each chromosome pair is inherited from mother while the other is inherited from father. Each chromosomal pair is either inherited from either father or mother with equal probability. The homologous chromosomes are exactly same length for every individual. Each chromosome consists of two DNA chains.

Sex chromosomes: There is also a pair of chromosomes distinct from the autosomes called the sex chromosomes. As the name implies these pair determine the phenotypical sex of the individual. In males the sex chromosomes are designated XY while in females they are designated XX.

DNA (Deoxyribonucleic acid) and RNA (Ribonucleic acid)

All inheritable materials are encoded in the macromolecule called deoxyribonucleic acid and abbreviated as DNA. The DNA is found in the nucleus of all cells and in association with proteins forms chromosomes. Embryologically, humans develop from a single cell (fertilized egg) formed at the fertilization of the female gamete called the oocyte by the male gamete called the spermatocyte. Subsequently, almost all cells that developed from this single cell has the same identical copy of DNA. Therefore, the DNA of each individual person in inherently unique in characteristics.

All the DNAs in the human are in the 46 chromosomes. This consists of 44 autosomal chromosomes and a pair of sex chromosomes. The sex chromosomes designated X or Y determine the sex of an individual. A pair of X chromosomes (XX) codes for females while an X and a Y chromosome codes for males.

The 46 chromosomes in each single cell constitutes the genome and is comprised of 2 identical copies. These are called two copies of a library. At fertilization as mentioned above, copy of the genome is derived from the spermatozoa while the other copy is derived from the oocyte. In other words, for every human 22 of the autosomal chromosomes are derived from the father, while the remaining 22 autosomal chromosomes are derived from the mother. For males, the X sex chromosome is derived from the mother, while the Y chromosome is derived from the father. For females, one of X chromosome is derived from the mother while the other is derived from the father.

The DNA plays an important role of transmitting genetic information from genes to the protein molecule.

Cellular division: Mitosis and meiosis

Mitosis: This is the normal process of cellular multiplication. It usually occurs in all cells. As cells grow old and die and new cells are grown.

During the process of mitosis, the double stranded DNA in each of the chromosomes split into two single-strands. Each strand of DNA subsequently replicates and thus each chromosome produces another identical one. All the 23 pairs of the chromosomes undergo this process of replication, producing two identical sets of 23 chromosome pairs. The subsequent set of chromosomes produced are separated and distributed into two daughter cells.

Meiosis: This is the process of cell division that results in the inheritance of chromosomal materials. As described above during mitosis, the 23 pairs of autosomal chromosomes in the cell are duplicated. However, the gametes are a general exception to this rule. The gametes are the oocytes and the spermatozoa which are produced exclusively in the primary sex organs of the ovary and the testes respectively. The gametes are produced via a special cell division called meiosis. The eventual daughter cells produced by meiosis: oocyte and spermatocyte contain only a haploid number of both the autosomes and the sex chromosomes: the 22 single autosomes and a single sex chromosome either X or Y.

Gene: A gene is a segment of DNA within a chromosome with a specific genetic function. It is not the smallest unit of genetic material as the smallest genetic unit is the DNA. Gene or DNA sequences essentially code for proteins and thus control or determine phenotypes or phenotypic expression through protein synthesis. Proteins are created from a template of DNA molecules. Each molecule is a linear chain of subunits called amino acids. There are 20 different forms of amino acids usually denoted by the first three letters of the amino acid name. The physical and chemical properties of a protein molecule are largely determined by its sequence of the amino acids

and its shape structure. The DNA sequence of a gene usually specifies the amino acids sequence and therefore the primary structure and possible functions of the protein.

The process of transmitting the genetic information in the gene or DNA sequence into proteins involve two steps essential called transcription and translation.

***Transcription*:** This occurs in the nucleus of the cell. It involves the synthesis of a single-stranded (Ribonucleic acid) RNA from an equally single strand of DNA. The resultant RNA chain formed is called messenger RNA (mRNA).

***Translation*:** This occurs in the cytoplasm of the cell. This is the step through which the mRNA is translated to protein molecule. The genetic code closely guides the relationship between the base sequences of the mRNA formed and the amino acid sequence of its protein synthesized.

Genotype, phenotype, and haplotype:

Genotype: This refers to two alleles at a specific locus in each of the two homologous chromosomes. The genotype describes the genetic basis of a particular inherited genetic trait.

Phenotype: A phenotype is a physically observable genetic trait that likely distinguishes an individual such as the colour of skin, hair and eye, shape of the nose, colour and presence hair whorls etc.

Common and easily understandable examples of the genotype and phenotype is the ABO blood group system. On the ABO locus are three alleles: A, B and O. The presence of the both the A and B mask the presence of the O allele. Therefore, both the A and B alleles are described as **dominant while the** O allele is described as recessive. Furthermore, both the A and B allele are described as codominant**.**

Genotype	Phenotype (blood group)
AA, AO	A
BB, BO	B
AB	AB
OO	O

Haplotype: Refers to the sequence of the alleles along a particular chromosome.

Biotechnology and the Human Genome

Introduction

Biotechnology is broadly defined as the science of using living organisms or the products of living organisms for the benefit of humans or the improvement of human surroundings via making a new product or solving an identifiable problem. The use of organisms for the benefit of humans dates several thousands of years ago.

Greeks, Romans, Babylonians, Chinese and Africans particularly Egyptians have been practicing biotechnology for over 4000 years.

Biotechnology is the science of selective manipulation of genes for the overall benefit of humans and the improvement of life in general. Biotechnology is a relatively new but rapidly expanding scientific discipline, that however, involves and utilises several old practices. Biotechnology is a science of many disciplines with vital contributions from varied and different fields of science. It is not a single narrow discipline of study but relies on contributions from biology, chemistry, mathematics, computer science and chemical engineering, biochemistry, statistics, and immunology. Contributions from philosophy, economics, molecular and cell biology, human physiology, and anatomy are also vital.

By its definition, ancient and obvious examples of the practice of biotechnology include animal domestication for livestock uses, fermentation with various microorganisms like yeast to make pastries, yoghurt and various alcoholic beverages like wine and beer. The selective breeding of plants and animals to nurture, preserve and transfer desirable genetic traits to off springs is both an old and a new biotechnological practice. The selection of animals and plants with desirable genetic characteristics and their use by humans is ultimately for human benefit.

Antibiotics are classical examples of biotechnological molecules. By definition, an antibiotic is a molecule that is produced by a microorganism and negatively influences the growth of another microorganism. A typical example is the mould *Penicillium* which produces penicillin an antibiotic that have proven historically useful in the treatment of various bacterial diseases in humans.

Some benefits of Biotechnology

Rapid and outstanding developments in the fields of genetics and molecular biology has led to advances biotechnology. A critical review identifies the following outcomes of biotechnology practice:

1. **Bioinformatics:**

The application of computer science to the study of DNA and proteins has created the field of bioinformatics

2. **Gene cloning:**

This refers to the ability to scientifically reproduce a particular gene of interest in either plant, animal or microorganisms. Once a particular gene has been identified and cloned, it can then be utilized in a variety of ways including drug development. The gene can also be useful in agriculture, marine and environmental applications. Products created via gene cloning are of utmost importance in biotechnology applications.

These products called recombinant proteins because it involves the transfer of genes from an organism to another organism. These products are produced by inserting human genes into bacteria to produce these proteins that are beneficial in treatment of specific human diseases. Examples of proteins manufactured through this process include Blood factor VII useful in the treatment of haemophilia, human growth hormone useful for the treatment of short stature and other growth hormone deficiency states, human insulin useful in the treatment of insulin deficiency found in insulin dependent diabetes mellitus, and recently Tissue plasminogen activator useful in the treatment of heart attacks and stroke.

3. **Genetic engineering:**

This refers to the deliberate manipulation of the DNA sequences of an organism by either deletion of specific genetic materials or addition of new genetic materials.

4. **Recombinant DNA technology:**

This refers to the technological process resulting in the combination of DNA materials from divergent sources. This resultant effect is the production of certain proteins of immense importance to humans with diverse medicinal value and benefit. These proteins include insulin, human Growth Hormone and several blood-clotting factors. Recombinant DNA technology has also led to the production of various disease resistant plants with greater yield of fruits and food for human benefit.

Recombinant DNA technology is beneficial for human health through obvious identification of genes involved in genetic diseases in humans.

5. **Gene therapy**

This involves the introduction and use of genetic materials into humans for the treatment of genetic diseases. This ultimately may involve the practice of growing organs and tissues for transplantation with the likely benefit of fewer rejection reactions. This would ultimately result in healthier a humanity and improved human lifespan.

6. **Antibodies**

Antibodies produced via biotechnology research and methods are useful to protect humans from diseases and inflammatory condition. These antibodies can offer either active or passive immunity.

7. **Transgenic animals**

This is an important outcome of biotechnology research. Transgenic animals are animals with genetic materials from another source. For instance, human genes can be introduced into cows for the production of specific types of proteins in these cows. These proteins can then be harvested and used for the benefit of humans.

8. **DNA fingerprinting**

This is an important forensic tool in biotechnology research. It is useful in the detection of the unique DNA pattern of organisms. It is an important tool for law enforcement agencies. For instance, minute sample of hair, skin, body fluids and other body tissues left at a crime scene are important specimens for use in solving a crime riddle and determining suspect innocence or potential guilty parties.

9. **Bioremediation**

This involves the use of biotechnological methods and instruments to degrade naturally occurring or man-made products that are contributing to environmental pollution. Bioremediation is useful environmental hazards brought about by industrialization particularly oil exploration and exploitation. Bioremediation usually depends on microbial technology. Bioremediation can also lead to the recovery of valuable metals from the environment.

10. **Aquaculture**

This is a branch of biotechnology involved with the culture of fish and other seafoods for human consumption.

11. **Medical Biotechnology**

This is a branch of biotechnology that is involved in human medicine. It includes prevention, diagnosis, and treatment of various human disease conditions.

Ethical issues in biotechnology research

Research in biotechnology has raised a number of ethical, legal, social and moral issues. This has obviously generated a lot of worldwide debate and discussions. Typically, the issue of human cloning has raised a lot of arguments amongst scientists.

The Human Genome

The human genome refers to the complete set of genes or indeed all the genetic material present in the human. This includes the totality of DNA characteristic of all the 23 pairs of chromosomes. The DNA is distributed in over 22 autosomal chromosomes (numbered from 1 to 22) and two sex chromosomes (X and Y). Basically, this includes all the complete set of DNA since the DNA is the basic unit of genetic material. Almost each of the different cells in the human has the complete and a similar set of genetic material. The human genome therefore refers to all the genetic material that necessary for phenotypic expression of each person. There are totally about 40,000 genes, over 5000 have been identified with are much more left for identification. For humans, most of the human genome are the same with a very small portions being different between different individuals.

Within the past two decades, several outstanding discoveries in genetics and genomics have made our understanding of the human genome clearer. For instance, genetic mutations causing disease to have become better understood with unravelling of the genetic code of humans. Indeed, the genetic basis of many disease processes has become better understood. Clearly, a proper understanding of the basic principles of the human genome have become necessary for effective medical practice. The elucidation of this genomic DNA sequence is of extreme interest, as this is the encrypted data for all the inherited information needed to develop and direct the functioning of the human body.

Clearly, the potential variations in the genome constitutes the basis for human diversity. This is because identification of the DNA sequence of a gene in different individuals from the same population some differences in the nucleotide sequence are often detected. Ultimately, the human genome project would reveal the genetic code for every huma characteristic and cellular processes. This would include characteristics like hair colour, weight, height and blood pressure. The specific genes involved with all genetic disorders would also be identified and characterised.

In conclusion, it might be expected that genomics and genetics will largely impact future medical practice. Several genomics-based applications are on their way to enter the clinic within the next few years, and many more will most probably follow in a later stage. For clinicians of the 21st century, it will be key to be well prepared and open-minded for this molecular future of medicine.

Summary

The subject of Physiology is as old as medicine. Physiology is the science of life. The human body is built on cells, tissues, organs and organ systems. These system needs a constant internal environment for proper functioning. Physiological control processes help achieve this. The study of Physiology is critical to academic, laboratory and clinical medicine. The autonomic nervous system is part of the nervous system concerned with most vegetative or visceral functions of the body such as gastrointestinal motility and secretion, sweating, arterial blood pressure, body temperature, heart rate, urinary bladder emptying. It's also called vegetative or involuntary nervous system. The central aspects of the ANS are located in hypothalamus, brain stem and spinal cord. Higher centres such as the limbic cortex and portions of the cerebral cortex also influence the activities of the ANS. It is divided into two: sympathetic and parasympathetic systems.

One classical feature of the ANS is the rapidity and intensity with which it can change visceral functions. It is also associated some responses such as

It is often associated with some responses such as **"fight-or -fligh**t response and "**rest-and -digest**" response. The Human Genome Project is a worldwide scientific project that was initiated in 1987 to unravel completely the DNA sequence of the human genome. Although the complete sequence of the whole human genome has been documented, it may require more decades before all this information will be fully understood. The scientific, medical and evolutionary benefits of the deciphering the the Human Genome Project can hardly be overestimated.

Exercise

1. Define Physiology. What is Human Physiology?
2. What are the critical differences between cells, tissues, organs, and organ systems?
3. Define the term milieu intérieur. What constitutes it and why is it critical for cellular survival?
4. What is homeostasis? Describe the roles the various organ systems play in its maintenance.
5. Differentiate between negative and positive feedback control. Which is more critical for survival of the human species?
6. Why is the Nobel Prize in the field of the life sciences or medicine in the subject of Physiology and is called the *Nobel Prize in Physiology or Medicine*.
7. Define the excitable tissues giving examples.
8. How do substances pass through the cell membrane?
9. Explain in the details the functions of components of the cell.
10. What is the role of calcium ion in muscle contraction?
11. How is muscle contraction switched on?
12. Describe the divisions of the autonomic nervous system
13. Describe functional anatomy of sympathetic nervous system.
14. Explain two basic characteristics of the ANS
15. Enumerate the autonomic nervous system effects on some organs in the body
16. Define genetics as the basis of inheritance
17. Describe the role of chromosomes in the process of inheritance
18. Differentiate between divisions: meiosis and mitosis. What is their role in the inheritance?
19. Define the following terms: genotype, phenotype and haplotype

20. Define biotechnology and describe the potential benefits of biotechnology to humanity?
21. Describe the potential ethical issues in biotechnology research.
22. Define the human genome and what are the potential benefits of unravelling the human genome?
23. How does the human genome contribute to human diversity?

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Chapter 2

PHS 202.RENAL PHYSIOLOGY, BODY FLUIDS AND TEMPERATURE REGULATION

Walter Chukwuma Nwafia and Maisaratu Aminu Tukur

Overview: The Kidney is a paired bean-shaped retroperitoneal organ that is responsible for a number of functions in maintaining homeostasis. The kidney is responsible for regulation. It also regulate water and electrolyte balance, arterial blood pressure and acid-base balance, excretion of metabolic waste, foreign chemicals, drugs, hormone metabolites and production of hormones

Objectives: Students should be able to;

i. List the various body fluid compartments and their ionic compositions
ii. Describe the methods used in measuring the body fluid compartments
iii. Describe the functions of the ECF in the body
iv. Describe general plan of the renal system
v. Mention the different regions/areas of the kidney and its function
vi. Describe the renal blood supply
vii. Define and differentiate the different types of nephrons
viii. Mention at least four parts of a typical nephron and its function
ix. Define Glomerular filtration
x. Mention the determinants of glomerular filtration rate
xi. Mention the physiologic control of renal blood flow and glomerular filtration rate
xii. Describe the process of urine formation
xiii. Mention the constituent of the filtration barrier
xiv. What are the determinants of GFR
xv. Mention the physiologic mechanism involved in the regulation of RBF and GFR
xvi. Describe the process of autoregulation of GFR and RBF
xvii. Describe tubular reabsorption of at least any three (3) substances
xviii. The role of Na-K Atpase in reabsorption across renal tubules
xix. Mention any three transport processes

THE SKIN

Definition

This is the structure that completely covers the human body and is continuous with the membranes lining the body orifices.

Functions of the Skin

1) **Protection**

It forms a relatively waterproof layer that protects the deeper and more delicate structures. As an important non-specific defense mechanism, it acts as a barrier against:

a) Invasion by microbes.
b) Chemicals.
c) Physical agents' e.g. mild trauma. Ultra violet light.
d) Dehydration.

The dermis contains specialized immune cells called **Langerhans cells.**

2) Regulation of body temperature

The body temperature remains fairly constant at about 36.8^{o}C (98.4F) across a wide range of environmental temperature. To ensure this constant temperature, a balance is maintained between heat production in the body and heat lost to the environment.

a) Heat production

This is brought about by the following:

i) Muscle shivering

ii) Liver, when chemically active produces heat as a by-product and also increases metabolic rate and heat production after eating

iii) Digestive organs produce heat during peristalsis and chemical reactions of digestion.

b) Heat loss

Most of the body heat loss occurs through the skin. Also small quantity is lost through urine, faeces and expired air. Heat lost through the skin is affected by:

i) Difference between body and environmental temperatures.

ii) The amount of the body surface exposed to the air.

iii) The type of clothes worn.

A balance is maintained between heat production and heat loss. A control is achieved mainly by thermo-receptors in the hypothalamus.

3) Formation of Vitamin D

7-dehydrocholesterol lipid based substances found in the skin form vitamin D (25 di hydro cholesterol) by ultra violet light.

4) Sensations

Sensory receptors consist of nerve endings in the dermis that are sensitive to:

a) Touch

b) Pressure

c) Temperature

d) Pain

Stimulation generates nerve impulses in sensory nerves that are transmitted to the cerebral cortex

5) Absorption

This function is limited. Substances that can be absorbed:

a) Some drugs in Trans – dermal patches e.g.

i) Hormones used as replacement therapy in post-menopausal women.

ii) Nicotine as an aid to stopping smoking .

b) Some toxic chemicals e.g. mercury.

6) Excretion

It is a minor excretory organ for some substances e.g.:

a) Nacl in sweat which when excess, leads to abnormally low blood Na^{+} levels.

b) Urea especially when kidney function is impaired.

c) Aromatic substances e.g. garlic and other spices.

Skin has a surface area of about 1.5- 2m^2 in adults and it contains glands, hair and nails. It has two main layers:
a) Epidermis
b) Dermis
Between the skin and underlying structures there is a layer of subcutaneous fat.

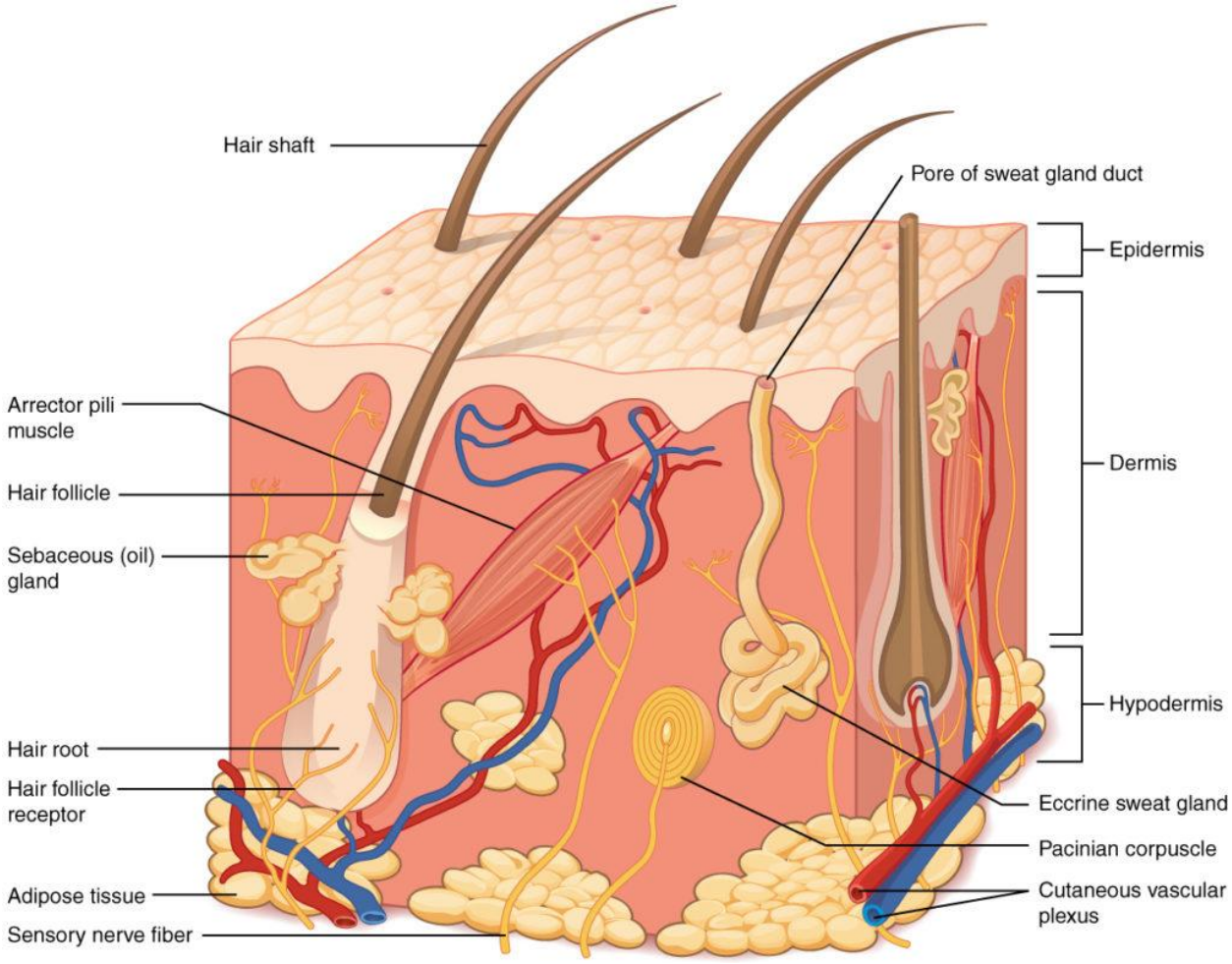


Fig. 2.1 Structure of the skin
Source: ***https://my.clevelandclinic.org>articles>10978-skin***

Epidermis
This is the most superficial layer of the skin composed of:
a) Stratified, keratinized squamous epithelium:
i) It varies in thickness in different parts of the body.
ii) It is thickest on the palms of the hands and soles of the feet.
iii) There are no blood vessels or nerve endings.
iv) Its deeper layers are bathed in intra cellular fluid (IF) from the dermis, which provides oxygen and nutrients and is drained away as lymph.

There are several layers (strata) of cells in the epidermis which extend from deepest **germinative layer** to the surface stratum corneum (a thick horny layer). The cells on the surface are flat, thin, non- nucleated, dead cells or **squames**, in which the cytoplasm has been replaced by the fibrous protein **keratin**. These cells are constantly being rubbed off and replaced by cells which originated in the germinative layer and have undergone gradual change as they progressed towards the surface complete replacement of the epidermis takes about **40days**.

The maintenance of a healthy epidermis depends upon three processes being synchronized:
1) Desquamation (shedding) of the keratinized cell from the surface.
2) Effective keratinization of the cells approaching the surface.
3) Continual cell division in the deeper layers with newly formed cells being pushed to the surface.
Hairs, secretions from sebaceous glands and ducts of sweat glands pass through the epidermis to reach the surface. The surface of the epidermis is ridged by projections of cells in the dermis called **papillae**. The pattern of ridges is different in every individual and the impression made by them is called **finger prints.**
The colour of the skin is affected by three main factors:
a) Melanin **(black)**.
b) Level of oxygenation of Hb **(pink)**.
c) Bile pigments in the blood and carotenes in the subcutaneous fat **(yellow)**.

DERMIS
This is a tough and elastic layer, formed from connective tissue. Its matrix contains collagen fibers interlaced with elastic fibers. If the elastic fibers rupture from overstretching of the skin, a permanent **striae** or stretch marks develop as found in pregnancy or obesity. Collagen fibers bind water and give the skin its tensile strength, but as this ability declines with age, **wrinkles** develop. Fibroblasts, macrophages and mast cells are the main cells found in the dermis. Underlying its deepest layers there is areolar tissues and varying amounts of adipose tissue.
The structures in the dermis are:

1) Blood vessels.
2) Lymph.
3) Sensory (somatic) nerve endings.
4) Sweat glands and their ducts.
5) Hairs, erector pili muscles.
6) Sebaceous glands.

Body Temperature and Its Regulation
Normal body temperature is regulated at an average of 37^{o}C (Range 35- 42^{o}C). Warm blooded animals are called **homeotherms** e.g. human beings because they maintain a constant body temperature while cold blooded animals are called **poikilotherms** e.g. reptiles because they have a variable body temperature. However the poikilotherms regulate their body temperature close to those of man by behavioural means rather than physiological means. If the human body temperature decreases down to less than 35^{o}C, a condition called **hypothermia** results, leading to loss of memory (**amnesia**), unconsciousness and death. If it increases beyond 42^{o}C, it results to a condition called **hyperthermia** which can present as heat stroke, delirium, hallucinations, mental confusion, unconsciousness and death.

Variations of Normal Body Temperatures
1) Due to site of measurement
a) Surface Temperature:

i) Skin temperature varies with that of the environment because of exposure.
ii) It is usually lower than body interior (core) temperature.
iii) The skin temperature is lowest at the extremes especially the fingers and toes.
iv) It is highest at the axilla.
v) The scrotal temperature is about 32^{o}C.
b) Core Temperature
i) This is measured orally with a thermometer under the tongue with the mouth closed.
ii) It is also measured rectally.
iii) The rectal temperature is greater that the oral temperature by about 0.5^{o}C.
iv) The oral temperature is affected by temperature of food and drinks.
v) The highest measured core temperature is from the tympanic membrane.
vi) The actual body temperature regulated is the core temperature.

2) Individual Variations
a) Daily core temperature varies with individuals.
b) The oral temperature ranges from 36.3^{o} to 37.7^{o} C (average 37^{o}C).
c) Some individuals have regular core temperature greater than normal and are said to be **constitutionally hyperthemic.**

3) Age
The body temperatures of newborns and young children are greater than those of adults because of increased basal metabolic rate.

4) Exercise
Vigorous exercise increases rectal temperature up to 40^{o} C.

5) Ovulation
Increased basal body temperature increases during ovulation by about 0.5^{o}C due to the hormone progesterone.

6) Diurnal Variations
a) Body temperature fluctuates within 0.5^{o}C in relation to time of the day or night as a result of circadian rhythm.
b) It is lowest at 6am and highest in the evenings.

7) Emotional Stress
This is due to hormones and autonomic nervous system.

8) Hormones
The hormones that affect body temperature includes; adrenaline, noradrenalin, thyroxine.

9) Eating and drinking
This affects body temperature especially the temperatures before ingestion.

Regulation of Body Temperature
This is via a negative feedback mechanism. It is an example of a homeostatic mechanism, having all the components. The body controls the temperature of the deep zone within a narrow range. Skeletal muscle

produces the heat. In temperate zones, this heat is channeled into the core but in the tropics or when we are hot, it is channeled to the skin. The skin temperature varies with that of surrounding. Heat gained in the body is equal to heat lost. If there is no mechanism for heat loss, the body temperature will increase by 1^{o}C per hour.

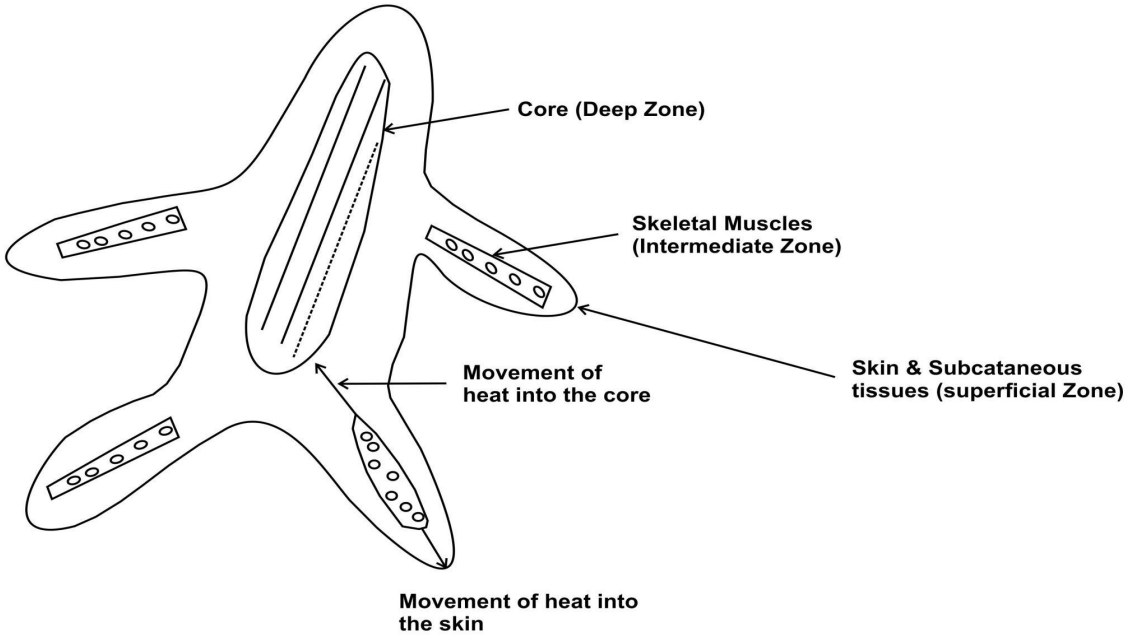


Fig. 2.2: Temperature regulating centre in the hypothalamus

Means of heat gain by the body

1) Cellular Metabolism

There are two types: basal metabolism (increased muscle tone) and muscle activities (physical exercise). It is under the control of the hormones thyroxine and adrenaline. It is increased in the following conditions:

a) Increased voluntary muscle activity
b) Increased cold via increased thyroxine and adrenaline.
c) Increased shivering.
d) Exposure to heat.
e) Meals, this increases specific dynamic action of food substances.

2) Hot environment

This is via conduction, convection and radiation.

3) Hot foods.

4) Pilo erection, also called goose flesh. This is more important in hairy animals than man.

5) Gastro intestinal tract (GIT) smooth muscles activities.

6) From a hot environment

This involves direct solar radiation and heat conduction by taking a hot bat.

Means of heat loss by the body

The major method of heat loss is sweating.

These include:

1) Radiation
If the environmental temperature is less than the body temperature, the body temperature decreases. It radiates the temperature to the environment. About 60- 70% of heat loss of the body is via radiation.
2) Conduction
The heat lost from conducted to the surrounding air is very small but considerable when inside water.
3) Convection
This is movement of the body relative to the air. Breeze, fan, running in cold air all reduces body temperature. This is negligible in still air but considerable in moving cold air.
4) Evaporation of water
It is the sweat that evaporates that functions to cool the body. The body looses water by insensible water loss and sweating.
5) Panting in dogs
This is an effective means of losing heat from the surface of the lungs and tongue.
6) Pigs roll themselves in the mud
This is not a dirty means but a behavioural means of keeping the body temperature low.
7) Insensible perspiration.
This is loss of water we are not aware of. This involves evaporation of water from the skin, mucosa of the mouth and the Lungs.
8) Insensible loss
This is through faeces and urine.
In environmental temperatures between 20- 31^{o}C (equitable climate), 70% heat lost is through radiation and conduction, 27% is through sweat and 3% is via insensible loss through urine and faeces. In hot environment (more than 31^{o}C), the main method of heat loss is sweat.

Thermoreceptors
These are receptors sensitive to temperature changes. There are two types:
a) Cutaneous/ Peripheral Thermoreceptors
They are peripherally located under the skin. There are about ten times as many cold as warm receptors. They are sensitive to change in temperature rather that absolute temperature. It sends signals to the brain..
b) Central Thermoreceptors
They are found in some parts of the brain especially the hypothalamus and are responsible for monitoring brain temperature. They are sensitive to hot or cold deviation of temperatures of about 0.5- 1.0^{o}C. They are the main sensors for increased body temperature. Most of them are sensitive to increase body temperature rather than decrease body temperature.
Thermoeffectors
These generate of cause the loss of heat. They include:
1) Metabolic machinery of all the cells of the body.
2) Blood vessels.
3) Sweat glands.
4) Subcutaneous fats of the skin.

REGULATION OF CONSTANT BODY TEMPERATURE
There are two means:
1) Physiological. This is automatic (reflex) and uncontrollable.
2) Behavioural which is of two type: conscious and instinctive.

	Physiological	Behavioural
Increased heat production	(a)Increased muscle tone leading to shivering	(a)Increased physical activity
	(b)Increased hormone secretion	(b)Increased food intake
+ (plus)		
Decreased heat loss	(a)Cutaneous vasoconstriction	(a)Coiling up leading to decreased surface area
	(b)Piloerection	(b)Adding of clothes and blankets
	(c)Increased insulative value of skin	
Increased Body temperature		
Decreased heat production	(a)Decreased muscle tone	(a)Decreased food intake
	(b)Decreased hormone secretion	(b)Decreased physical activity
+ (plus)		
Increased heat loss	(a)Cutaneous dilatation	(a)Cold shower, remove clothes and stretch out to increase surface area.
	(b)Sweating	
Decreased body temperature		

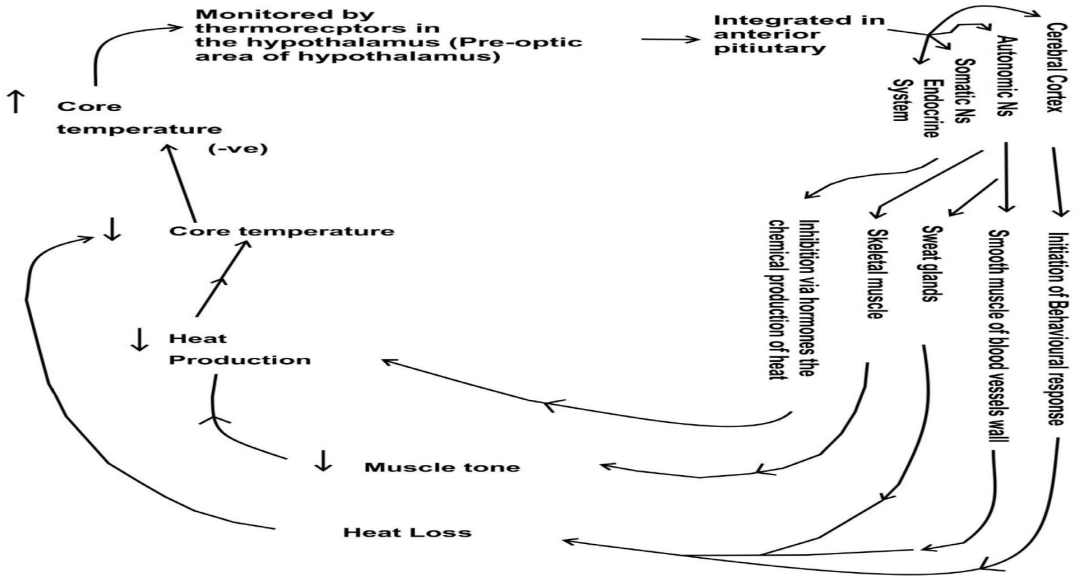


Fig. 2.3: Flow chart of increase in core temperature

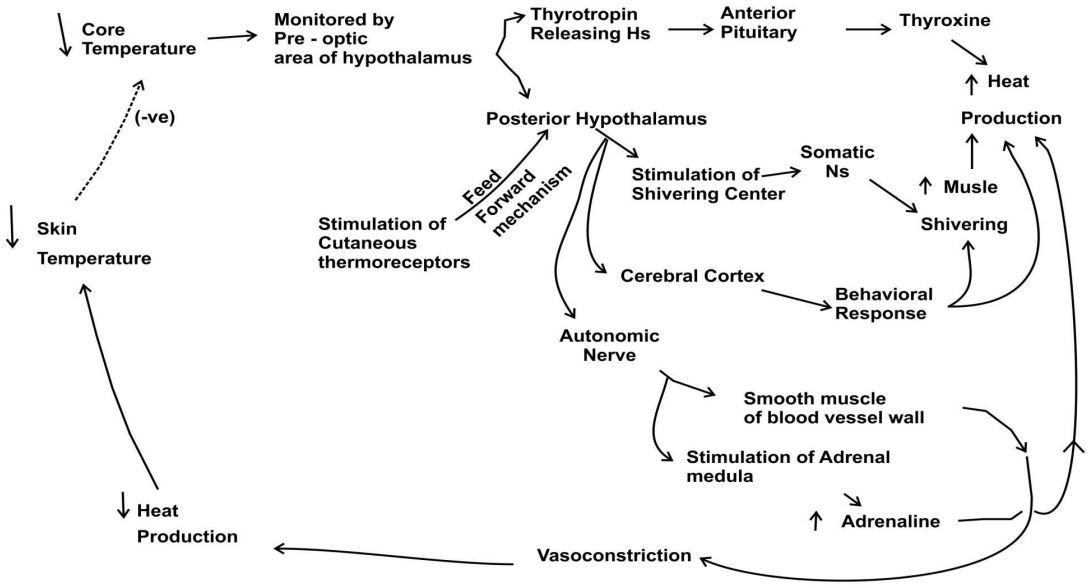


Fig. 2.4: Flow chart of response to decreased core temperature

Physiological Processes (Mechanisms) By Which the Body Maintains Constant Body Temperature

1) Ability to alter blood flow to the surface of the skin. This is mediated by the sympathetic nervous system which causes vasoconstriction or dilatation. Vasoconstriction causes decreased blood flow to the skin leading to decreased heat loss while vasodilation causes the opposite.
2) Increased wetness of skin surface for evaporative heat loss. The lower the sweating, the lower the heat loss. This is mediated via the ANS.
3) Increased metabolic heat production. This is achieved by shivering and exercise that go via the skeletal muscles and is mediated by the somatic nervous system.
Hormones e.g. thyroxine also contribute

Role of Skin in Thermoregulation

a) Insulation

This involves:
1) The cutaneous fat and is more in females.
2) In the infants, the brown fat generates heat.
3) There is trapping of layer of warm air around the skin for animals.
4) In the birds, there is erection of furs or fluffing of the feathers called horripilation. This is not important in humans but goose pimple occurs which resembles it.

b) Cutaneous vasoconstriction or vasodilation

Sympathetic cutaneous vasoconstriction leads to decreased cutaneous blood flow, leading to increased skin insulation.

c) Sweating

There are two types of sweat glands:
i) Eccrine: This is more on the palms, soles and the head. They are secreted in response to heat (thermal sweating).
ii) Apocrine: This responds to emotion (emotional sweat). They are found in the axilla, nipples, labia majora, mons pubis etc. The secretion is milky and odourless except after bacterial action on it.

Integrating Center for Temperature Regulation

This is located in the pre-optic area of the hypothalamus. It has two parts:
a) Anterior heat loss center. When stimulated, it causes vasodilatation and sweating.
b) Posterior heat gain center. This is concerned with maintenance and conservation of temperature

Role of the Integrating Center in Temperature Regulation

The temperature of the body is regulated almost entirely by nervous feedback mechanism and this almost has its operation through the temperature regulating center located in the hypothalamus. Heat and body temperature control is by the pre-optic area of the hypothalamus and to a lesser extent the adjacent regions of anterior hypothalamus.
Then body temperature is monitored by sensors located in the hypothalamus:

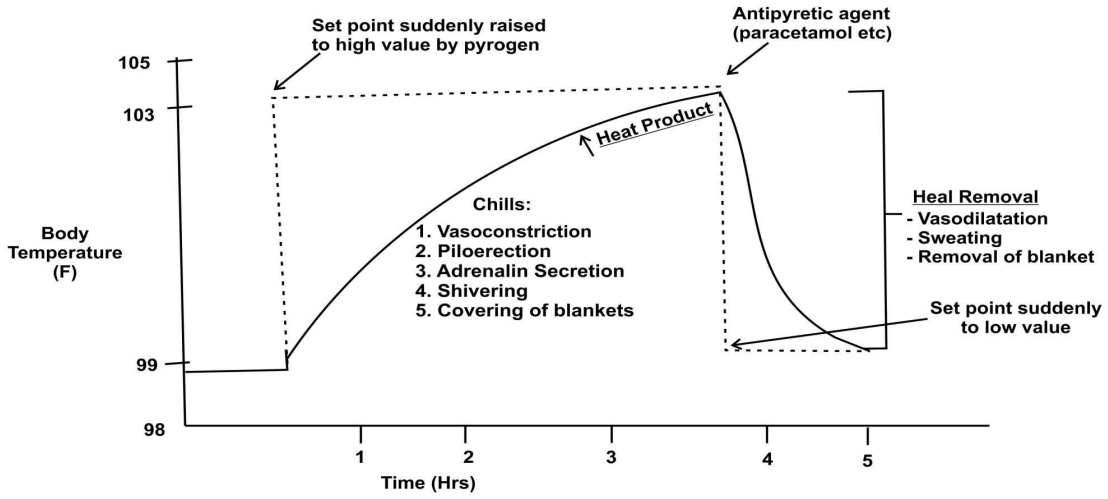
a) Heat sensitive neurons (heat sensors)

These are located in the pre-optic area of the hypothalamus. When the temperature rises, these sensors increase their firing rate.

b) Cold sensitive neurons (cold sensors)

They are also found in the hypothalamus, in the septum and reticular substance of the midbrain.
The sensors increase their rates of firing either when exposed to heat or cold. When the body temperature changes, the receptors on the skin send out signals which cause the higher rate of firing of neurons in response to signals transmitted to the brain from cold and warmth receptors. When these signals get to the brain, they stimulate the hot and cold sensitive neurons of the hypothalamus to increase their rate of firing and when the rate of firing is increased the pre-optic area becomes heated up and sends stimulus through the autonomic pathway to the spinal cord hence through the sympathetic outflow to the skin everywhere in the body, causing the production of sweat which will be transported to the skin via blood to the outside. The pre-optic area of the hypothalamus has the capability of serving as a thermostatic body temperature control center.

Abnormality of Temperature Regulation
A major abnormality is fever or pyrexia.
Fever
This is also called pyrexia. It is an abnormal increase in body temperature which can be caused by pyrogens in the blood due to bacteria, viruses, parasites, foreign proteins etc. During fever, there is no breakdown of body's thermoregulatory mechanisms. What happens is that pyrogens re-set the thermostat to a higher level. This results in physiologic as well as behavioural responses.



Effects of Changing the hypothalamic thermostat during fever

Fig. 2.5: ?????

Metabolism

This can be defined as the chemical reactions or changes in the body's cells that change food into energy and other materials, which are required for organisms to grow, reproduce, and stay healthy. The key to key to metabolism is nutrition. There are two categories:

a) **Catabolism**, which is the breakdown of molecules to obtain energy.
b) **Anabolism,** the synthesis of all compounds needed by the cells.

The components of metabolism are as follows:
a) **Basal metabolic rate (BMR)**: This 50- 80% of an individual's daily energy
b) **Thermogenesis**: This is 5-10% of an individual's daily energy.
c) **Physical Activity**: It is approximately 20% of an individual's daily energy use, though this percentage varies based on lifestyle.

There are three major energy systems which are responsible for the synthesis of ATP. They can be categorized as:

a) The phosphagen system.
b) The glycolytic system.
c) The Mitochondrial respiration.

Regulation of Metabolism

Several hormones of the endocrine system help control the rate and direction of metabolism. e.g. thyroxine helps in the determination of how fast or slow the chemical reactions of metabolism go in a person's body. Also the pancreas secretes hormones that help determine whether the body's activity at any one time is anabolic or catabolic.

The factors regulating metabolism are as follows:

a) Muscle mass: i.e. the amount of muscle tissue on your body. Muscle requires more energy to function than fat. So the more the muscle tissue you carry, the more energy your body needs just to exist.

b) Age: As you get older, your metabolic rate generally slows. This is because of a loss of muscle tissue and changes to hormonal and neurological processes. During development children go through periods of growth with extreme rates of metabolism.

c) Body size: Those with bigger bodies have a larger BMR because they have larger organs and fluid volume to maintain.

d) Gender: Men generally have faster metabolisms than women.

e) Genetics: Some families have faster BMR than others with some genetic disorders also affecting metabolism.

f) Physical activity: Exercise increases muscle mass and powers up your metabolic engines turning kilojoules at a faster rate, even when at rest.

g) Hormonal factors: Hormonal imbalances such as hypo and hyperthyroidism can affect your metabolism.

h) Environmental factors: Environmental changes such as increased heat or cold forces the body to work harder to maintain its normal temperature and increases BMR.

i) Drugs: Caffeine and nicotine can increase your BMR whilst medications such as antidepressants and steroids increase weight gain regardless of what you eat.

j) Diet: Food changes your metabolism. What and how you eat has a big influence on your BMR.

Conditions for measuring BMR

The BMR is the metabolic rate of a person measured under basal conditions as follows:

a) The subject must be awake.
b) In absolute physical and mental rest.

c) After twelve hours of absolute fasting.
d) Environmental temperature must be between 20- 25^{o}C.
Compartmentalization and composition of body fluids

Body Fluids

Body fluids are water and contained solutes found inside the body. In a 70kg man, body water makes up 60% (about 42 liters) with a range of 45- 75%. The body water is divided into two main compartments:
(a)Intracellular fluid compartment (ICF) (b) Extracellular fluid compartment (ECF)

INTRACELLULAR FLUID (ICF) COMPARTMENT

These are fluids found inside the cells. It is about 28 liters and makes up 40% of total body weight. The common features of all intra cellular fluids are:
a) They are contained within the boundaries of cell membranes.
b) They have similar electrolyte composition, with K^+, and Mg^{2+} as principal cations, and HPO_4 and Pr^+ as the main anions.

EXTRACELLULAR FLUID (ECF) COMPARTMENT

This is made up of all the fluid outside cells. It is about 14 liters and makes up 20 % of total body weight. It is not one homogenous compartment. It surrounds the cells of the body, providing them with nutrients and oxygen, hormones, etc. While removing their waste products, and is the "internal environment" of the body.

The ECF is further divided into:

a) Plasma compartment (3.5 liters)
b) Interstitial fluid (IF) compartment (10.5 liters).
c) Transcellular fluid compartment:
    i) Aqueous and vitreous humour of the eyes
    ii) Synovial fluids of joints
    iii) Secretions of the gastro intestinal tract (GIT)
    iv) Cerebrospinal fluid (CSF)
    v) Fluids of the peritoneal cavity, pleural cavity, pericardial space.

The components are in free communication among themselves, with separation by only by a thin endothelial lining of capillaries.

Electrolyte Concentrations in ICF and ECF

Electrolytes	**[Plasma] meq/ l**	**[Interstitial fluid]meq/l**	**[Intracellular Fluid] (skeletal muscle) meq/kg H_20**
Cations			
Na^+	142	145	10
K^+	4	4	160
Ca^{2+}	5	2.5	2
Mg^{2+}	3	1.5	26

Total cations	154	153	198
Anions			
Cl^-	103	114	3
$HCO3^-$	27	30	10
HPO_4^{2-}	2	2	100
SO_4^{2-}	1	1	20
Organic acids	5	5	-
Pr^-	16	0	65
Total anions	154	152	198

(Adapted from Gabriel C. Ezeilo: Textbook of Physiology. 4th Impression, 2009; Oxford University Press, New Delhi, India)

Kidney Functions

Regulation

i. Body fluid osmolarity , primarily through regulating H_2O balance by excreting dilute or concentrated urine
ii. Proper plasma volume via Na^+ and water excretion
iii. Electrolyte balance by adjusting quantity and concentration of most ECF ions(Na_, K_, Ca2_, Mg2, Cl, bicarbonate(HCO3), phosphate, and sulfate
iv. Acid-base balance of the body by adjusting urinary output of H^+ l in excess acid and HCO3– in excess base
v. Blood pressure by altering Na^+ excretion and producing various substances

2. Excretion

i. Metabolic products, such as urea (from proteins), uric acid (from nucleic acids), creatinine (from muscle creatine), bilirubin (from hemoglobin), and hormone metabolites. If allowed to accumulate, many of these wastes are toxic, especially to the brain.
ii. Foreign substances such as drugs, food additives and other exogenous nonnutritive materials that have entered the body. (Pesticides, chemicals etc.)
iii. Excess substance (water, etc)

3. Synthesis

i. Erythropoietin, a hormone that stimulates red blood cell production
ii. 1,25-dihydroxy vitamin D_3 (vitamin D activation)
iii. Renin,, an enzymatic hormone that triggers a chain reaction important in salt conservation by the kidneys.
iv. Prostaglandins, thromboxane A2 , bradykinnin and kallikrein
v. Ammonia, hydrogen diphosphate partake in acid-base balance

4. Degradation

- Insulin, glucagon, and parathyroid hormone.

5. Gluconeogenesis

Physiologic Anatomy of the Kidney

The paired kidneys in an adult are bean-shaped, about 10 cm long, 5 cm wide and 4 cm thick. They have an upper and a lower *pole* and a medial and a lateral margin. The kidney has the size of a clinched fist, weighs between 120 and 300 g and lie in the lumbar region in a connective tissue space behind the abdominal cavity (retroperitoneal space}. If the kidney is sectioned, it shows an outer granulated reddish region and an inner striated medulla.

The right kidney lies below the liver, the left below the spleen. In most people the upper pole of the right kidney lies about half a vertebra lower than that of the left. The side facing the vertebral column is notched and contains the hilum, through which the blood vessels, nerves, and renal pelvis enter and leave.

Each kidney contains a million nephrons averagely and each nephron consists of a filtering component called the renal corpuscle initially and a tubule that extends out of the renal corpuscle. The renal corpuscle forms a filtrate from blood that is free of cells and proteins. The filtrate then leaves the renal corpuscle and then enters the tubule. Substances are added or removed from it. The final fluid remaining at end of the nephron combines in the collecting duct and ends as urine. Each renal corpuscle contains a compact tuft of interconnected capillary loops called the glomerulus.

A longitudinal bisection of the kidney reveals an outer cortex and the inner medulla.

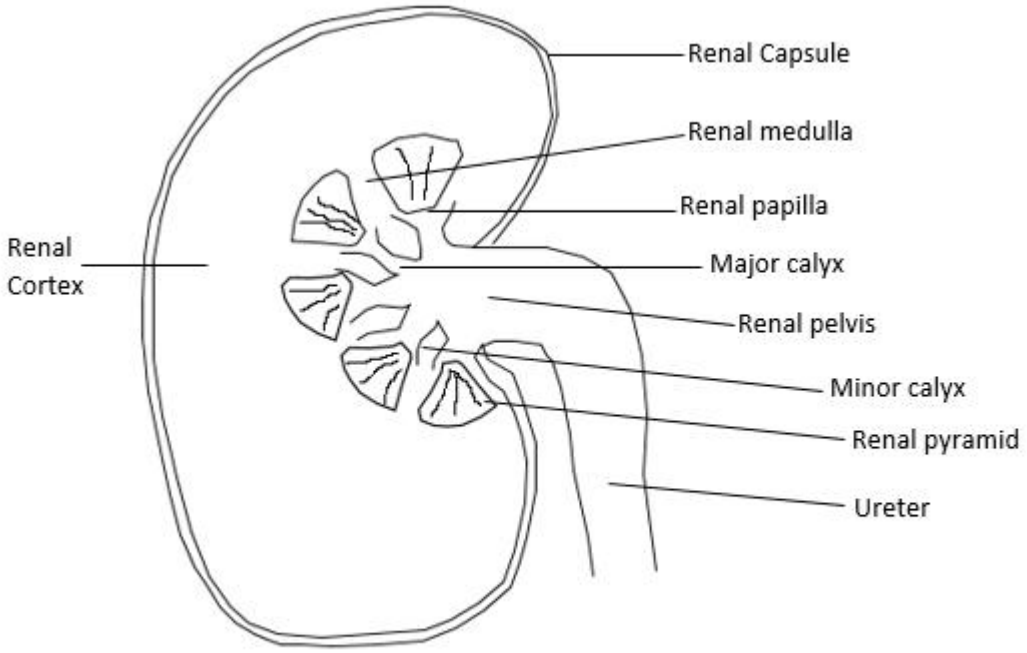


Fig. 2.6: Physiologic anatomy of the kidney

A longitudinal section of the Human kidney
The Medulla is characterized by several renal pyramids with their base at the border between the cortex and the medulla while apex is projected towards the renal pelvis to form the renal papillae. The renal pelvis is continuous with the ureter below it which conveys urine to the urinary bladder. The renal pelvis also has the minor and major calyces that serve as urine collection point from the renal papillae. The smooth muscle present in the walls of these structures helps in propelling urine towards the bladder.

Nephron

The nephron: is the basic functional unit of the kidney with over 1.3 million nephrons capable of forming urine within each respective kidney.

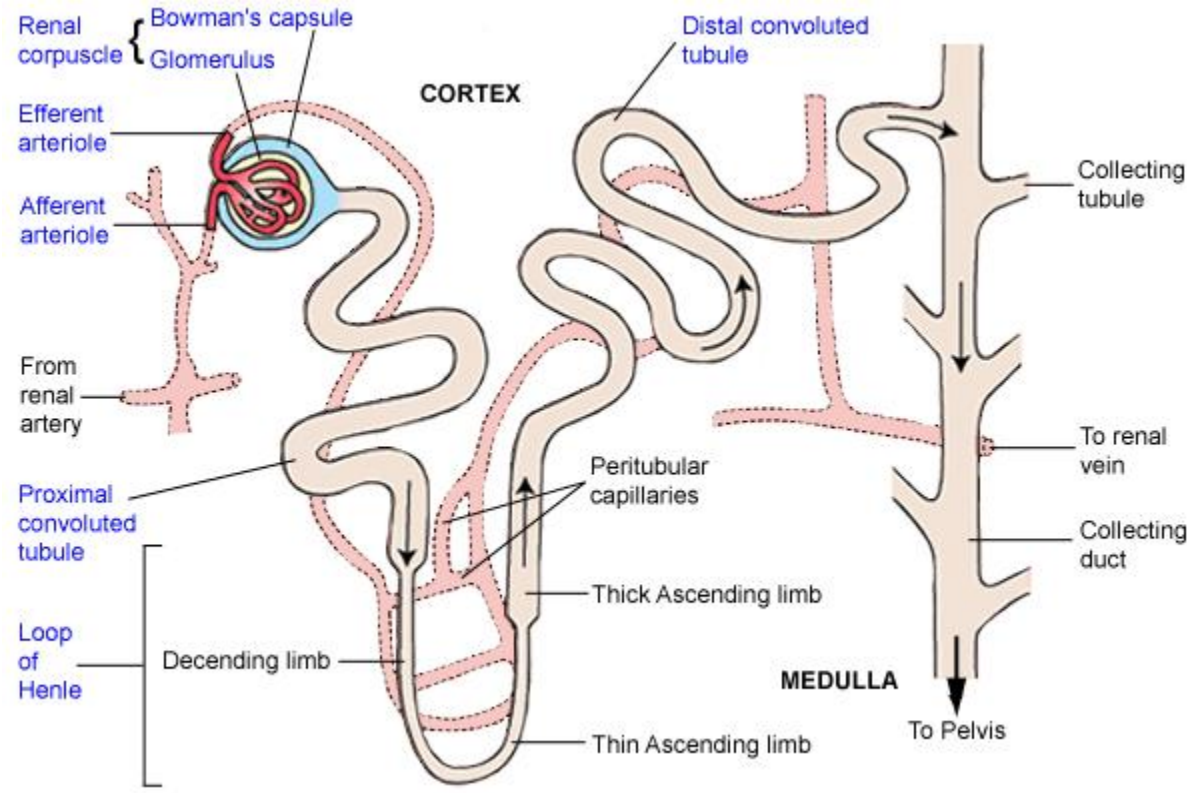


Fig. 2.7: Typical structure of a nephron

Each nephron comprises of two major components (renal corpuscle and renal tubule) with several functionally and histologically distinct regions. The renal corpuscle is made up of tuft of capillaries, called the **glomerulus** surrounded by dilated **Bowman's capsule.**

Glomerulus, the filtration unit of the kidney is uniquely situated between two resistance vessels (afferent and efferent arteriole). The afferent arteriole supplies blood to the glomerulus and drained by the efferent arteriole. The glomerulus protrudes into dilated fluid filled capsule known as the Bowman's capsule. The combination of a glomerulus and a Bowman's capsule forms the renal corpuscle. Blood in the glomerulus is separated from the fluid of the Bowman's space by a filtration barrier. Each glomerulus is lined with mesangial cells, proximal layer of

fenestrated endothelium (70-100nm), followed by a glomerular basement membrane, a meshwork of type IV collagen, proteoglycans, fibronectins . There is also a distal layer of visceral epithelial cells called the podocytes.
The renal tubule has a total length of between **45 – 65 mm** segmented into
Proximal tubule: The Proximal tubule (15 mm) lies in the cortex and is composed of single layer of cells whose apexes are united by tight junctions, rich in mitochondria and have distinct brush border. The base of the cells lining the proximal convoluted tubules extends to the extracellular spaces called lateral intercellular spaces. It is divided into convoluted tubule and straight tubule. The part of the tubule nearest the glomerulus is the proximal convoluted tubule. The PCT is most active and selective in absorption

Loop of Henle: The Loop **of Henle** is a U shaped tubule that dip into the medulla and comprises of the descending limb, hair pin bend, thin ascending limb made up of flat epithelium and the thick ascending limb, which have specialized cuboidal epithelial cells that forms the macular densa (dense spot), which consists of densely packed tubular epithelial cells on the side of the thick ascending limb that faces the glomerular tuft; these cells monitor the composition of the fluid in the tubule lumen at this point. The macular with the neighbouring lacis cells and the renin-secreting juxtaglomerular cells in the afferent arteriole forms the juxtaglomerular apparatus.

Distal convoluted tubule (DCT) lies in the cortex and it is about 5 mm long, have few microvilli but no distinct brush border. DCT coalesce to form the collecting duct

Collecting ducts (CD): The collecting duct is 20mm long and passes through the cortex and medulla. The ducts empty into the pelvis at the apexes of the pyramids. They **are** of two types the cortical CD and the medullary CD is made up of principal cells (P cells) and intercalated cells (I cells), the P cell predominant are involved in Na reabsorption and vasopressin stimulated water reabsorption. The I-cells which are smaller in number are concern with acid secretion and HCO_3 transport.
The DCT and CD are permeable to Na+ and water under the influence of antidiuretic hormones, aldosterone and natriuretic hormone**.**

Types of Nephrons
There are two types of nephrons. The cortical nephrons (85%) and the Juxtamedullary nephrons constitute (15%).The glomeruli of cortical nephrons are situated in the outer cortex, the loops of Henle are short and dip into the junction between outer and inner medulla. The juxtamedullary nephrons have their glomeruli deep in the cortex and the loops of Henle are long mostly extending into medulla towards the renal papillae. The Juxtamedullary nephrons are vital in urine concentration and greater reabsorption of glomerular filtrate.

Juxtaglomerular Apparatus (JA)
It is the area of contact between the distal convoluted tubule, afferent and efferent arterioles of the same nephron. The JA is composed of

i. Macula densa, are modified cells on the first part of the distal tubule. It detects changes in fluid volume and sodium ions in the distal tubule. The golgi apparatus of the macula densa secretes a substance directed at the arterioles.
ii. Juxtaglomerular Cells: are granular cells located at the middle of the afferent arterioles and secretes renin.
iii. Lacis' cells are agranular cells located between afferent and efferent arterioles. They store renin.

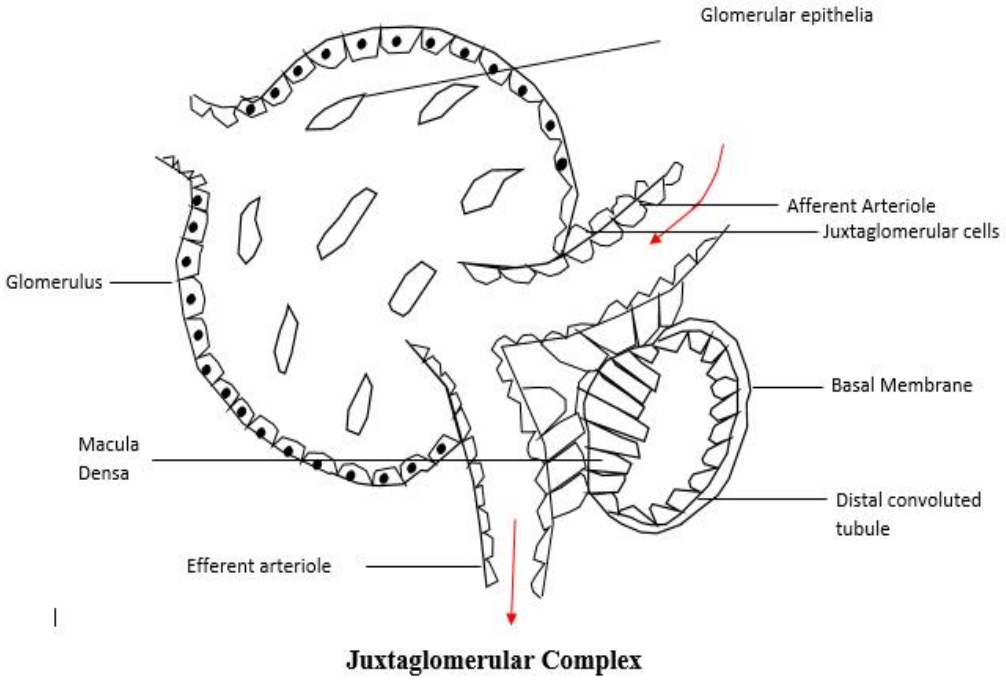


Figure 2.8: Justaglomerular complex

Renal circulation and autoregulation

Renal Blood Flow (RBF)

- In resting, healthy, young adult man, renal blood flow averages about 1.2 L/min (about 20% of the cardiac output (5 to 6 L/min). This rate of perfusion exceeds that of all other organs in the body, except the neurohypophysis and carotid bodies. The high blood flow to the kidneys is necessary for a high GFR and is not due to excessive metabolic demands. Hence the mechanism involved in RBF regulation is in close relation to the regulation of GFR. Renal extraction of oxygen is low, and renal venous blood has a bright red color (because of high oxyhemoglobin content). Blood flow is highest in the cortex (4 to 5 mL/min per gram of tissue). The high cortical blood flow permits a high rate of filtration in the glomeruli. Blood flow (per gram of tissue) is about 0.7 to 1 mL/min in the outer medulla and 0.20 to 0.25 mL/min in the inner medulla. The relatively low blood flow in the medulla helps maintain a hyperosmolar environment in this region of the kidney.

AUTOREGULATION OF RENAL BLOOD FLOW

Renal autoregulation is an intrinsic property that keeps renal blood flow relatively constant, despite fluctuation in arterial blood pressure (80-180mmHg).

Two main mechanisms are responsible for the renal autoregulation

- myogenic and
- tubuloglomerular feedback

Myogenic mechanism:

Stretch on blood vessel walls due to increased arterial blood pressure opens stretch-activated cation channels in smooth muscle cells. Membrane depolarization occurs and open voltage-dependent Calcium channels and intracellular calcium rises, causing smooth muscle contraction. Vessel lumen diameter decreases and vascular resistance increases. Decreased blood pressure causes the opposite changes.

Tubuloglomerular feedback mechanism:

Elevation of blood pressure (BP) leads to increase in GFR which result in increased solute (tubular fluid/ NaCl]) delivery to the macula densa. This cause in increased NaCl reabsorption by macula densa cells and constriction of the nearby afferent arteriole, resuting to the vasoconstrictor agent, may be adenosine or ATP; it does not appear to be angiotensin II, although feedback sensitivity varies directly with the local concentration of angiotensin II. In the end, blood flow and GFR are lowered to a more normal value.

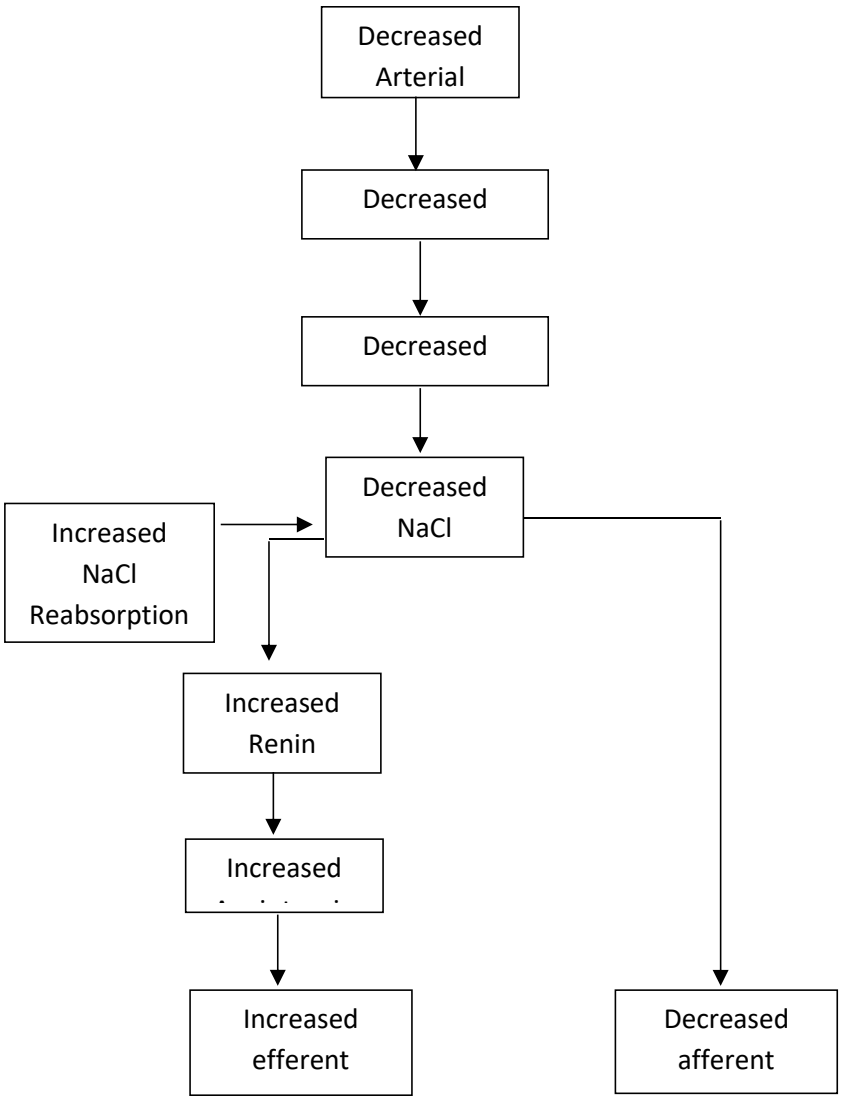


Fig. 2.9: An illustration of tubuloglomerular feedback mechanism.

Regulation of Renal Blood Flow

- Stimulation of renal sympathetic nerves leads to renal vasoconstriction of afferent arteriole via α receptors and decrease in renal blood flow.
- Second, the catecholamines strongly enhance Na+ reabsorption in proximal-tubule cells.
- Third, as a result of the dense accumulation of sympathetic fibers near the granular cells of the JGA, increased sympathetic nerve activity dramatically stimulates renin release
- Renal sympathetic innervation are activated by cold temperatures, deep anesthesia, fearful situations, hemorrhage, pain, and strenuous exercise.

Renal Vasoconstrictor Substances

Endothelin,21-amino-acid peptides, synthesized by endothelial cells, acts on vascular smooth muscle cells in arterioles to increase intracellular Ca2+ by releasing it from intracellular stores and thus increasing arteriolar resistance. Endothelin has been implicated in the nephrotoxicity of some drugs such as cyclosporine, other renal vasoconstrictor substances are epinephrine, norepinephrine, thromboxane A2, and vasopressin.

Renal Vasodilation Substances

They include atrial natriuretic peptide, dopamine, histamine, kinins, nitric oxide, and prostaglandins E2 and I2.
Nitric oxide (NO) is a potent vasodilator in most arterioles including the afferent and efferent renal arterioles. The binding of acetylcholine, bradykinin, or histamine to endothelial cells results in the production of NO and decreased arteriolar resistance.
Some of these substances (e.g., prostaglandins E2 and I2) are produced locally in the kidneys.
Note: Non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in renal diseases because they undermine arachidonic production of PGE. Hence, no PGE to correct renal flow

Urine Formation

Urine formation involves three processes
Glomerular filtration
Tubular reabsorption and
Tubular secretion
Formation of urine begins with glomerular filtration of the plasma into the Bowman's capsule.The filtrate is modified as it passes through renal tubules by selective reabsorption and tubular secretion
During urine formation substances are handled in one of four different ways;

i. Filtered only
ii. Filtered and partially reabsorbed (water, elctrolyte)
iii. Filtered and completely reabsorbed (Nutrients)
iv. Filtered and secreted by tubules (urea)

Excreted amount = Glomerular filtrate, tubular secretion – Tubular reabsorption

GLOMERULAR FILTRATION (GF)

Is the first step of urine formation and allows for rapid removal of metabolic waste and a precise control of volume and composition of body fluids
Glomerular filtrate is defined as the volume of plasma filtered from the glomeruli into the Bowman's space per minute. GFR can also be defined as the product of the net driving pressure forcing fluid out of the glomerular

capillary and the permeability of the filtration barrier. In an average adult man the GFR is about 125ml/min or 180L/day.

Glomerular filtrate is the protein free ultra-filtrate fluid found in the Bowman's space, normally does not contain cells, but contains all substances in the plasma except substances like calcium ion and fatty acids bound to proteins that are not filtered. Glomerular filtration is a bulk flow process in which water and all low-molecular weight substances (including smaller peptides) move together. Most plasma proteins- the albumins and globulins are excluded almost entirely from the filtrate. Glomerular capillaries are relatively impermeable to proteins hence glomerular filtrate is devoid of plasma proteins and cellular elements.

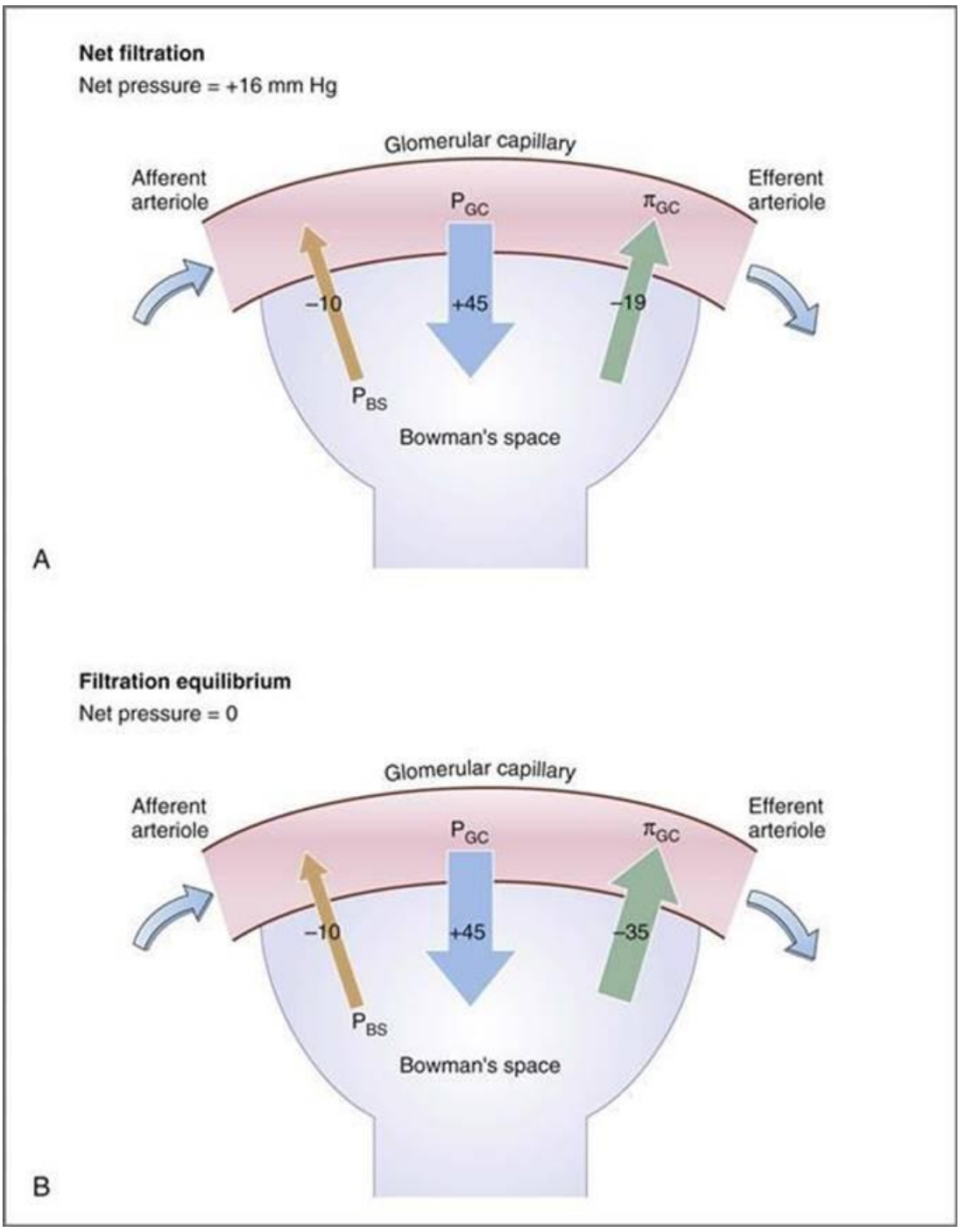


Figure 2.10: Forces involved in glomerular filtration

GLOMERULAR FILTRATION RATE (GFR)

Is defined as the volume of plasma filtered by the glomeruli into the Bowman's space per minute. GFR can also be defined as the product of the net driving pressure forcing fluid out of the glomerular capillary and the permeability of the filtration barrier. In an average adult man the GFR is about 125ml/min or 180L/day i.e. 60 times the plasma level in healthy kidneys (less by 10% in females). GFR is expressed in standardized terms with reference to 1.73 m^2 body surface area. In many kidney diseases, GFR is an important parameter of kidney function, as decreased GFR is an undesirable condition.

The filtration barrier which is essentially the glomerular capillary membrane is comprised of; three layers

i. A fenestrated capillary endothelium perforated by many large pores (70-90nm) that make it over 100 times more permeable to water and solutes than capillaries elsewhere in the body.
ii. A common basement membrane, which is an acellular (lacking cells) gelatinous layer with negative charge.

A layer of epithelial cells; the podocytes octopus-like cells that encircle the glomerular tuft with slit pores size of 25nm

Factors that affects filtration of macromolecules

Size (weights less than 10,000 are freely filterable, provided they are not bound to plasma proteins. Molecules with weights greater than 10,000 are restricted)

Shape, (slender and flexible molecule will pass through the glomerular filtration barrier more easily than a spherical, non-deformable molecule) and

Electrical Charge(Glomerular endothelial cells and podocytes have a negatively charged surface coat (glycocalyx), and the glomerular basement membrane contains negatively charged sialic acid, sialoproteins, and heparan sulfate)

Negative charges impede the passage of negatively charged macromolecules by electrostatic repulsion and favor the passage of positively charged macromolecules by electrostatic attraction

The determinants of GFR are;

i. Net filtration pressure equivalent to the sum of hydrostatic and colloid pressure across the membrane
ii. The glomerular capillary filtration coefficient which is a measure of hydraulic conductivity and surface area of the glomerular capillary.

The filtration pressure which is referred to as the Starling force comprises of;

i. A Positive glomerular hydrostatic pressure (60mmHg)
ii. A negative Bowman's capsule hydrostatic pressure (18mmHg)
iii. A negative glomerular capillary oncotic pressure (32mmHg)
iv. And when present a positive Bowman's capsule oncotic pressure (0mmHg), this is because protein concentration is low here

Factors that can affect GFR include the following;

i. Renal disease, diabetes mellitus and hypertension affects the surface area and thickness of the filtration barrier (Coefficient of filtration) thereby ultimately decreasing the GFR
ii. Urinary tract obstruction such as kidney stones causes increased tension in the renal tubules thereby increasing the Bowman's capsule hydrostatic pressure which eventually leads to a decreased GFR.

iii. Decreased renal blood flow and increased plasma protein concentration could increase the Bowman's glomerular oncotic pressure which eventually leads to decreased GFR
iv. Decreased arterial blood pressure, angiotensin II and increase in sympathetic nervous activity and vasoconstrictor hormones could ultimately lead to a decrease glomerular hydrostatic pressure that could result in decreased GFR

It should be noted that conditions that might bring about opposite effects on these physical determinants could also result to an opposite effect on GFR

Mechanism of Tubular Transport

- Trans-cellular
- Para-cellular

Tubular Reabsorption and Transport

Tubular reabsorption is a selective process that involves transport of some substances by diffusion, often across the tight junctions connecting the tubular epithelial cells. The reabsorption of all other substances involves mediated transport, which requires the participation of transport proteins in the plasma membranes of tubular cells.

i. Tubular epithelial membranes into renal interstitial fluids
ii. Through peritubular capillary membrane back into blood.

Reabsorbed substances are transported either actively or passively

Active transport involves movement of solutes against electrochemical gradient and requires energy derived from metabolism. It can be either primary active transport which occurs directly due to hydrolysis of ATP or secondary active transport which occurs due to ion gradient indirectly coupled to energy source. Energy hydrolyzed comes from membrane bound ATpase. Examples of primary active transporters include Na^+-K^+ ATpase, H^+ ATpase, H^+-K^+ Atpase, and Ca^{2+} ATpase. The Na^+-K^+ ATpase Pumps out Na^+ from the cell into the interstitium and K^+ into the cell thereby favouring passive Na^+ diffusion into the cell from the lumen.

In secondary active transport, two or more substances interact with specific membrane bound proteins and are transported together across the membrane. Substances transported via secondary active transport include glucose and amino acids. Transport proteins can either be co-transporters (Symporters) when the substances are transported in the same direction or counter transporters (Antiport) when substances are transported in opposite direction. Another form of active transport mechanism for the reabsorption of protein in some part of the renal tubule is pinocytosis. Proteins attach to the luminal membrane which invaginates into the interior of the cell as a vesicle before they are digested into their constituent amino acids.

A passive transport system in the renal tubules is osmosis. Water is reabsorbed in the renal tubules via osmosis as a result of a concentration gradient caused bay active transport of sodium. Chloride ions, urea and other solutes are reabsorbed by passive diffusion.

Tubular reabsorption is regulated via;

i. Local control mechanism (Glomerulotubular balance)
ii. Hormonal control mechanism
iii. Nervous control mechanism

Tubular secretion is the transportation of substances from the blood into the renal tubules. The P-cells and I-cells of the distal convoluted tubules (DCT) and collecting duct (CD) play a vital role in tubular secretion during urine formation. The P-cells reabsorb water and Na^+ and then secrete K^+ into blood from lumen and the I-cells reabsorb K^+ and secrete H^+ into the tubular lumen from blood. This is achieved by the presence of Na^+-K^+ATpase and H^+ ATpase.

Counter-current system: Is a system where inflow is parallel to and counter to outflow. It consists of the loop o Henle and vasa recta. Loop of Henle is responsible for counter-current multiplier, while the vasa recta are responsible for counter-current exchanger. This system produces a hyperosmotic renal medullary interstitium. The concentration mechanism depends upon the maintenance of a gradient of increasing osmolality along the medullary pyramids. The gradient is produced by the operation of the loops of Henle as countercurrent multipliers and maintained by the vasa recta as counter-current exchanger. This is achieved through major factors that contribute to the buildup of solute concentration into the renal medullar as follows:
Active transport of Na^+ and co-transport of K^+, Cl^- and other ions out of the thick portion of the ascending limb of the loop of Henle into the medullary interstitium.

i. Active transport of ions from the collecting ducts into the medullary interstitium
ii. Passive diffusion of large amounts of urea from the inner medullary collecting ducts into the medullary interstitium
iii. Diffusion of only small amount of water from the medullary tubules into the medullary interstitium, which is far less than the reabsorption of solutes into the medullary interstitium

Counter- current multiplier: This process is mainly achieved by using energy to generate osmotic gradient that enable individual's to produce concentrated urine, in order not to produce large quantity of urine which can lead to dehydration. The counter current- current multiplication is achieved by the loops of Henle which have both cortical and juxtaglomerular nephrons (see anatomy of kidney) that regulate concentration of both solutes and water in the blood. Counter-current multiplication in the juxtamedullary nephron of the loops of Henle is largely responsible for developing the osmotic gradients that are needed to concentrate urine. Fluid leaving the ascending limb of the loop of Henle enters the DCT, where its composition is further adjusted, and then drains into the CT, these tubules empty into collecting duct that descends back through the medulla and eventually connect to the ureter which transports urine to the bladder. Although, the loops of Henle are essential for concentrating urine, the specialized capillary network (vasa recta) that surrounds the loops is equally important. The vasa recta capillaries are long, hair pin-shaped blood vessels that run parallel to the loops of Henle. The hair pin turns slow the rate of blood flow which maintains the osmotic gradient required for water reabsorption.

CHARACTERISTICS OF THE THREE SEGMENTS OF THE LOOP HENLE THAT ENABLE COUNTER-CURRENT MULTIPLIER

The three segments of the loops of Henle have different characteristics that enable countercurrent multiplication.

- The thin descending limb is passively permeable to both water and small solutes such as NaCl and urea. As active reabsorption of solutes from the ascending limb of the loop of Henle increases the concentration of solutes within the interstitial space (space between cells), water and solutes move down their concentration gradients until their concentrations within the descending tubule and the interstitial space have equilibrated. As such, water moves out of the tubular fluid and solutes to move in. This means, the tubular fluid becomes steadily hyperosmotic (compared to blood) as it travels down the thin descending limb of the tubule.
- The thin ascending limb is passively permeable to small solutes, but impermeable to water, which means water cannot escape from this part of the loop. As a result, solutes move out of the tubular fluid, but water is retained and the tubular fluid becomes steadily more dilute or hyposmotic as it moves up the ascending limb of the tubule.
- The *thick ascending* limb actively reabsorbs sodium, potassium and chloride. This segment is also impermeable to water, which again means that water cannot escape from this part of the loop. This segment called the "diluting segment".

Countercurrent multiplication moves sodium chloride from the tubular fluid into the interstitial space deep within the kidneys, although in reality it is a continual process.

COUNTER-CURRENT EXCHANGE

Absorbed water is returned to the circulatory system via the vasa recta, which surrounds the tips of the loops of Henle. Because the blood flow through these capillaries is very slow, any solutes that are reabsorbed into the bloodstream have time to diffuse back into the interstitial fluid, which maintains the solute concentration gradient in the medulla. This passive process is known as countercurrent exchange.

- The concentration of urine is controlled by antidiuretic hormone, which helps the kidneys to conserve water. Its main effects in the renal tubules are to increase water permeability in the late distal tubule and collecting ducts by promoting the facultative reabsorption of water from the distal convoluted tubules. This is achieved by causing either an increase in the number of water permeable "pores" or an increase in the size of such pores, cAMP acts as a second messenger in the process. Increase active transport of sodium chloride in the thick ascending limb of the loop of Henle, and enhance countercurrent multiplication and urea recycling, all of which increase the size of the osmotic gradient.
- **Recycling of urea: R**ecycling of urea in the inner medulla also contributes to the osmotic gradient generated by the loops of Henle. Antidiuretic hormone increases water permeability, but not urea permeability in the cortical and outer medullary collecting ducts, causing urea to concentrate in the tubular fluid in this segment. In the inner medullary collecting ducts it increases both water and urea permeability, which allows urea to flow passively down its concentration gradient into the interstitial fluid. This adds to the osmotic gradient and helps drive water reabsorption.
- Note: The kidneys are able to separate the reabsorption of water and solutes in the loop of Henle, distal nephron and collecting ducts. This means urine can be made more concentrated or more dilute than plasma, depending on the level of body hydration. This process is mainly controlled by antidiuretic hormone, a hormone that is made in the hypothalamus of the brain and stored in the pituitary gland. The release of antidiuretic hormone by the pituitary gland is controlled by sensors in your heart and blood vessels that detect drops in blood pressure, or increased concentrations of salt in the bloodstream that may occur when dehydrated. Alcohol inhibits the release of antidiuretic hormone, which increases urine production.

Water volume and Ionic Regulation

Although water and ions are constantly moving, their concentration in the various compartments remains fairly relatively constant. Naturally, Increase in water output must be compensated by an increased water intake. Osmo-receptors in the hypothalamus detect changes in osmolality of body fluids which increases during dehydration.

During dehydration, there is increased thirst sensation characterized by dryness of the mouth and less salivary secretion. As a result volume of water consumed is readily absorbed in the gastric mucosa and intestine to restore the normal osmolality. Release of ADH by the posterior pituitary gland during dehydration increases renal tubular reabsorption of water which leads to preservation of blood volume and decreased urine output.

Aldosterone also released from the suprarenal cortex as a result of decreased blood sodium ion concentration or significant decrease in arterial blood pressure increases renal reabsorption of sodium ions which causes water from the filtrate to move into blood hence restoring its osmolality. Other factors such as vomiting, diarrhea, excessive sweating, haemorrhage; severe burns and fever may also cause water loss which must be replaced by increased water consumption or intravascular administration.

A less common occurrence is water intoxication characterized by too much water in the body due to over consumption of fluids usually unchecked intravenous infusion. Its symptoms include dizziness, abdominal cramps, nausea and lethargy and in severe cases convulsion hence fluid intake must be restricted until the excess water is excreted by the kidneys. Atrial natriuretic peptide (ANP), which is release by the atria during increased blood volume and pressure decreases renal sodium absorption thereby increasing urinary output of sodium ion and water. Also decrease ADH secretion results to greater urinary output which also returns blood osmolality to normal.

Some of the ions that help create osmolality of body fluids and regulate osmosis between compartments include; Na^+, K^+, Ca^{2+}, Mg^{2+}, Fe^{2+}, H^+, Cl^-, HCO^{3-},SO_4^{2-}, HPO_4^{2-} and protein anions. The distribution of electrolytes varies with the compartment with K+, HPO_4^{2-}, and protein anions being the most abundant cation and anion in the intracellular fluid (ICF) respectively. Some hormones also regulate ionic concentration in the extracellular fluid (ECF). Aldosterone increases renal reabsorption of sodium ion and potassium ion excretion, Atrial Natriuretic peptide also increases sodium ion excretion by kidneys and decreases sodium ion blood.

Parathyroid hormone increases calcium and phosphorous reabsorption from bones and increase absorption from the intestine. Calcitonin increases removal of calcium and phosphate ions from blood to form bone matrix. Electrolytes are commonly lost in urine, sweat and faeces.

Acid-Base Balance

The human body produces 80mEq of non-volatile acids from protein metabolism daily which cannot be excreted by the lungs. The primary mechanism for removal of these acids is renal excretion which must also prevent bicarbonate loss in urine.

The kidney filters about 4320mEq of bicarbonate daily which must be reabsorbed almost entirely thereby conserving the primary buffer system. Both reabsorption of bicarbonate and hydrogen ion excretion is achieved through H^+ secretion by the tubules. The kidney regulates extracellular fluid (ECF) H^+ concentration via three fundamental mechanisms;

i. Secretion of H^+
ii. Reabsorption of Bicarbonate
iii. Production of New Bicarbonate

H^+ secretion and Bicarbonate reabsorption occurs in all parts of the renal tubules except the thin descending and ascending limb of Henle. The kidney regulates Acid-Base balance through the following buffer system: bicarbonate, phosphate and phosphate buffers.

i. Bicarbonate Buffer system

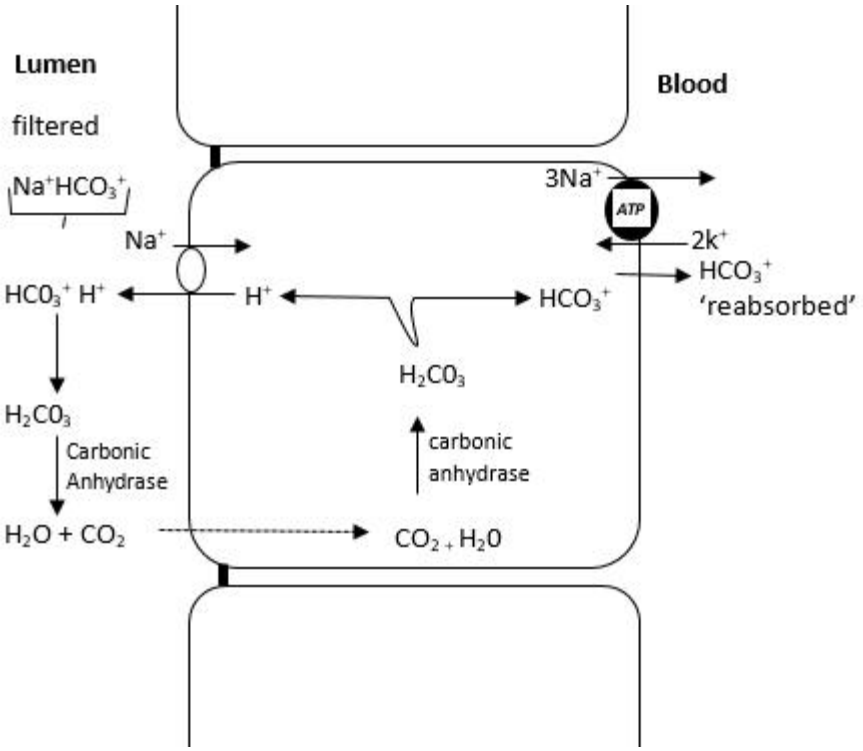


Fig. 2.11: Bicarbonate buffer system

ii. Phosphate Buffer system

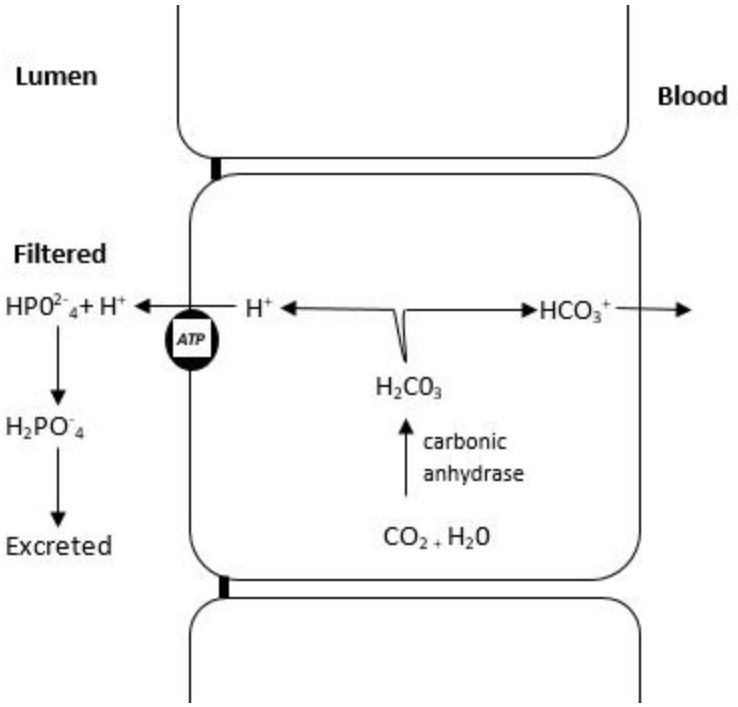


Fig. 2.12: Phosphate buffer system

iii. Ammonium-Ammonia Buffer system

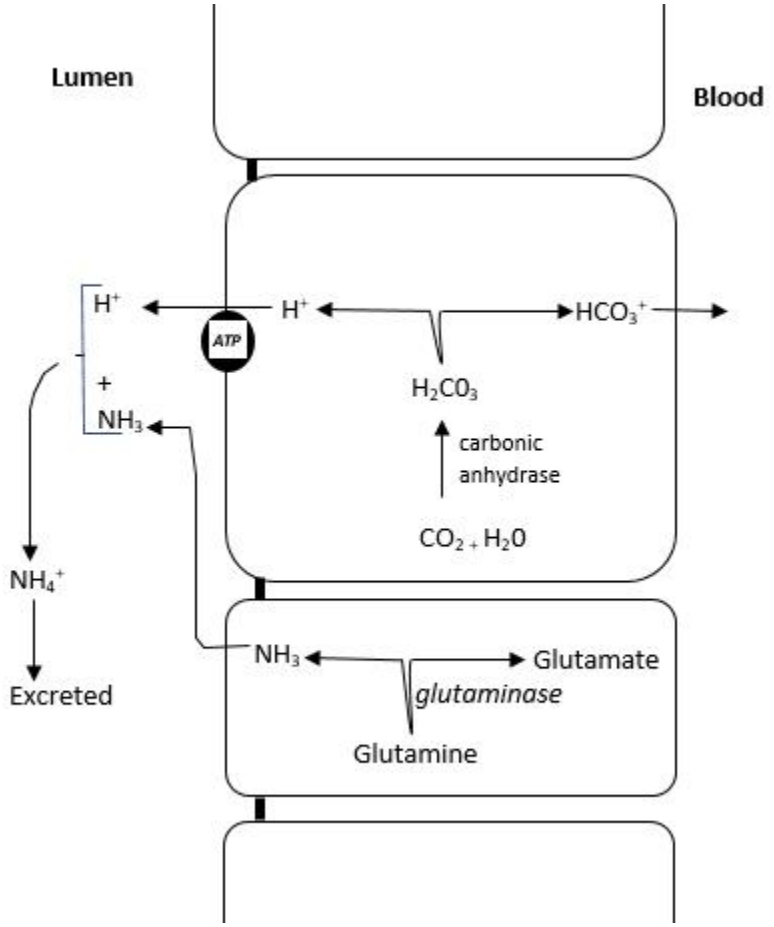


Fig. 2.13: Ammonium-Ammonia buffer system

MICTURITION: Is the ejection of urine stored in the bladder through the urethra to the outside world. Urine flow from the kidneys to the bladder by contraction of the smooth muscle of the ureter for the urine to be stored for excretion when the environment is conducive.

The bladder is a balloon-like chamber with walls made special smooth muscle called the detrusor muscle. The contraction of this detrusor muscle squeezes on the urine in the bladder lumen to produce urination. The part of the detrusor muscle at the neck (base) of the bladder where the urethra begins function as a sphincter called the internal urethral sphincter. It has a natural tone that keeps the bladder neck and posterior urethra empty of urine, this prevents emptying of the bladder until the pressure in the main part of the bladder rises above a critical

threshold. Immediately below the internal urethral sphincter, a ring of skeletal muscle surrounds the urethra called the external urethral sphincter, its contraction can prevent urination even when the detrusor muscle contracts it can be to consciously prevent urination even when involuntary controls are attempting to empty the bladder. The urinary tract consists of both skeletal and smooth muscles; the detrusor muscle (smooth muscle), internal urethral sphincter (smooth muscle) and the external urethral sphincter (skeletal muscle). The factors that influence the bladder structures are:

a. The detrusor muscle is innervated by way of the pelvic nerves, which connect with the spinal cord through the sacral plexus, mainly S-2 and S-3. Coursing through the pelvic nerves are both sensory and motor nerve fibers. The sensory fibers detect the degree of stretch in the bladder wall which causes muscular contraction. Because of the arrangement of the smooth muscle fibers, when the detrusor muscle is relaxed, the internal sphincter is closed. The motor nerves are transmitted by way of parasympathetic neurons which cause the detrusor muscle contracts, changes in its shape tend to pull open the internal urethral sphincter.
b. The internal urethral sphincter which is a smooth muscle receives sympathetic innervation, which causes contraction of the sphincter.
c. The external sphincter which is a skeletal muscle is innervated by somatic motor neurons transmitted through the pudendal nerves, which causes contraction of external sphincter. This causes the voluntary control of micturition

   Urine is transported from the kidneys to the bladder through the ureters which are muscular tubes that are made up of smooth muscles and are innervated by both sympathetic and parasympathetic nerve fibers as well as an intramural plexuses of nerve fibers. The two ureters enter the bladder at a triangular area called the trigone which is found above the bladder neck on the posterior wall. Urine flowing from collecting ducts into the renal calyces stretches the calyces and increases their inherent pacemaker activity, which in turn initiates peristaltic contractions that spread to the renal pelvis and then down along the length of the ureter, thereby forcing urine into the bladder.

   As the bladder fills with urine, the pressure within increase and this stimulate stretch receptors in the bladder wall. The afferent fibers from the receptors enter the spinal cord and stimulate the parasympathetic neurons, which then cause the detrusor muscle to contract. The afferent input from the stretch receptors reflexly inhibits the sympathetic neurons to the internal urethral sphincter, which contributes to its opening. The afferent input also reflexly inhibits the somatic motor neuron of the external urethral sphincter, thereby causing it to relax. Now, both sphincters are now open, and contraction of the detrusor muscle can produce micturition.

   In addition to the local spinal reflexes discuss in micturition above, there are descending reflexes from the brain which can also profoundly influence this reflex, determining the ability to prevent or initiate micturition voluntarily. The loss of these fibers (descending pathways) as a result of spinal cord damage eliminates one's ability to voluntarily control micturition.

Micturition Reflex

Stimulus: Distension (300ml and above)
Receptors: Tension
Afferent impulses: Pelvic nerve
Centre: 2,3 and 4
Efferent impulses: Pelvic nerve
Response- Contraction of bladder wall and relaxation of internal sphincter

ABNORMALITIES OF RENAL FUNCTIONS

Diseases of the kidneys initially evolve from predorninant involvement of one of the morphologic component i.e. the glomeruli, renal tubules, interstitium or blood vessels, eventually all components are affected leading to end stage kidneys.

Major renal diseases are caused by infectious or toxic agents or due to immunologically mediated, due to pressure as in hypertension or due to impaired renal blood flow. Irrespective of the cause, renal disease results into two pathological syndrome; acute renal failure and chronic renal failure.

ACUTE RENAL FAILURE

Is a syndrome that is characterized by acute onset of renal dysfunction with symptoms of oliguria or anuria and sudden increase in metabolic waste products like urea and creatinine in blood with consequent development of uraemia.

Acute renal failure can be classified according to the area affected into three; it can be pre-renal, intra-renal or post-renal

i. Pre-renal causes: can be due to diseases which cause sudden decrease in the flow of blood to the nephron. The decrease in blood flow will result in functional disorders or decrease GFR or both. These can be due to vascular disorders, hypovolaemia due to sudden loss of blood, low cardiac output leading to low perfusion of blood to the kidneys.

ii. Intra-renal causes: these are diseases affecting the renal tissue, which can affect either the arteries and arterioles like blood clots, or cholesterol deposits the block blood flow within the kidney, diseases affecting the glomeruli e.g. glomerulonephritis, acute tubular necrosis, pyelonephritis, effect of toxins such as alcohol, heavy metals, medication certain chemotherapy, antibiotics and dyes used in imaging etc.

iii. Post-renal causes: these are diseases that can cause obstruction to the flow of urine anywhere along the renal tract distal to the opening of the collecting ducts. It can be due tumour within the lumen e.g bladder cancer or kidney stones, or affecting the lumen or from surrounding tissues compressing on the lumen of the urinary tract like cancer of the colon, cervix or enlarge prostate.

Symptoms: include decreased urinary output, swelling due to fluid retention, nausea, fatigue and shortness of breath. Sometimes symptoms may mild or not at all.

Treatment: treat the underline cause.

CHRONIC RENAL FAILURE: is a syndrome characterized by progressive and irreversible deterioration of renal function due to slow destruction of renal parenchyma, eventually leading to death when sufficient number of nephrons have damaged. The kidneys are involved in the filtering and removal of waste and excess fluid from the body. CKD if advanced can cause dangerous level of fluids, electrolytes and waste to build up in the body.

Symptoms: may be few, patient might not even realize that there are kidney problems until when it is advanced. Advanced CKD patients may present with nausea, vomiting, loss of appetite, urinating more or less sleep problems, muscle cramps, swelling feet and ankles, shortness of breath, hypertension etc.

CAUSES

i. Diabetes mellitus (type 1 or type2).

ii. High blood pressure (hypertension)

iii. Glomerulonephritis
iv. Polycystic kidney disease
v. Prolonged obstruction of the urinary tract
vi. Interstitial nephritis

Treatment: mainly focuses on slowing the progression of kidney damage by controlling the cause, this will only slow the progression of the kidney damage. Chronic kidney disease can progress to end-stage-kidney failure if dialysis is not commenced.

Summary: The unique anatomical presentation and arrangement of the renal structures enables it to perform its multiple functions in the maintenance of homeostasis. The success of urine formation and excretion of metabolic waste by the kidney depends on the integrity and efficiency of the various mechanisms involved. The regulation of renal blood flow and glomerular filtration rate is achieved by intrinsic regulatory mechanisms that use alteration of renal arteriolar resistance to maintain a fairly constant internal environment. Tubular reabsorption and various transport mechanism employed across renal tubules enables filtered substances to be reabsorbed and excreted at various rates and quantity depending on the body needs. This enables the kidney to regulate solutes excretion independently of one another, a capability essential in control of composition of body fluids.

Learning Outcomes On completion of this course, the student should be able to;
1. Sketch a cross section of a kidney; identify the renal cortex, renal medulla, renal calycies, medullary pyramids, renal pelvic space, renal artery, renal vein, and ureter;
2. Describe renal blood flow, renal plasma flow, glomerular filtration rate, and filtration fraction and list typical values;
3. Explain the concept of renal clearance. Use the clearance equation and an appropriate compound to estimate the glomerular filtration rate, renal plasma flow, and renal blood flow;
4. Describe the effects of reductions in GFR on plasma creatinine concentrations and plot the relationship;
5. Discuss the role of the ascending limb of the loop of Henle in producing a high renal interstitial fluid osmolality. From the loop of Henle, contrast the tubular fluid and interstitial fluid osmolality changes that allow either dilute or concentrated urine to be produced and excreted;
6. Describe processes that lead to acid-base disturbances and list the common causes;
7. Identify major routes and normal ranges for water intake and loss, and predict how changes in intake and loss affect the distribution of total body water.
8. List the various body fluid compartments and their ionic compositions
9. Describe the methods used in measuring the body fluid compartments
10. Discuss the role of the kidney in maintaining homeostasis of body fluids
11. Describe in details the response of the body to cold weather
12. Explain the response of the body to fever
13. Describe the functions of the ECF in the body
14. Explain in details the conditions for measuring basal metabolic rate (BMR).

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2) Nwafia, W.C.(2023). "Unpublished lecture notes on Skin and Body Temperature, Body fluids and Kidneys.

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Chapter 3

PHS 203. BLOOD PHYSIOLOGY

Maisaratu A. Tukur and Ahmed Ibrahim Salisu

OVERVIEW: Blood is a composed of formed elements (cells) suspended in a liquid called plasma. Suspended in plasma are proteins, nutrients electrolytes, waste product of metabolism, and other molecules. The formed elements are red blood cells (RBC), white blood cells (WBC) and platelets. It is a transport medium in the body, highly specialized tissue usually red in colour, degree of redness depends on the vessels from which it is taken. The specific gravity ranges between 1.055 - 1.065 and PH 6.8 - 7.2. Blood constitutes 7.7% of the total body weight. The total blood volume ranges from 5.0 - 6.0 liters. It performs several functions in the body such as respiratory, gastrointestinal, regulation of body temperature, immunity, excretion, buffering action and haemostasis.

OBJECTIVES OF THE STUDY: the objectives are:

a. To explain main functions of blood
b. To make the students understand the composition of blood
c. To understand the origin, lifespan, destruction of blood cells
d. To discuss the factors that affect red blood cell production
e. To classify the cellular component of blood
f. To describe how blood confers immunity to the body
g. To explain the haemostasis function of blood
h. To describe anaemia and the classification of anaemia
i. To enable the student understand the principle of blood grouping
j. To understand the basis of blood transfusion and its consequences
k. To explain the basic principle of immunity
l. To describe how the body confers immunity to the body
m. To explain how HIV affect the immune system
n. To enable student understand how to use blood to diagnose ailments and treat it adequately

General Physical Characteristics of Blood

Blood is a liquid connective tissue, denser and more viscous than water, slightly alkaline with a pH of 7.40, sticky to touch, and salty in taste. It clots on standing owing to the presence of fibrinogen. As a whole, blood consists of plasma and the suspended cells made up of the red blood cells, white blood cells and the platelets. The total circulating blood volume constitutes 6-8% of the body weight in an average adult male weighing 70kg. This is equal to 5–6 liters in volume. The circulating volume is less than the total because some amount is deposited in the reticuloendothelial system like liver and spleen. The interplay of various hormones that control salt and water excretion in the urine keep the blood volume remarkably constant.

Composition: Liquid plasma constitutes 55-60% of the blood volume and contains various proteins and other solutes dissolved in it. The rest of 40- 45% are the formed elements— mainly the red blood cells (RBCs), which are also called the Erythrocytes, white blood cells (WBCs), which are also called the Leucocytes and the platelets (cell fragments), which are also called the Thrombocytes. The RBCs are the most numerous (4.5–5.5 million/mm^3) with the diameter of approximately 7–8 µm. The total WBC count is 4,000–11,000/mm^3 and vary in size from 8 to 20 µm. The platelets count ranges from 150,000 – 450,000/mm^3, they are rounded or oval in shape with the size of 1.5 – 3.0µm in diameter.

The Plasma is made up of water (90-92%) and dry substances (8-10%). The dry substances include proteins, inorganic minerals and organic substances. The inorganic minerals consist of the cations and the anions. The cations are mainly the Na^+, K^+, Ca^{2+} and Mg^{2+}, while the anions are the Cl^-, $PO4^-$ and $HCO3^-$. The organic components of the plasma include; the proteins, lipids and the carbohydrates. The plasma proteins include the Albumin, Globulins and the Fibrinogen. The Albumin functions in transport of substances in the blood, regulation of oncotic pressure and pH regulation. The Globulins are mainly three types; α, β and γ types. They are all involved in transport of substance within the blood, allergic reactions and defense mechanism in the body. The Fibrinogen is involved in blood clotting (hemostasis). The major plasma carbohydrate is the glucose with value raging 3.3 – 5.5 mmol/L. The plasma lipids include the Triglycerides (< 150 mg/dL or 1.7mmol/L), High Density Lipoproteins (HDL) (60 mg/dL or 1.5mmol/L), Low Density Lipoproteins (LDL) (130mg/dL or 3.4mmol/L), Very Low Density Lipoproteins (VLDL) (2 – 30 mg/dL) and the Chylomicrons. In addition plasma normally contains varying amounts of enzymes, vitamins, pigments, hormones and waste products of metabolism. The composition of plasma and the various substances contained within it depend on the body's physiological and metabolic activities.

Properties of Plasma Proteins

Plasma proteins exhibit certain characteristics that are necessary for the normal physiological functions in the body. They include;

Molecular weight: The three major plasma proteins; Albumin, Globulin and Fibrinogen have different molecular weights which help them to distinctly carryout their functions. Albumin has a molecular weight of 69,000; Globulin has 156,000, while the Fibrinogen has 400,000 respectively.

Specific Gravity: The specific gravity of plasma protein is 1,026.

Buffer Action: Plasma proteins readily accept hydrogen ions in the blood, making them to be good buffers in the body.

Oncotic Pressure: This is a pressure exerted by the plasma proteins. It is a suction pressure, trying to draw fluids into the vascular compartment. It is called a colloid osmotic pressure and usually it is 25 mmHg.

Functions of Blood

Blood performs several functions in human body such as;

Transport of substances like gases, nutrients, hormones and waste products across the body

Regulation of body temperature by transporting heat from the tissues (mainly liver and muscles) to the skin from where it can be lost.

Regulates body pH through the different buffers it contains

Regulates osmotic pressure thereby maintaining water content of cells through the actions of its dissolved proteins and ions

Protects the body against diseases caused by harmful organisms by transporting leukocytes and antibodies against the foreign invaders.

Maintaining the viscosity of the blood

Blood grouping

Hemostasis by forming blood clots to prevent excess blood loss in the body

HAEMOPOIESIS

This is the formation of blood cells. Haemopoiesis takes place in 3 stages in life, starting from intrauterine life.

a. Mesoblastic phase- up to the 3rd month of intra-uterine life, blood cells are formed from mesoderm (yolk sac).

b. Hepatic phase- from the 3rd - 5th month of intrauterine life, blood cells are formed in the liver and spleen.

c. Myeloid phase- from the 5th month of intrauterine life onward, the bone marrow of all bones of the body manufacture blood cells.

After the age of 20 years blood cells are formed exclusively by flat bones of the skull, sternum, ribs, upper end of humerus, vertebra, crest of ileum and upper end of femur. Except in the areas mentioned above, all the other parts of bone marrow are filled up with fatty substance and are referred to as yellow bone marrow and cannot produce blood cells.

HAEMOPOIESIS occurs in the bone marrow, the mother cell which is a giant cell known as Pluripotent stem cells residing in the bone marrow, gives rise to large numbers of red cells, neutrophils, basophils, eosinophils, monocytes, platelets and lymphocytes circulating in the blood. Many of these blood elements are short lived and must be continuously replaced.

Cell division and differentiation is dependent on the continuous supply of highly specific protein factors which act as regulators of haemopoiesis. These protein regulators are called the haemopoietic colony stimulating factors (CSFs).

Some colony stimulating factors (CSFs) that influence blood cells

Factor	■ Target cells	Production cells

1. Erythropoietin	CFU-E	Kidneys, Liver
2. Interleukin-3	Pluripotent stem cell, Most progenitor cells many Terminally differentiated cells	T-lymphocytes
3. Granulocyte-Macrophage CSF (GM-CSF)	Granulocyte- macrophage progenitor cells	T-cells, fibroblast
4. Granulocyte CSF (G-CSF)	Granulocyte-M acrophage progenitor cells, and neutrophils	Macrophages, fibroblast
5. Macrophage CSF CSF	Granulocyte-Macrophage progenitor cells and	Fibroblast, macrophages

All of the above CSFs except erythropoietin are Lymphokines. Lymphokines are a group of polypeptides produced by activated leucocytes and acting on other cells in a hormonal, paracrine or autocrine fashion. Lymphokines may also be referred to as cytokines.

Erythropoietin is a glycoprotein hormone produced by the kidneys and liver, and it acts as the hormonal regulator of erythropoiesis, affects all committed erythroid cells and enhancing their activity. Normal erythropoiesis also required the presence of Vitamin B_{12}, folic acid, iron etc.

ERYTHROPOIESIS

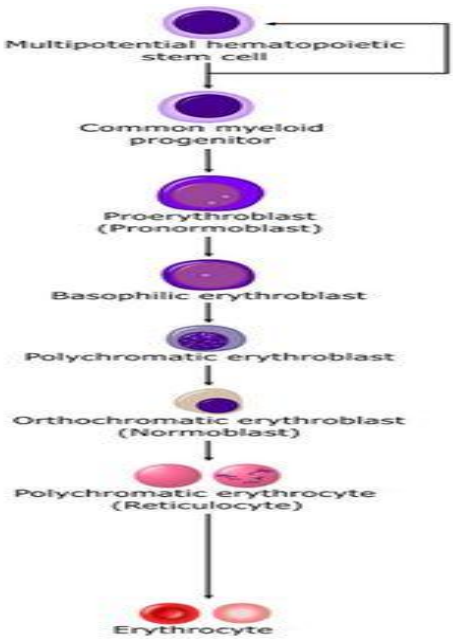


Fig. 3.1: Erythropoiesis

RED BLOOD CELLS

Size is about 7.2 μ non-nucleated, biconcave disc. The thickness of both ends is 2μ and at the middle 1 μ approximately. Average volume of RBC is $90mm^3$

Shape-The RBCs are non-nucleated biconcave disc. This particular shape is advantageous to them as

a. It enables them to pass or squeeze through narrow capillaries.

b. The biconcave shape minimizes diffusion distance between cell surface and individual hemoglobin molecule.

c. It acts as an osmometer and helps to respond to osmotic pressure change in the peripheral capillaries.

STRUCTURE- The red cell membrane has a semi permeable membrane. The cell membrane has got three layers. The outer and inner layer is made up of proteins. The middle layer is made up of phospholipids. The outer layer of the membrane composed principally of glycoproteins which carry several major blood group antigens which are A, B, M, N etc.

The cell membrane is permeable to water, H*, urea, glucose uric acid etc. It is relatively impermeable to sodium. The membrane is impermeable to proteins, K and Hb.

RBC STRUCTURE

diagram

The stroma contains Hb, proteins, lipids and others e.g. enzyme and salts. The enzyme include carbonic anhydrase which catalysis the reaction between CO_2 and H_2O to form carbonic acid. 50% of the lipid present in the stroma are found in combination with proteins and are known as lipoproteins complex.

FUNCTIONS OF RED BLOOD CELLS (RBC)

1. Transportation of O_2 from the lungs to other tissues and CO_2 from tissues to the lungs.

2. Maintenance of acid-base balance by the buffering action of Hb.

3. Pigment formation various pigments are derived from Hb after destruction of the RBC e.g. bilirubin and biliverdin.

FACTORS AFFECTING ERYTHROPOIESIS

1. Dietary factors-Foods rich in first class proteins are very important as it supplies essential amino acids necessary for synthesis of globin portion of haemoglobin. It is also necessary for the formation of nucleoprotein and stroma protein of RBC.

2. Hypoxia- Stimulates bone marrow indirectly through the mechanism of erythropoietin. It stimulates the kidneys which produces renal erythropoietic factor (REF); it also stimulates the liver to form α_2-globulin. These two together forms a hormone called erythropoietin which is a glycoprotein in nature and acts on the bone marrow. It increases RBC production by stimulating the conversion of the primitive stem cells to committed erythroid cells (Haemocytoblast).

3. Role of endocrine glands - Certain endocrine glands influences erythropoiesis. Testosterone increases RBC. In hyperthyroidism and hyper functioning of adrenal glands (adrenal cortex) red cell count also increases. In pituitary insufficiency, hypothyroidism and adrenal insufficiency (hypo-adrenalism), there is decrease in red cell counts.

4. Maturation factors-These are factors that are responsible for the maturation of nucleated cells up to late normoblast. They include vitamin B_{12}, and folic acid. Vitamin B_{12} is an extrinsic factor; it needs intrinsic factor before absorption. Intrinsic factor is produced by the lining of the stomach. Disease of the stomach results to megaloblstic anaemia.

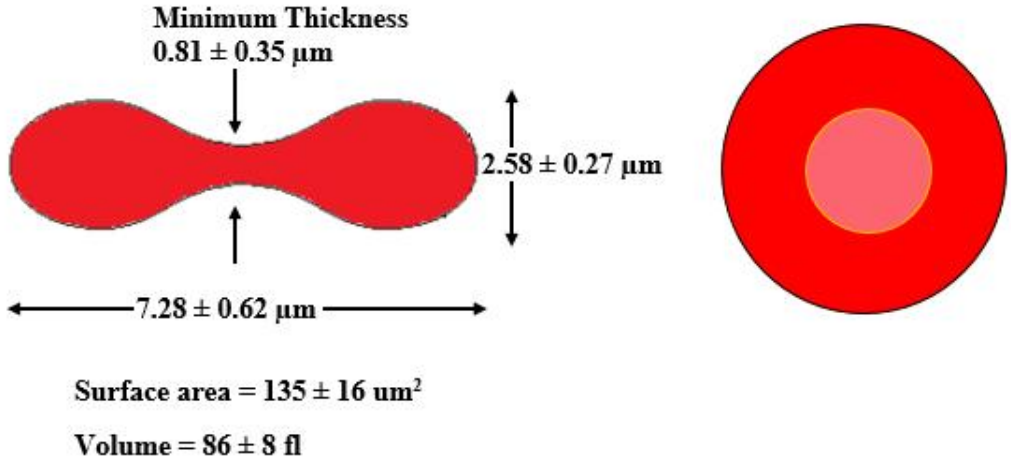
5. Factors controlling Hb formation (haematinics), Iron, copper, amino acids vitamin B_6 etc. are required for synthesis of Hb.

Normal RBC count of male is 4.5 - 6.0million cells/mm^3

Female is 4.0 - 5.5million cells /mm^3.

Value below the lower limit is referred to as anaemia

Value above the upper limit is referred to as polycythemia.



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PHYSIOLOGIC VARIATION IN RBC COUNT

1) At high altitude -the fall in oxygen tension results in hypoxia which stimulates erythropoiesis

2) At birth and in infancy, the count is very high.

3) Diurnal variation-variations during the 24 hours of the day. The count is lowest during sleep, then gradually rises and becomes maximal in the evening.

PATHOLOGICAL VARIATION IN RBC COUNT

1) Decrease in RBC count is called anaemia. Anaemia is the quantitative or qualitative reduction in circulating RBC.

2) Increase in RBC is called polycythemia.

VARIATION IN SIZE AND SHAPE OF RBC

a) Normocytes (7.2μ)

b) Microcytes (less than 7μ)

c) Macrocytes (greater than 8μ)

SHAPE

1) In certain diseases, RBCS are not biconcave, but spherical. These cells are called Spherocytes.

2) They could be sickle shaped as in sickle cell anaemia.

HAEMOGLOBIN

Haem-Blood

Globin-Protein

Haemoglobin is a conjugated protein. It consists of a simple protein-globin, to which are attached four molecules of an iron containing pigment called Haem. By virtue of its iron, Hb can combine with oxygen to form oxvhaemoglobin.

H ← α β → H

H← α β → H

Hb contains 4 haem groups and a globin moiety. The globin moiety consists of a pair of α- polypeptide chain and another pair of β-polypeptide chain.

The haem portion is a combination of an iron atom with a molecule of porphyrin. Porphyrin itself consists of four pyrolle rings joined together by methane bridges. The carbon atom of the methane bridges are labelled as α, β, γ, and δ.

FACTORS NEEDED FOR SYNTHESIS OF HAEMOGLOBIN

1. Iron, copper, vitamin B_{12}, B_6, Nicotinic acid and pantothenic acid are required for haem synthesis.

2. For the synthesis of globin, Amino acids (Proteins) are required. In protein deficiency, globin is not synthesized.

FUNCTIONS OF HAEMOGLOBIN

1. Carry oxygen from the lungs to the tissues
2. To carry carbon dioxide from the tissues to the lungs for excretion
3. Act as a buffer
4. When degraded, they produce bile pigments

TYPES OF HAEMOGLOBIN

HbA, HbF, HbSc

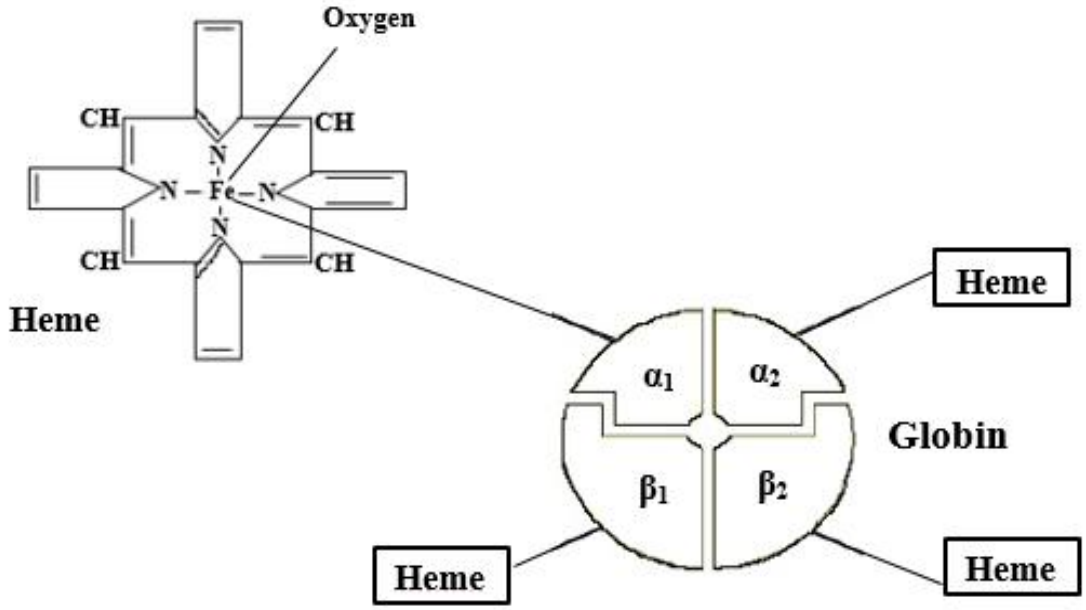


Fig. 3.4: Normal Adult Heamoglobin A

FOETAL HAEMOGLOBIN

The globin moiety consists of two α and two γ globulins.

H ← α γ → H

H← α γ → H

In foetal Hb, there is one pair of α--polypeptide chain. The β -polypeptide chain is replaced by γ -polypeptide chain. The foetal Hb has greater affinity for oxygen than adult Hb, so due to more affinity, oxygen binding will also be strong. So the amount of oxygen released by RBC at the tissue level is decreased. So to compensate for the decreased oxygen availability, the number of RBC's increased.

In some individuals the foetal Hb (HbF) may persists in adult life.

Normal values for Hb Male 14 -18g/dl Female 12.5 - 15.5g/dl

In normal physiological conditions like pregnancy, the haemoglobin concentration may drop to about 10-12g/dl of blood. This is because, during pregnancy, the body gains fluid and the RBC become less concentrated, also, due to the increase in demand. In polycythemia e.g. in high altitude Hb concentration goes up.

WHY IS Hb INSIDE RBC?

1. If Hb comes out into the plasma, it will be filtered by the glomerular capillaries in the kidneys and will be lost in the urine as Haemoglobinuria. Also in the kidneys, it will be converted to acid-haematin which could be toxic to the kidney cells and can lead to destruction of renal tubules or tissues and consequent kidney breakdown (failure).

2. Presence of Hb in plasma will elevate the colloid osmotic pressure. The colloid osmotic pressure may rise up to 100 mmHg. This will disturb the trans-capillary fluid exchange.

3. It will be destroyed by the reticulo-endothelial cells (REC) in the liver, bone marrow and spleen to form bile pigments.

SICKLE HAEMOGLOBIN

The sickle Hb has two α and two β -polypeptide chains as in normal adult Hb, but there is substitution of amino acid sequence at position 6 of the β chain amino acid is VALINE instead of GLUTAMIC ACID. Other abnormal haemoglobin's are HbC (Hb-C), HbSC (Hb-SC) and HbS (Hb-S).

CATABOLISM OF RBC

After a lifespan of about 120 days RBCS are destroyed by the reticulo-endothelial cells found in the liver, spleen as well as bone marrow, they are recognized as their cell membrane becomes worn out. The haem part of the haemoglobin is altered by the oxidation of one of its methane bridges. The tetra-pyrolle ring structure is thus broken and the four pyrolle groups become arranged as straight chain to form a compound called verdo-haemoglobin (so called because it is green in colour). Next, both iron and globin are split off and biliverdin is formed.

The biliverdin is later reduced to bilirubin. The iron is stored in the liver and could be re-utilized for the synthesis of haemoglobin. The globin moiety enters the general pool of proteins in the body. Bilirubin is released into plasma bound to plasma proteins particularly albumin. In this form bilirubin is transported to the liver. On reaching the liver, bilirubin enters the hepatic cells and therein undergoes conjugation with glucoronic acid to form bilirubin mono-glucuronide and bilirubin di-glucuronide. These compounds pass by way of the bile duct to the intestine where they are converted to bilinogen by bacterial action in the large intestine. About 45% of the bilinogen is further converted to stercobilinogen which is then eliminated through the faecal matter. On exposure to air, stercobilinogen is oxidized to stercobilin which impacts the characteristic yellow or brownish colour to stool. Some of the bilinogen (50%) is reabsorbed in the terminal ileum and goes via the portal system to the liver where it is reconverted into bilirubin glucuronide and re- excreted into the intestine via the bile duct. This process is known as enterohepatic circulation of bile pigments. About 5% of the bilinogen reaches the kidney through the systemic circulation where it is converted to urobilinogen. Urobilinogen is voided through the urine. On reaching the outside world, urobilinogen is oxidized to urobilin. Urobilin gives the characteristic yellow colour to urine. Normal serum bilirubin content is 0.2 to 1.1 mg%.

JAUNDICE OR ICTERUS OR HYPERBILIRUBINAEMIA

This is the yellow colouration of the skin, sclera of the eye and mucus membrane by bilirubin. Jaundice is detectable when the plasma bilirubin content becomes greater than 2mg% of blood. Jaundice can be classified into three types:

1. Pre-hepatic or hemolytic jaundice (due to excessive destruction of RBCs).
2. Hepatic or infective jaundice (due to toxic damage to the liver cells), e.g. hepatitis.
3. Post hepatic or obstructive jaundice (due to the obstruction to flow of bile) as occurs in gallstone.

PHYSIOLOGICAL JAUNDICE

In newborn babies between 2-7days of their life, the liver sometimes is not capable of conjugating bilirubin with glucoronic acid. Therefore unconjugated bilirubin circulates in the blood and causes mild jaundice. After 10 days, the liver can now adequately conjugate bilirubin with glucoronic acid and this mild jaundice disappears.

ANAEMIA

It is the quantitative or qualitative reduction in circulating RBCs. The number of RBC's, may be less or the amount of haemoglobin may be low or both may occur simultaneously in anaemia.

CLASSIFICATION OF ANAEMIA

A. Dis haemopoietic-This is due to deficiency of factors which normally help erythropoiesis such as deficiency of iron, vitamin B_{12}, folic acid or thyroid hormones. E.g. include, nutritional anaemia like iron deficiency anaemia.

B. Haemolytic anaemia-this is due to excessive destruction of RBCs, it can be;

a. Intra- capsular causes (within) e.g. abnormal structure as in Cooley's disease -Abnormal shape e.g. sickle cell anaemia, and spherocytosis

b. Extra capsular causes- This is brought about by external agents

1 Infection e.g. malaria and viral infection

2 Mismatched blood transfusions.

C. Anaemia due to depression of bone marrow i.e. hypo-plastic or aplastic anaemia. Depression of bone marrow may be brought about by infection

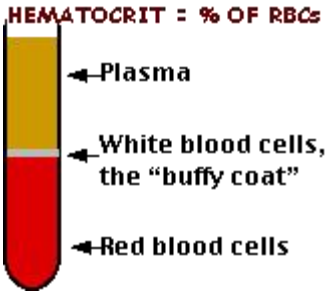
a. X-ray radiation

b. Drug toxicity

D. Anaemia due to blood loss

E. Anaemia of uncertain origin.

Hematocrit:
The percentage of red blood cells volume to the total blood volume is called hematocrit . It could be calculated dividing the red blood cells volume by total blood volume and multiplying by 100. The normal average is about 42.10% in male and 38.16% in female (Maiduguri, Nigeria).



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FACTORS AFFECTING ERYTHROPOIESIS

1. Dietary factors-Foods rich in first class proteins are very important as it supplies essential amino acids necessary for synthesis of globin portion of haemoglobin. It is also necessary for the formation of nucleoprotein and stroma protein of RBC.

2. Hypoxia- Stimulates bone marrow indirectly through the mechanism of erythropoietin. It stimulates the kidneys which produces renal erythropoietic factor (REF); it also stimulates the liver to form α_2-globulin. These two together forms a hormone called erythropoietin which is a glycoprotein in nature and acts on the bone

marrow. It increases RBC production by stimulating the conversion of the primitive stem cells to committed erythroid cells (Haemocytoblast).

3. Role of endocrine glands - Certain endocrine glands influences erythropoiesis. Testosterone increases RBC. In pituitary insufficiency, hypothyroidism and adrenal insufficiency (hypo-adrenalism), there is decrease in red cell counts. In hyperthyroidism and hyper functioning of adrenal glands (adrenal cortex) red cell count increases.

4. Maturation factors-These are factors that are responsible for the maturation of nucleated cells up to late normoblast. They include vitamin B_{12}, and folic acid. Vitamin B_{12} is an extrinsic factor, it needs intrinsic factor before absorption. Intrinsic factor is produced by the lining of the stomach. Disease of the stomach results to megaloblastic anaemia.

5. Factors controlling Hb formation (haematinics), Iron, copper, amino acids vitamin B_6 etc are required for synthesis of Hb.

DESTRUCTION OF RED BLOOD CELLS: after a lifespan of one hundred and twenty days RBC's are destroyed by the reticuloendothelial cells of the liver, spleen and bone marrow. After destruction of the RBC's, the iron and globin are splitted, iron is transported as transferrin to the bone marrow for production of new RBC's and some stored in other tissues like liver as ferritin. The porphyrin portion of haemoglobin is converted to bilirubin which is released into plasma bound to plasma proteins particularly albumin. In this form bilirubin is transported to the liver. On reaching the liver, bilirubin enters the hepatic cells and therein undergoes conjugation with glucoronic acid to form bilirubin glucoronide. This compound passes by way of the bile duct to the intestine where they are converted to bilinogen by bacterial action in the large intestine. About 45% of the bilinogen is then eliminated through the faecal matter. Some of the bilinogen (50%) is reabsorbed in the terminal ileum and goes via the portal system to the liver where it is reconverted into bilirubin glucuronide and re- excreted into the intestine via the bile duct. This process is known as enterohepatic circulation of bile pigments. About 5% of the bilinogen is voided through the urine. On reaching the outside world, urobilinogen is oxidized to urobilin. Normal serum bilirubin content is 0.2 to 1.1 mg%.

BLOOD GROUPS

Although, the RBC of all races has identical appearance, on the cell membrane are found a variety of antigens (agglutinogens) which vary in type in different individuals. When these antigens combine with appropriate antibodies (agglutinins), the cells become sticky and clump together, the process is called agglutination. The most common antigens are the A and B antigens. In this classification individuals are grouped into four major classes. A, B, AB, and O.

The group A has antigen A on its surface, group B the antigen is B, group AB has both, while group O has neither A or B present.

Red blood cell	**Plasma**
Group A	Anti B
Group B	Anti A

Group AB

Group O Anti A and B

Normally the absence of A or B antigen in a person's RBC is always associated with the presence of appropriate antibody in their serum e.g. the absence of A antigen in the RBC means that anti A antibody is present in the plasma. The practical importance of the blood groups is that cells from one person transfused into another must be matched so that, they are not agglutinated by the antibody present in the recipients plasma. It should be noted that the donors serum has little effect on the recipient cell because of the large dilution which take place, thus the effect of transfusion are tested for directly by testing the donors cell with recipients serum before transfusion. This is called **cross matching**. The severity of a mismatch blood varies from mild to severe reactions like fever, chills and rigors to severe hyper sensitivity reaction.

The distribution of the ABO blood group in Maiduguri Tukur et al 2017, showed blood O have the highest percentage with 49.1%, followed by B 22.1, A 19.3%, while AB has the least 9.3%. The group O individual is known as **universal donor**, while blood group AB is known as **universal acceptor**.

In addition to the ABO blood group system there are other agglutinogens system containing many antigenic material in the RBC. The most important of this is the Rh system which is really a group of many antigens; the most important quantitatively is the D- antigen. Blood groups are inherited in the Mandelian way in a given person. Blood is a complex of the mother and the father's blood grouping gene and individual of blood group B may be BB or BO, being homozygous or heterozygous.

WHITE BLOOD CELLS (Leucocytes)

Leuco-means white Cyte -means cell, total leucocyte count is 4-11000 cells/mm^3 of blood

ORIGIN OF WHITE BLOOD CELLS White blood cells, also known as leukocytes, originate in the bone marrow. They are produced by stem cells in the bone marrow known as pluripotent haemopoetic stem cells which are undifferentiated cells capable of giving rise to precursors of any different blood cells. When the pluripotent stem cell divides and become committed to lymphoid stem cell, which give rise to lymphocytes and the second stem cells called the colony forming unit spleen which give rise to colony forming unit that matures to become granulocytes (neutrophil, eosinophils and basoils) and monocytes, they circulate throughout the body in the blood as white blood cells

CLASSIFCATION OF WBCs can be classified into two: granulocytes and agranulocyte

- Granulocytes (possess granules in their cytoplasm), they are the neutrophils, eosinophils and basophils
- Agranulocytes (do not possess granules in their cytoplasm), are the monocytes and lymphocytes

PROPERTIES OF WBC's

The white blood cells have some properties that differentiate them from other blood cells.

All WBCs are nucleated

They do not possess Hb

Their sizes vary from 8-10 in diameter

Some of them show active amoeboid movement.

They function in immunity e.g. phagocytosis and antibody formation

FUNCTIONS OF WBC

Neutrophils

These cells are the most numerous in circulation. Neutrophils leave the circulation and enter tissues via the process of “diapedesis” which involves insinuation of the cells through capillaries between endothelial cells.

Functions of neutrophil are to seek out, ingest and kill bacteria. They therefore act as the body's first line of defense in combating infection.

Neutrophils are attracted to the site of bacterial invasion by a substance known as chemotaxins. Chemotaxins are chemical mediators which are attractants and cause cells to move towards them. Upon arrival at an invasion site, neutrophils are able to actively ingest bacteria through the process of phagocytosis.

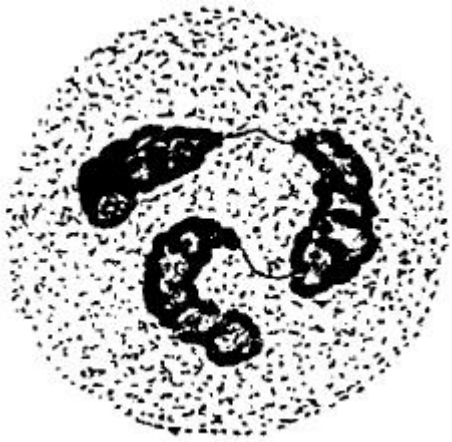

Fig. 3.6: Neutrophil

Phagocytosis may be enhanced by bacterial opsonization. Opsonins are substances able to coat the surface of bacteria and in so doing make the bacteria more tasty and aid phagocytosis. E.g. of Opsonins include some immunoglobulin classes and certain complement components.

The phagocytic vesicles (phagosomes) formed as a result of bacterial ingestion then fuse with the lysosomes of the neutrophils. This process is referred to as degranulation and is associated with a sharp increase in oxygen consumption as well as an increase in the cells rate of metabolism i.e the “respiratory burst”.

Eosinophil

The cytoplasm contains coarse reddish granules, oval in shape and highly refractive. Large parasites such as helminths, cannot be physically phagocytosed, and extra cellular killing by eosinophils must take place. Eosinophils have granules that contain;

Eosinophilic cationic proteins (damage microbial cell membranes).

Myeloperoxidase, Phospholipase D etc.

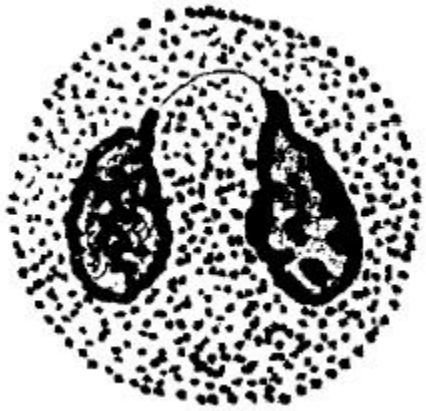

Fig. 3.7: Eosinophil

Eosinophils are cells which are involved in the body's response to foreign proteins e.g. allergic reactions, asthma, and parasitic infestation. Upon activation, eosinophils are capable of launching their extra cellular attack mechanisms which lead to damage of the foreign cell membrane by releasing the toxic substances in its granules.

Basophils

These leucocytes contain granules which stain well with basic dyes, and are the smallest type of leucocytes present in circulation. They have a diameter of about 8- l0 µ. The nucleus is usually bilobed or S-shaped. The cytoplasm contains large granules (blue). The granules of basophils contain histamine, heparin, slow reacting substance of anaphylaxis and eosinophil chemotactic factor.

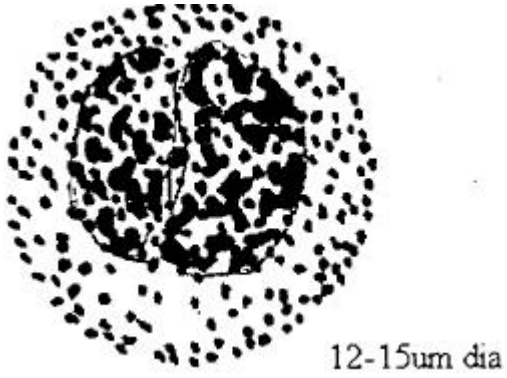

Fig. 3.8: Basophil

Basophil resembles mast cell (are fixed cells in tissues). The mediators released cause adverse symptoms of allergy, but on the positive side, they may also play a role in immunity against parasites.

AGRANULOCYTES

Monocytes- These cells are regarded as the body's second line of defense, being mobilized along with neutrophils in the inflammatory response.

Monocytes leave the circulation after 24hrs to become fixed phagocytic cells in tissues. These cells are referred to as macrophages.

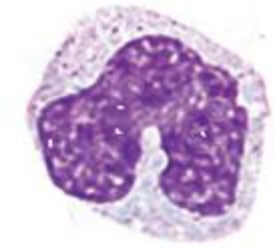

Fig. 3.9: Monocyte

The mononuclear- phagocytic system is a group of cells composed of the macrophages present in tissues. These cells are particularly concentrated in the lungs (alveolar macrophages), the liver (kupffer cells) and lining the spleen sinusoid and lymph node medullary sinuses where they filter off foreign materials. The microglia cells of the nervous system, mesangeal cells of the kidney, and osteoclasts in the bone are examples of tissue macrophages.

Lymphocytes

Lymphocytes are produced in the primary lymphoid organs (Thymus and bone marrow). In the foetus, the liver and spleen may also form primary lymphoid organs.

All cells which migrate to specific areas in the bone marrow will result in the production of B-lymphocytes, while lymphocytes produced in the thymus are called T-lymphocytes.

Lymphoid cells represent 20% of the total white blood cells present in circulation. Matured lymphoid cells are long lived and may persist as memory cells for several years.

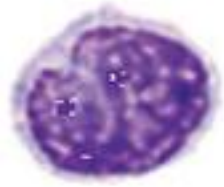

Fig. 3.10: Lymphocyte

Antigenicity

Self-recognition is pivotal to immunologic surveillance and responses, and integral to the functionality of the immune system.

Antigenicity is the ability of a foreign material (antigen) to interact with products of cell-mediated responses such as B-cell or T-cell responses.

Antigenic determinants are characteristic biomolecules which constitute structural features on antigens and are known as epitopes.

In T-cells, antigenic determinants are structural biomolecules, usually linear, hydrophobic peptides produced by antigen processing within antigen presenting cells (APCs). These peptides are then bound to major histocompatibility complex (MHC) molecules and then become recognizable to T-cell receptors. However, lipids and glycolipids can also be presented to T-cells by molecules MHC-like molecules.

In B-cells however, MHCs are not required, as the entire antigen, in either soluble or membrane-bound form can trigger the secretion of immunoglobulins, which bind to them.

Platelets

Platelets are also called thrombocytes; they are small colorless, non-nucleated cells that constitute part of the formed elements of blood. They are formed in the bone marrow from *megakaryocytes*, which are extremely large cells of the hematopoietic series in the marrow. The normal concentration of platelets in the blood is between 150,000 and 350,000 per microliter. Platelets have the half-life of 8 to 12 days in the blood after which it is eliminated from the circulation mainly by the tissue macrophage system. Platelet count increases in conditions such as hemorrhage, surgical operation and splenectomy. The count is low in Aplastic anemia, purpura and splenomegaly.

Haemostatic Mechanisms

Haemostasis is the process that arrest bleeding in the injured blood vessel. The haemostatic process involves three stages; vasoconstriction (vascular spasm) platelet plug formation (formation of Platelet aggregates) and the blood coagulation (or fibrin formation) proper.Following an injury to a blood vessel, there is an immediate vasoconstriction of the vessel in order to approximate the site of the injury. The vaso-constriction response is believed to be triggered by several chemicals called endothelins that are released by vessel-lining cells and by pain receptors in response to vessel injury. This phenomenon typically lasts for up to 30 minutes, although it can last for hours.

This is then followed by the formation of platelet aggregates to seal off the site of the injury. The platelets stick and adhere to collagen in the vascular endothelium and also to von Willebrand factor that leaks into the injured tissue from the plasma. The platelets also secrete large quantities of:

- Adenosine diphosphate (ADP), which helps additional platelets to adhere to the injury site, reinforcing and expanding the platelet plug
- Serotonin, which maintains vasoconstriction
- Prostaglandins and phospholipids, which also maintain vasoconstriction and help to activate further clotting chemicals.
- Thromboxane leads to occlusion of blood vessel by fueling of blood clots inside the blood vessel

The final stage in haemostatic mechanism is the formation of fibrin which is the definitive clot. Fibrin is formed from fibrinogen in a reaction catalyzed by thrombin. The formation of thrombin is by the prothrombin activator, formation of which can occur through two distinct pathways of extrinsic and intrinsic routes.
There are thirteen clotting factors which are proteins synthesized in the liver. These clotting factors are numbered using Roman numeral numbering system from I – XIII. Some of these clotting factors were named after the scientists who discovered them except the Christmas factor IX that was named after the patient in whom the disease was discovered, the others were name in relation to their activities in the body, Ca and vitamin K.

Clotting factors and their corresponding names

Clotting Factors	Corresponding Names
Factor I	Fibrinogen
Factor II	Prothrombin
Factor III	Tissue Thromboplastin
Factor IV	Calcium
Factor V	Proaccelerin or Labile factor
Factor VII	Proconvertin or Stable factor
Factor VIII	Antihemophilic factor
Factor IX	Christmas factor or Antihemophilic factor B
Factor X	Stuart-Prower factor
Factor XI	Plasma Thromboplastin antecedent
Factor XII	Hageman factor
Factor XIII	Fibrin-stabilizing factor
Prekallikrein	Fletcher factor
High-molecular-weight Kininogen (HMWK)	Fitzgerald factor
Platelets	

Blood Coagulation
The process of blood coagulation occurs in three steps; the intrinsic or extrinsic pathway that leads to the formation of prothrombin activator, the common pathway conversion of prothrombin into thrombin and finally conversion of fibrinogen into fibrin.
Formation of prothrombin activator

Prothrombin activator is formed through two distinct different pathways; extrinsic and intrinsic pathways.

Extrinsic Pathway

The quicker responding and more direct **extrinsic pathway** (also known as the **tissue factor** pathway) begins when damage occurs to the surrounding tissues, such as in a traumatic injury. Upon contact with blood plasma, the damaged extravascular cells, which are extrinsic to the bloodstream, release factor III (thromboplastin). Sequentially, Ca^{2+} then factor VII (proconvertin), which is activated by factor III, are added, forming an enzyme complex. This enzyme complex leads to activation of factor X (Stuart–Prower factor), which activates the common pathway discussed below. The events in the extrinsic pathway are completed in a matter of seconds.

Intrinsic Pathway

In this pathway, the blood gets in contact with collagen from the traumatized blood vessel wall and activates factor XII. The activated factor XII then acts enzymatically to activate factor XI. This reaction also requires HMW (high-molecular-weight) kininogen and is accelerated by prekallikrein. The activated factor XI, then activates factor IX in the presence of calcium ion. The activated factor IX then activates factor X in the presence of activated factor VIII, calcium ion and the phospholipids. Factor VIII is the factor that is deficient in person with classic hemophilia, for this reason factor VIII is called antihemophilic *factor*. Platelets deficiency results in a bleeding disease called *thrombocytopenia*. The activated factor X together with activated factor V and calcium ion form the prothrombin activator.

Conversion of Prothrombin to Thrombin

The prothrombin activator in turn initiates the cleavage of prothrombin to form thrombin, thereby setting into motion the final clotting process. Formation of thrombin is the rate limiting step in clotting mechanism once it is formed clotting must always occurs.

Conversion of Fibrinogen to Fibrin

The thrombin converts the fibrinogen in to fibrin with a loss of 2 pairs of polypeptides from each fibrinogen molecule to form the fibrinogen monomer. Fibrin monomer polymerizes with other monomer molecules to form loosely arranged strands of fibrin. Thrombin also activates factor XIII to factor XIII activated, the activated factor XIII in the presence of calcium ions converts the lose strands into a dense fibrin threads which aggregate to form a meshwork of a stable clot.

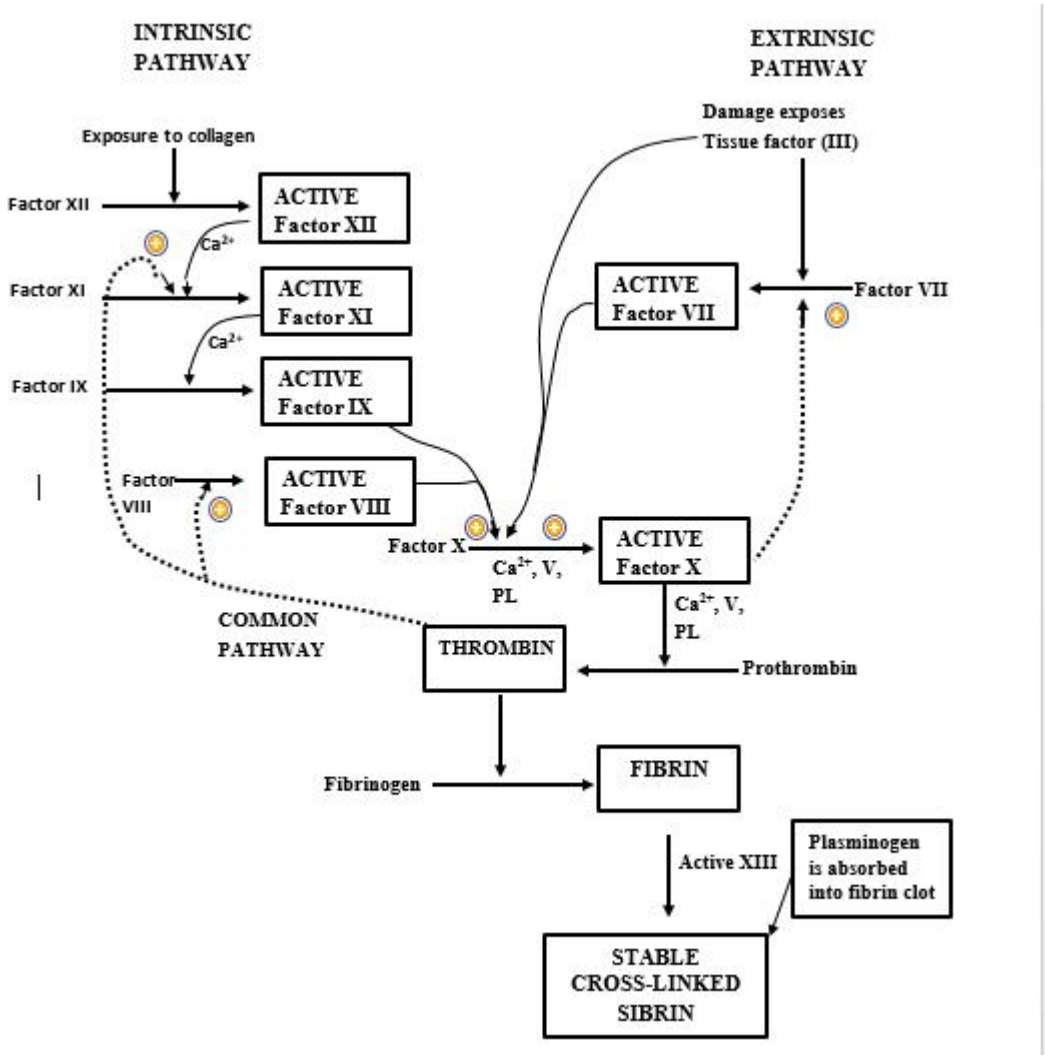

Fig. 3.11: Clotting pathways

Reticuloendothelial System

This is the system of immune phagocytic cells, which play an important role in defense mechanism of the body. It is called the Monocyte-Macrophage System. The monocytes are mobile immune cells that spend roughly 72 hours in circulation before they enter different tissues to become macrophages. Both cells have the same capabilities to phagocytize large quantities of bacteria, viruses, necrotic tissue, warn out cells or other foreign particles in the body. Macrophages occupy the Endothelial lining of vascular and lymphatic channels and they are found in connective tissues of spleen, liver, lungs, lymph nodes and bone marrow as mononuclear phagocytic cells. They are located in different tissues called with different names depending on the organ in which they are found; they are called kupffer cells in the liver, pulmonary alveolar macrophages in the lungs, peyer's patches in

the gastrointestinal tract, astrocytes in the brain and histoicytes, osteocytes in the bone marrow or Langerhans cells in the skin.

Functions of Reticuloendothelial System

1. Phagocytic function i.e. they engulfed bacteria, viruses and other foreign materials.
2. Secrete hydrolytic enzymes to destroy connective tissues of unwanted foreign antigen and by extension destroy the human tissues in uncontrolled secretions.
3. Secrete reactive oxygen and nitrogen species in form of superoxide free radicals to destroy the foreign antigens.
4. Destroy the senescent red blood cells and release hemoglobin
5. Secrete tumor necrosis factor α and β to help destroy the tumor cells.
6. Secrete transforming growth factor which prevents rejection of the transplanted tissues
7. Secrete platelet-derived growth factor which promotes wound healing and tissue repair.

Fibrinolytic System (Anticlotting Mechanisms)

This is the system that prevents blood clotting or breaks down any clot that formed inside the blood vessels. The system includes both the physical and chemical factors that aid in keeping the blood in a fluid state. The physical factor involves the presence of smooth endothelial surface of the blood vessels, while the chemical factor involves the presence of Antithrombin III, a circulating protease inhibitor and the thrombomodulin, a thrombin-binding protein produced by the endothelial cells in the body except those of the cerebral vessels.

The Antithrombin III blocks the activity of the clotting factors II, VII, IX and X by binding to the serine protease of these clotting factors thereby inhibiting their actions. The binding of the Antithrombin III to the serine protease is facilitated by heparin.

Thrombomodulin is a thrombin binding protein that forms thrombomodulin-thrombin complex. The complex activates protein C and together with its co-factor protein S accelerates the formation of plasmin which ultimately breaks down the fibrin into fibrin degradation products.

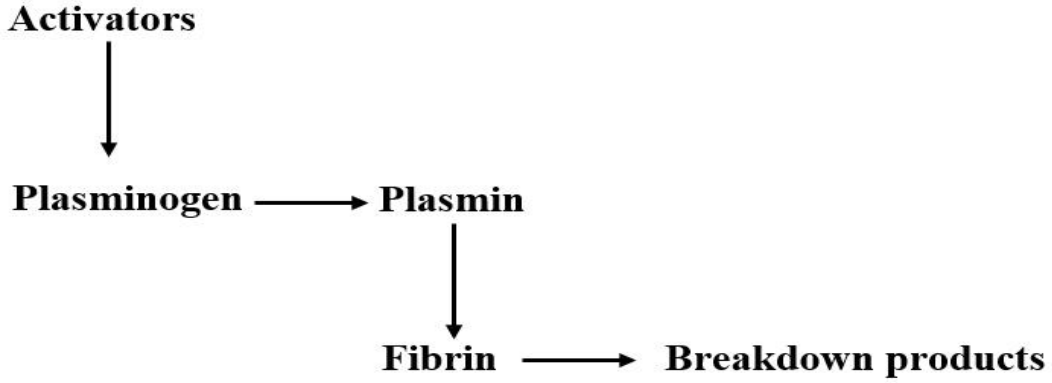

Fig. 3.12: Fibrinolytic System

Plasmin (Fibrinolysin formation)

Plasmin is formed from its inactive precursor plasminogen by the action of thrombin and tissue-type plasminogen activator (t-PA). In addition to t-PA, there is another plasminogen activator called urokinase plasminogen activator (u-PA) which is derived from the blood, this also catalyzes the formation of plasmin.

The thrombomodulin-thrombin complex is the initial step in the formation of plasmin. This complex together with its co-factor S inhibits factors V and VII and the tissue-type plasminogen activator (t-PA). The inactivation of the t-PA inhibitor produces the activated t-PA which favors plasmin formation and leads to degradation of the clots.

Anticoagulants

These are substances that prevent blood clotting either in vivo (inside the body) or in vitro (outside the body). There are naturally occurring anticoagulants like heparin which is used in treatment of blood coagulation disorders and synthetic types like the citrate and oxalates that are mainly used in the laboratories for storing of blood and other laboratory experiments.

1. **Heparin**

This is a naturally occurring anticoagulant produced in the liver, lungs, mast cells and the Basophils. It inhibits the action of thrombin and combines with antithrombin III to remove thrombin from the circulation. Heparin also inhibits the action of clotting factors involved in the intrinsic pathway; factors XII, XI, X and IX. Heparin serves both in vivo and in vitro functions as it prevents intravascular blood clotting during major surgical procedures and is used as an anticoagulant in many laboratory investigations.

2. **Citrate**

Citrate removes calcium ion from the blood and therefore prevents blood clotting. It exists in form of sodium, potassium or ammonium salts. Citrate is used in laboratories for platelets and red blood cell counts.

3. **Ethylene diamine tetraacetic acid (EDTA)**

EDTA is an anticoagulant that is used for both in vivo and in vitro experiments in the treatment of lead poisoning and laboratory experiments respectively. It exists in the form of sodium and potassium salts.

4. **Coumarin Derivatives**

These include dicumarol and warfarin. They inhibit the action of vitamin K dependent clotting factors; II, VII, IX and X. Both can be used orally to treat stroke or myocardial infacrtion.

5. **Oxalates**

These are substances that precipitate calcium ion and prevents blood coagulation. They are only used as in vitro anticoagulants because of their toxicity in the body.

IMMUNITY: Is the physiological responses by which the body recognizes foreign or its own abnormal cell and destroys or neutralizes them.

Types of immunity

Three types of immunity are recognized. We have the natural, passive, and an active immunity.

1. Natural immunity-this is also known as inborn or innate immunity and is referred to as immunity that is not acquired by a previous attack of the disease or in any way at all. Human beings are naturally immune to diseases that affects animals e.g. hog cholera. Conversely animals are naturally immune against human diseases e.g. measles.

2. Active immunity-this refers to immunity that has developed as a result of the activity of the body's own cell such as when a person has recovered from an attack of an infectious disease e.g. small pox cannot contract the disease again except on rare instances.

3. Passive immunity-this refers to immunity produced by immunization.

DEFINITIONS

Antigen- a foreign molecular component which can be cellular or non-cellular that elicits an immune response.

Complement- a group of plasma proteins which upon activation, kill microbes directly, also facilitate every step of the inflammatory process by acting as Opsonins.

IMMUNE MECHANISMS

Are divided into two major categories, it is produced by both immediate measures. The immediate measure or respond is phagocytosis or cellular immune system while the longer time response which occurs between two to three weeks is the production of antibodies against the infecting agents and is also known as humoral immune system.

Cellular immediate phagocytosis—non specific

Humoral Delayed Antibodies—specific.

Both cellular and the humoral immune system are involved in the protective reaction to a specific protein called antigens.

The humoral response is very specific in that it can only respond to a particular antigen e.g., the antibody that is responsible for immunity against small pox is inactive against measles or any other infectious disease. On the other hand, cellular immune response is nonspecific and can be evoked by many antigens. The development of the immune response is brought about by two populations of small lymphocytes. The first of these called the T-lymphocytes or cells are in response for cellular immunity and they populate the thymus. They do not secret antibodies but act as killer cells which attack foreign grafts. The second populations of Cells are called the B-cells which are responsible for humoral immunity and they populate the liver and spleen. The B-lymphocytes often requires the presence of T-lymphocytes in order to be ligand by antigens. B-lymphocytes are known to mature into two types. These are;

1. The plasma cells
2. The memory B-cells.

B-lymphocytes are characterized by a large nucleus and bright blue cytoplasm when wrights stain are used.

Plasma cells are usually loaded with secretory vacuoles or granules for they are highly specialized to synthesize a variety of antibodies.

Immunoglobulins (antibodies)

Antibodies are heterogeneous group of proteins molecules all being capable of reacting with the specific antigen and are separable into classes and subclasses on the basis of their chemical properties.

In humans, immunoglobulins are of five major types.

1. Immunoglobulin G IgG
2. Immunoglobulin A IgA

3. Immunoglobulin M IgM

4. Immunoglobulin E IgE

5. Immunoglobulin D IgD

Note: All occurs in serum, IgA also occurs in body secretions like colostrum. Saliva, tears etc.

CELLULAR IMMUNE MECHANISM

Cellular immunity is mediated by killer T-cells. When antigens are present in the body they are ingested by the macrophages which expose a small part of the antigen. This exposure stimulates the inducer \helper T-cells which mediate immunity. The killer cells immediately differentiate into memory T-cells, and suppressor T-cells, each of which swing into their respective actions. The cytotoxic or T killer- cells have toxic molecules which destroy membranes of the target cells. After the immune response is achieved, the actions of the cytotoxic or killer cells are put to an end by the suppressor T- cells which develop much later. They do this by inhibiting the helper T-cells. Furthermore, memory T-cells usually stay longer in the system in order to detect a subsequent exposure to the same antigen and make adequate and fast response.

HUMORAL IMMUNE RESPONSE

Like in cellular immunity, the presence of any foreign proteins like bacteria or virus results in activation of macrophages which ingest and expose a small part of the antigen. The exposure of the antigen by macrophages activates the inducer (helper) T-cells. The T-helper cells in turn contact the B- cells which quickly proliferate and transform into B- memory and plasma cells. The antibodies which are subsequently produced by the plasma cells are then put to use by reacting with the specific antigen.

Immunodeficiency Diseases

This is a condition in which some components of immune system are either reduced or defective. When the defense mechanism becomes defective, the body is vulnerable to opportunistic infections where organisms of even low virulence produce severe disease. Immune deficiency diseases are classified into types:
1. Congenital immune deficiency diseases
2. Acquired immune deficiency diseases.

Congenital Immune deficiency diseases;

i. Disorders of phagocytic functions

In this condition, there is depression of the neutrophil function. Patients with these diseases are prone to infections that are relatively mild when only the neutrophil system is involved, but can be severe when the monocyte-tissue macrophage system is also involved. In neutrophil hypomotility syndrome, actin in the neutrophils does not polymerize normally, and the neutrophils move slowly. In chronic granulomatous disease, there is a failure to generate superoxide radicals (O^{2-}) in both neutrophils and monocytes and consequent inability to kill many phagocytosed bacteria. In severe congenital glucose-6-phosphate dehydrogenase deficiency, there are multiple infections because of failure to generate the NADPH necessary for superoxide radicals (O^{2-})

production. In congenital myeloperoxidase deficiency, microbial killing power is reduced because hypochlorous acid is not formed.

ii. Congenital diseases can also be due to the defects in B cell or T cell or both. The common examples are DiGeorge syndrome (due to absence of thymus) and severe combined immune deficiency (due to lymphopenia or the absence of lymphoid tissue).

iii. Acquired Immune deficiency diseases

iv. Acquired immune deficiency disease is caused by an acquired immune deficiency virus, leading to the development of the acquired immune deficiency syndrome (AIDS). AIDS is an infectious disease caused by immune deficiency virus (HIV). It attacks the T lymphocytes leading to the destruction of these cells. It causes slow and progressive decrease in immune function, resulting in opportunistic infections of various types. The common opportunistic infections, which affect the AIDS patients, include the pneumonia (Pneumocystis carinii) and malignant skin cancer (Kaposi sarcoma). After entering the body of the host, the HIV activates the enzyme called reverse transcriptase. HIV utilizes this enzyme and converts its own viral RNA into viral DNA with the help of host cell DNA. Now, the viral DNA gets incorporated into the host cell DNA and prevents the normal activities of the host cell DNA. At the same time, the HIV increases in number inside the host's body. The infected host cell ruptures and releases more number of HIV into the bloodstream. After exposure to HIV, no symptoms develop for several weeks. This is the incubation period. The patient develops symptoms only when sufficient number of infected cells is ruptured. The HIV virus attacks and destroys the T helper cells, this weakens the immune response. The common symptoms are fatigue, loss of weight, chronic diarrhea, low-grade fever, night sweats, oral ulcers, vaginal ulcers, etc. This phase progress for about three years before the disease is diagnosed.

SUMMARY: blood is a tissue that plays a vital role in the life of all cells and organs. It is a semi liquid that contains cellular component (RBC's, WBC's and platelets) and fluid component called plasma. It has several functions in transport, respiration, excretion, digestion immunity, haemostsis etc. The cell membrane of RBC's have blood group antigens on them which differentiate individuals into different four different blood groups (A,B,AB and O), which helps in understanding the concept of blood transfusion and consequences that can arise from it. The science explains how the body can minimize blood loss when there is an injury to a blood vessel. It also explains how the WBC's confers immunity to the body through phagocytosis or production of antibody.

Exercise:

1. Classify the composition and functions of blood
2. Enumerate plasma proteins, and their functions
3. Explain erythropoiesis, and the fate of RBC's
4. Discuss the various types of anaemia
5. Classify the WBC's and describe their functions
6. What is haemostasis? Describe the stages involved
7. Describe the principle of blood group and complications of blood transfusion
8. Define immunity and its classification
9. Describe the mechanism of cellular and humoral immune response

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Chapter 4

PHS 204. RESPIRATORY PHYSIOLOGY

Adesoji A Fasanmade and Ahmed Ibrahim Salisu

Physiologic Anatomy of the Respiratory Apparatus

Overview:

The Respiratory System is made up of the Upper and Lower Respiratory Tracts: The conducting airways and the Lungs. The conducting airways conduct air from the atmosphere into the lungs for gaseous exchange within the lungs. Having understood the basic gas laws and the simple applications of these in respiratory physiology, one should now turn attention to transportation of oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. Remember that the blood is the medium for the transportation of these gases.
Now that the ways by which the body controls respiration to meet the demand of the body are understood, consideration should be given to those common conditions in disease and in health that the body is called upon to readjust to. In most of these conditions, the respiratory and cardiovascular adjustments are the most obvious. It should always be kept in mind that changes in oxygen requirement and/or changes in carbon dioxide production lead to respiratory adjustments. Cardiovascular adjustments follow circulatory changes that are important in readjusting tissue oxygen supply and carbon dioxide removal from the body.

Objectives: The objectives are to;

Describe functions and structures of the conducting airways, the alveolar–capillary unit, and the chest wall.
Describe Gas laws of primary importance in respiratory mechanics
Describe the pulmonary circulation and pulmonary vascular bed pressure gradients
Describe the carriage of oxygen and carbon dioxide in the blood
Describe the relationship between arterial carbon dioxide tension and acid-base balance in the body.
Describe hypoxia and the response of the body to hypoxia.

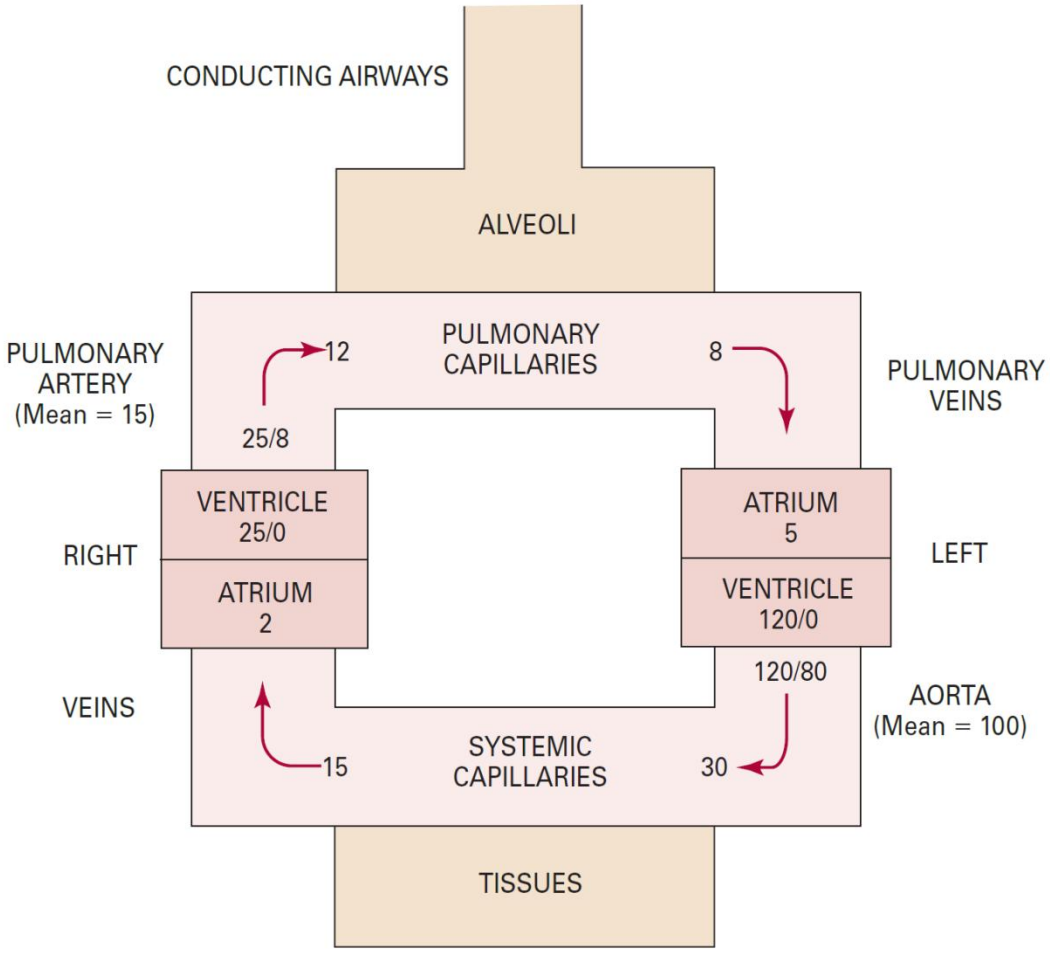
THE UPPER RESPIRATORY TRACT

The upper respiratory tract starts in the nose through the pharynx (naso-pharynx, oro-pharynx and laryngo-pharynx), and the larynx. The lower respiratory tract comprises the divisions of the airways beyond the larynx, from the trachea, bronchi, respiratory bronchi, alveolar ducts and the alveoli. The alveolus is the functional unit of the lungs.

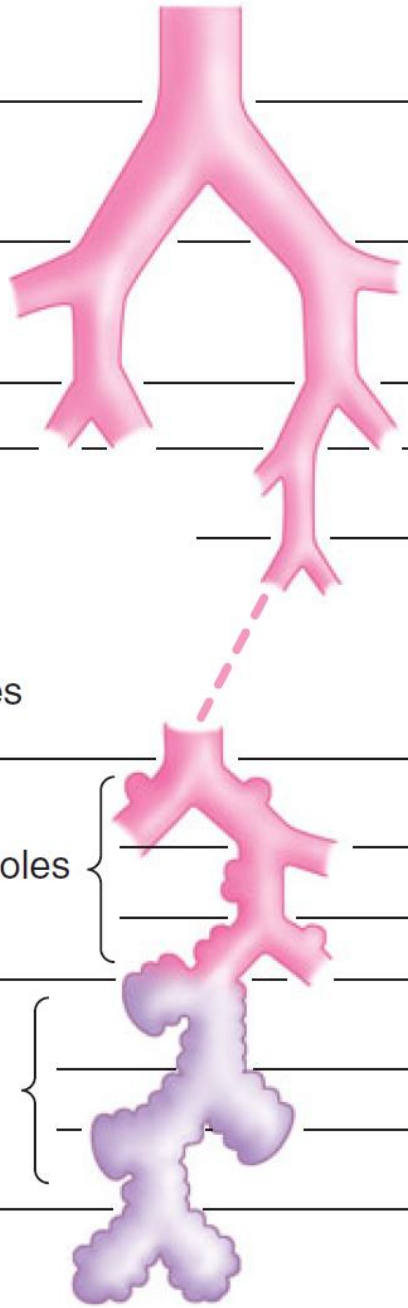
The major function of the upper airway is to maintain the temperature and humidity of the air breathed in. This helps to maintain constant body temperature and helps to prevent fluid loss through breathing. The upper airways also filter the air as it goes into the lungs. The hairs in the nasal cavity and the turbinates (three pairs of ridges along the lateral walls of the nasal cavity) help trap particles that are suspended in the air. The particles get stuck

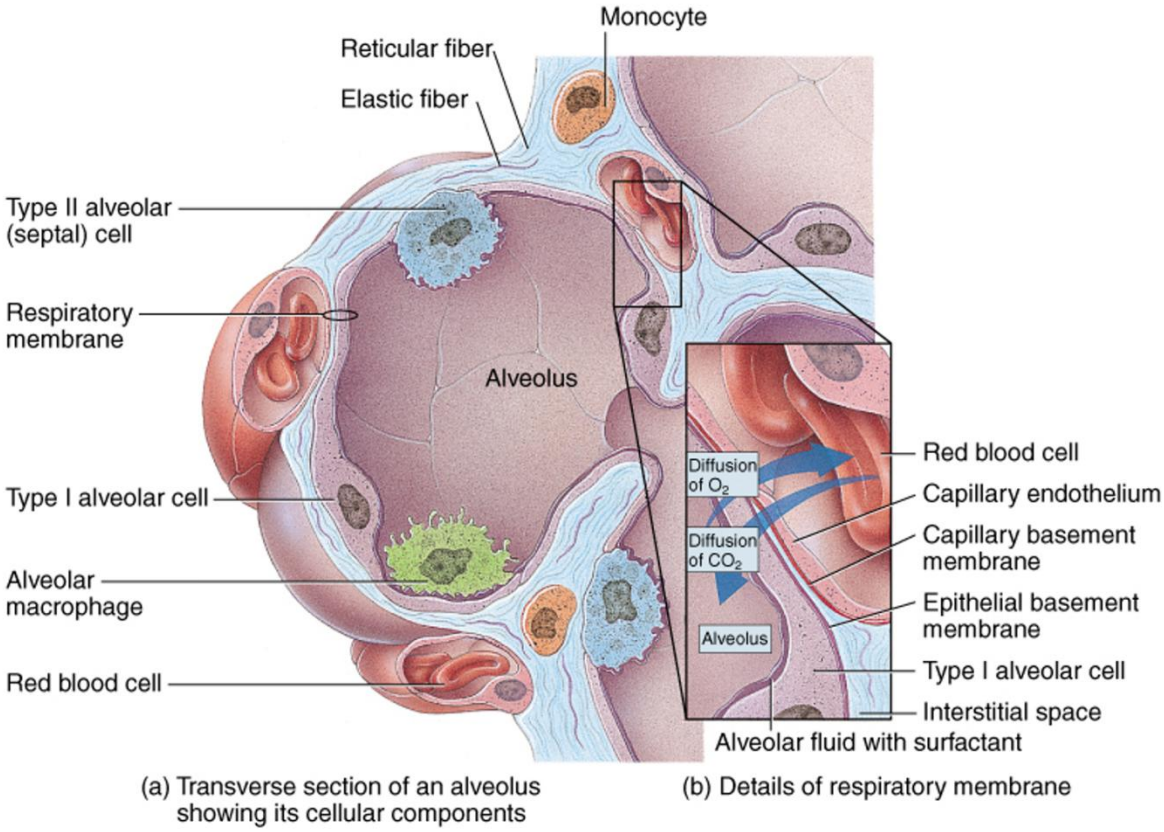
to the mucus, produced by the mucosal lining of the nose and the pharynx, and get eliminated out of the body through sneezing and coughing.

The alveolus is the functional unit of the lung. In an adult, there are about 500 million alveoli in both lungs. Each alveolus is spherical and is lined by four types of cells, called pneumocytes. Type I pneumocytes are squamous epithelial cells. They are the most numerous and function as membrane for gaseous transfer. Type II pneumocytes are spherical in nature and contain granules which contain surfactant. Pneumocyte types III and IV are scanty and are of less known physiological function. They are thought to take part in metabolic functions of the lungs. Pulmonary capillaries form a mesh-like network around the alveoli and the red blood cell within the capillary is separated from the air in the alveolus by a very thin membrane made up of the respiratory membrane (alveolar epithelial cell, basal membrane and capillary endothelial cell).The respiratory membrane is about 0.5mm thick. The thickness can be altered by conditions causing fibrosis and fluid accumulation in the lungs.



	Name of branches	Number of tubes in branch
Conducting zone	Trachea	1
	Bronchi	2
		4
		8
	Bronchioles	16
	Terminal bronchioles	32 ↓ 6×10^4
Respiratory zone	Respiratory bronchioles	↓ 5×10^5
	Alveolar ducts	↓
	Alveolar sacs	8×10^6





Surfactant

Surfactant is a phospholipid, dipalmitoyl lecithin *(*dipalmitoylphosphatidylcholine*)* and other proteins and lipids. It is a detergent-like substance – reduces surface tension of fluid in the alveoli, thus reducing the force of expansion of the alveoli. Its production is facilitated by thyroid hormones and maturation by glucocorticoids. This is usually during the end of the third trimester of pregnancy.

Respiratory distress syndrome (Hyaline membrane disease) of newborn is due to deficiency of surfactant. This is usually seen in premature infants. Cigarette smoking results in decrease of surfactant and lung collapse is a consequence of reduced surfactant.

Chest Wall and Muscles of Respiration

The lower respiratory tract and the lungs are within the chest, an air-tight space which also has the heart and part of the great blood vessels located within the space. The chest wall is made up of the rib cage, which covers the sides and the anterior part of the chest and the muscles covering the rib cage. The posterior part of the chest is covered by the spine and the sternum covers part of the anterior chest wall. The muscles of respiration comprise two types, muscles of inspiration and those of expiration. Muscles of inspiration are the diaphragm and the external intercostal muscles. The diaphragm is supplied by the phrenic nerve (C2,3,3) and it separates the thorax from the abdomen. The muscles of expiration are internal intercostal and anterior abdominal muscles.

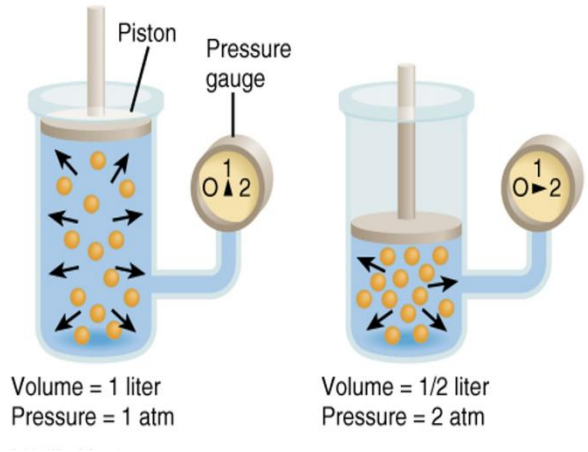
Accessory muscles of respiration include those muscles that are attached to the rib cage and the axial skeleton. Examples include sternocleidomastoid muscle, latissimus dorsi, pectoralis major and minor muscles and the scalenus anterior and posterior muscles. Contraction of these muscles move the chest wall outwards, causing the intrathoracic volume to increase.

Lining the rib cage and the lungs is a thin sac of continuous membrane which forms the parietal and visceral pleura membrane. The space between the two layers is very small and contains a thin film of fluid which serves as a lubricant for the moving parts of the lungs and chest wall during inspiration and expiration. Air and fluid may accumulate in the potential space between the two layers of the pleura resulting in pneumothorax, hydrothorax, haemothorax etc.

Gas Laws and Mechanism of Breathing

The basic properties of gases include the fact that gas molecules move at random creating a pressure on the containing vessel. The pressure is proportional to the bombardment of the wall of the vessel. The number of gas molecules is also proportional to the pressure and the rate of bombardment is proportional to the temperature of the gas.

Boyle's Law states that the volume of a known mass of gas is inversely proportional to its pressure, at constant temperature: $P_1V_1 = P_2V_2$. Thus, as the volume of that mass of gas increases, its pressure will decrease. This law is relevant to inspiration and expiration. During inspiration, the muscles of inspiration contract leading to increase in the thoracic cavity. Since the thoracic cavity is air tight, the intrathoracic pressure will fall, leading to bulk movement of air from the atmosphere into the lungs through the airways. As the lungs and chest wall recoil at the end of inspiration, the intrathoracic volume decreases leading to increased intrathoracic pressure and resulting expiration.



Dalton's law: Pressure exerted by a mixture of gases is the sum of the pressures each of the component gases would exert if it alone occupied the space:

$P = p_1+p_2+p_3+\ldots+p_n$.

Atmospheric Pressure: sum of partial pressures of gases in the atmosphere: O_2, N_2, H_2O, CO_2, Inert gases all exert different pressures that are proportional to their relative percentage mass in the mixture of gases making up the air. Thus oxygen, with 20.83% of air will, at sea level exert a pressure of 20.83% of 760, i.e., 158mmHg. At an altitude of atmospheric pressure of 380mmHg, partial pressure of oxygen would be 79mmHg.

Henry's law: Amount of gas dissolving in a liquid is proportional to the partial pressure of the gas and the solubility of the gas in the liquid. Different gases dissolve to different extents in the same liquid, and this is independent of the other gases.

Fick's law of diffusion: Amount of gas moving across a sheet of tissue is proportional to the area of the sheet, solubility of the gas in the tissue and concentration gradient of the gas across the tissue, and also inversely proportional to the thickness of the tissue. This is perfectly demonstrated by the diffusion of gases across the respiratory membrane in the lungs. Fluid in the lungs will increase the thickness of the membrane and reduce gaseous diffusion. Lung collapse will also reduce gaseous diffusion by reducing the lung surface area.

LUNG VOLUMES AND CAPACITIES

Tidal volume (TV): Amount of air moving in or out of the lungs, during quiet respiration at rest, per breath. Normal value is 0.5L.

Inspiratory reserve volume: Amount of air that can be further breathed in by maximal inspiratory efforts after a normal inspiration. Normal value in men is 3.3L and 1.9L in women.

Expiratory reserve volume: Amount of air that can be further breathed out by maximal expiratory efforts after a normal expiration. Normal value in men is 1L and 0.7L in women.

Residual volume: Amount of air remaining in the lungs after a maximal expiratory effort. The value is 1.2 L in men and 1.1L in women.

Functional Residual Capacity: Amount of air remaining in the lungs after a normal expiration. This is the air that exchanges with the blood in the alveoli. Normal value in men is 2.2L and 1.8L in women.

Vital capacity: Amount of air that be expired by a maximal expiratory effort after a maximal inspiration. The normal value is 4.8L in men and 3.1L in women. The value is dependent on the size of the lungs.

FEV_1: Fraction of the vital capacity expired in one second. Normal physiological value is 83% of the total vital capacity.

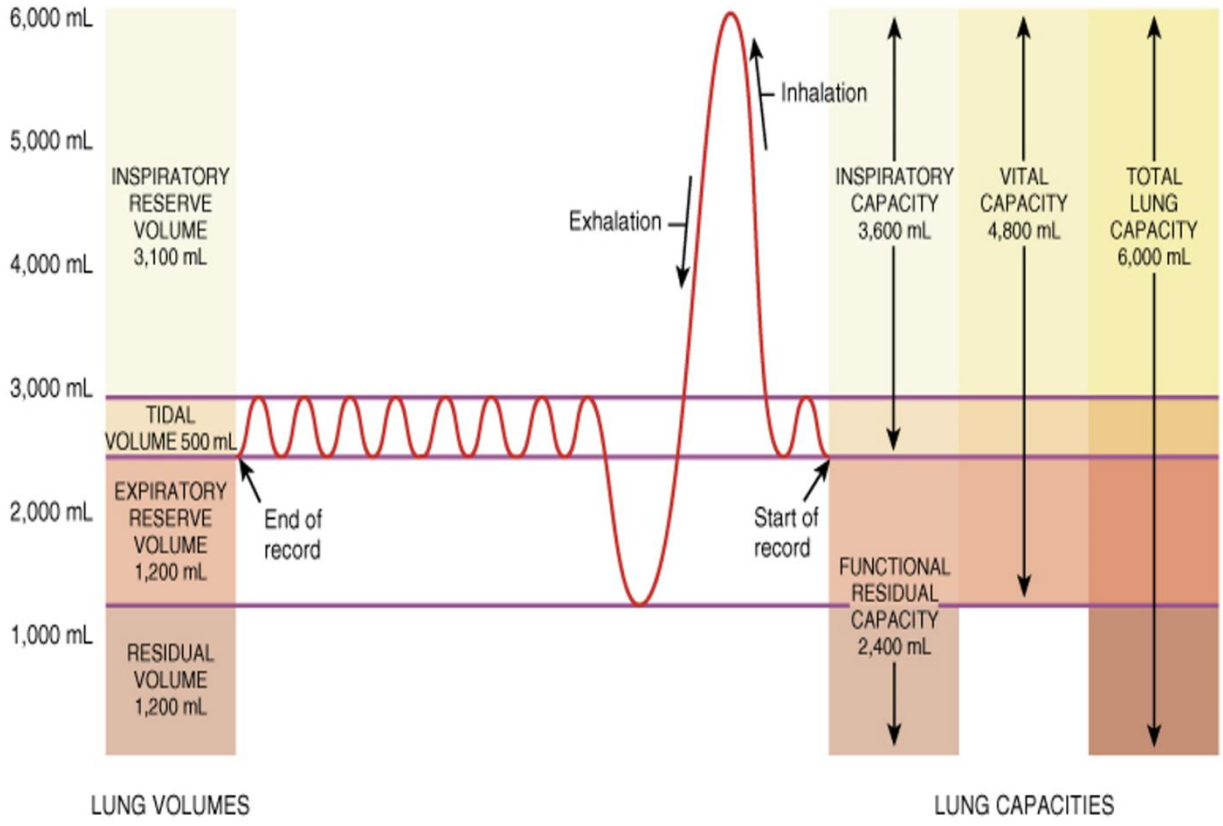
Dead space: Amount of air remaining in the airways and any unperfused area of the lungs. This air is not utilised in gaseous exchange in the lungs.

Anatomical Dead Space: due to the fact that gaseous exchange takes place in the respiratory bronchioles, alveolar ducts and sacs. Airway above these is dead space.

Physiological Dead Space: Anatomical dead space plus volume of lungs not perfused but well ventilated. In a normal lung, the physiological dead space is equal to the anatomical dead space.

Alveolar ventilation: Amount of air getting into the alveoli per minute = (tidal vol – dead space vol) x respiratory rate (RR).

Pulmonary ventilation: Amount of air breathed in per minute = TV x RR.



Pulmonary Circulation

The heart is a dual pump. The right side of the heart pumps blood through the lungs for oxygenation while the left side of the heart pumps blood though the systemic circulation. The pulmonary circulation is made up of thin-walled vessels, with low perfusion pressure within the vessels, whereas the systemic circulation develops greater pressure range for effective perfusion of organs remotely placed from the heart. There are no arterioles in the

pulmonary circulation, and so the blood flow is pulsatile. This is necessary for proper oxygenation of the blood passing through its capillaries.

Pressures in the pulmonary vessels/capillary bed:

Pulmonary arterial Pressure: 25/8mmHg (mean Pressure = 15mmHg)

Right atrial Pressure: 2mmHg; Left atrial Pressure during diastole: 5mmHg

Mean aortic Pressure: 100mmHg

Pulmonary gradient (Pulmonary capillary Pressure): 15 – 5 = 10mmHg

Systemic gradient: 100 – 2 = 98mmHg

Plasma oncotic Pressure: 25mmHg (mainly from plasma albumin component of plasma proteins).

This ensures that the lungs are kept dry all the time, except when the pulmonary gradient exceeds the plasma oncotic pressure. This may be seen in left-sided heart failure, when the left atrial pressure exceeds the pulmonary arterial pressure.

Transit time of blood in Pulmonary Capillaries: 0.75sec

Volume of blood at any given time in the lungs: 1L

Volume of blood within the pulmonary capillaries: 100ml

The lungs can thus be said to be a reservoir for blood.

Other functions of the pulmonary circulation include filtration of the blood and trapping of white blood cells.

Physiologic Shunt:

Bronchial arteries supply the lungs and bronchial tree, draining into the pulmonary veins. Similarly, the coronary circulation drains directly into Left ventricle. Thus the drainage of deoxygenated blood through these will dilute the blood going out of the left ventricle into the systemic circulation. PO_2 in the systemic arteries is thus about 98mmHg whereas it is 100mmHg in the alveoli. This is due to the effect of this physiologic shunt.

Ventilation – Perfusion Relationship:

Ventilation-perfusion ratio determines the gas exchange in any lung unit or region

In normal adult lung in resting position, V/P ratio = alveolar ventilation/cardiac output

= 4L/min ÷ 5L/min = 0.8

Distribution of air flow to the lungs (Ventilation): ventilation per unit of alveolar volume decreases with distance up the lung (the rate of change of ventilation is much less than that for blood flow).

Distribution of blood flow to the lungs (perfusion): steady fall in blood flow per unit volume from base to apex of lung, such that flow is negligible at the apex. This distribution pattern is affected by posture and exercise. Both ensure almost equal flow to base and apex

Lung zones:(P_a=arterial pressure, P_A =alveolar pressure, P_v =venous pressure).

I (apex) - $P_a < P_A :\rightarrow$ No blood flow: (not present under normal conditions).

II (middle) - $P_a > P_A$, but $P_A > P_v :\rightarrow$ increase in flow with distance.

III (base) - $P_v > P_A : \rightarrow$ increase in flow with distance down the lung; capillary distension occurs down the lung.

Not all capillaries are open at any one time. As pressure increases down the lung, morel capillaries open. This phenomenon is called *Recruitment.*

Due to the effect of gravity on air and blood distribution in the lungs, V/P at the lung apex is 3.0; alveoli are greatly over-perfused in relation to their ventilation. At the lung base, V/P = 0.5; alveoli are slightly over-perfused in relation to their ventilation.

It should be noted that the Specific Gravity of blood is 1.0 and that of air containing lung is 0.25.

Transportation of Gases

Oxygen (O_2) and carbon dioxide (CO_2) are the gases that are of interest in respiratory physiology. O_2 is freely available in the atmosphere. It is taken into the lungs as a component of the inspired air. The body tissues use it for metabolism, producing CO_2 as a waste product of metabolism. CO_2 is eliminated from the lungs, as a component of the expired air, into the atmosphere.

The composition of atmospheric air at sea level (Atmospheric Pressure = 760mmHg), with their partial Pressures is as follows:

Nitrogen (N_2): 79% – 596mmHg

Oxygen (O_2): 20.83% – 156mmHg

Carbon dioxide (CO_2): 0.03% – 0.3mmHg

Inert gases and others in minor quantities (about 1% – 7.6mmHg)

Water vapour – variable (depending on humidity and temperature – at 37^0C, water vapour, at full humidity, exerts a pressure of 47mmH).

At heights above sea level, air becomes increasingly rarified and so the partial pressures of the gases decrease even when the composition remains the same.

Alveolar air: (Temperature: 37^0C**)**

N_2: 80% – 573mmHg

O_2: 14% – 100mmHg

CO_2: 6% – 46mmHg

Water vapour: 47mmHg

Expired air: (Temperature: 37^0C**)**

N_2: 74% – 565mmHg

O_2: 15% – 116mmHg

CO_2: 4% – 32mmHg

Water vapour: 47mmHg

Gas pressures in systemic blood and the alveoli:

	venous	**arterial**	**alveoli**
PO_2 (mmHg)	40	98	100
PCO_2(mmHg)	46	40	40

Notice that the Physiologic shunt phenomenon is what makes the PO_2 at the arterial blood to be less than 100mmHg.

Movement of O_2 from the alveoli into the blood is by simple diffusion, governed by pressure gradient. CO_2 also moves in the reverse direction by simple diffusion.

Diffusion of the gases is governed by Fick's Law, the large surface area of the alveoli as well as the thin respiratory membrane of the alveoli, together make diffusion of the gases easy and fast.

Certain conditions can lead to reduction of the alveolar surface area. These include lung collapse, alveolar destruction, lung infection and lung oedema. The thickness of the respiratory membrane can also be increased by fibrosis and lung oedema. Both reduction in alveolar surface area and thickness of the respiratory membrane will reduce the quatity and rate of transfer of the gases.

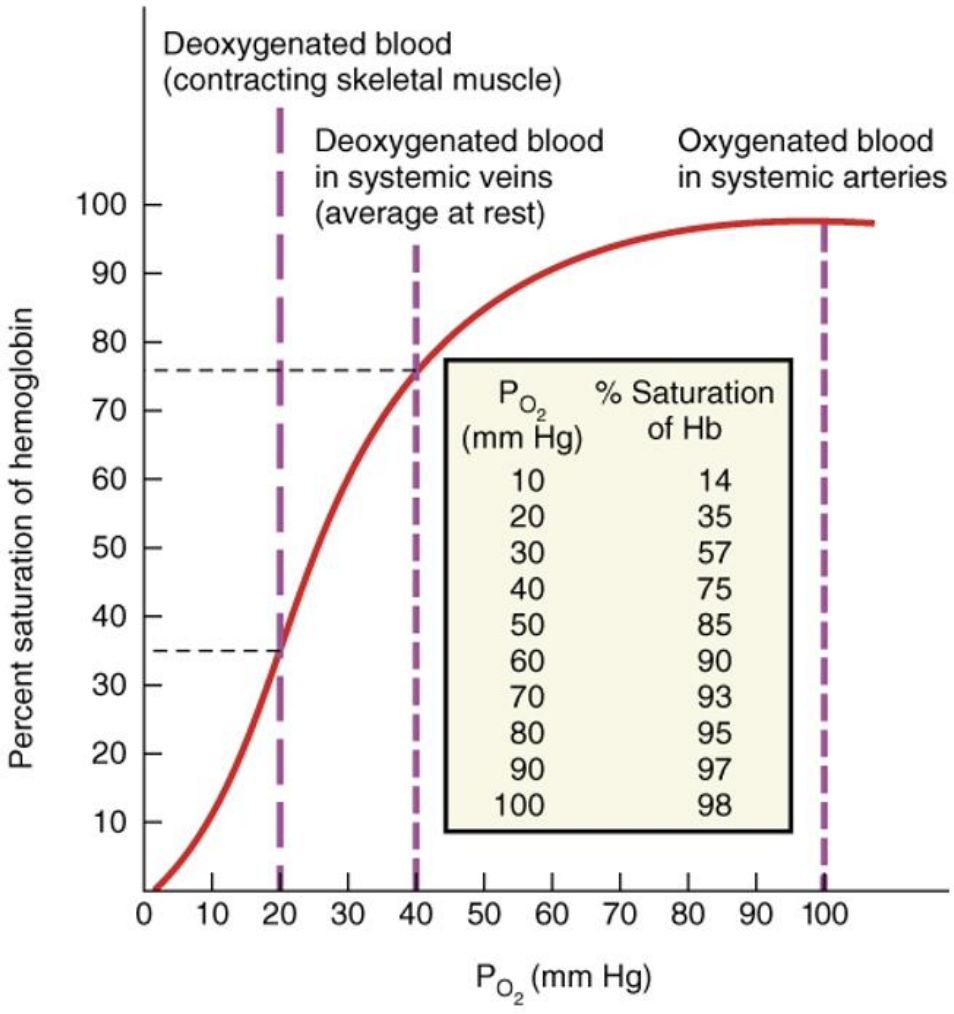
It should be noted that diffusion problems in the lungs are almost always restricted to O_2 and do not affect CO_2 elimination, because it is much more soluble than O_2 .

Carriage of Oxygen (O_2) in the blood

Once O_2 enters the blood from the alveoli, it is carried in the blood by two methods. First in simple solution according to Henry's Law and secondly in combination with haemoglobin in the red blood cells.

Only a negligible amount of O_2 is carried in solution. 0.003ml of O_2 dissolves in 100ml (or 1dL) of blood per mmHg of PO_2. Thus, in the venous blood (P O_2 of 40mmHg), 0.13ml of O_2 is carried per 100ml in solution. In the arterial blood (PO_2 of 100mmHg), 0.3ml of O_2 is carried in solution per 100ml of blood. This amount of O_2 that is physically dissolved in blood cannot meet the metabolic demand for O_2.

The bulk of O_2 carried to the tissues is in the form of oxyhaemoglobin. Haemoglobin is a blood pigment responsible for the red colour of the red blood cells. It is made up of four haem groups, each with a ferrous atom which can combine with a molecule of O_2. Each haemoglobin molecule can thus combine with four O_2 at full saturation. The combination of haemoglobin with O_2 is an oxygenation reaction and not an oxidation reaction. The reaction is thus freely reversible such that at high PO_2, O_2 attaches and at reduced PO_2, O_2 is dissociated from the oxyhaemoglobin (HBO_2). The combination is not linear due to the quaternary structure of the haemoglobin. The curve of percentage haemoglobin saturation with oxygen per PO_2 is sigmoid in shape.



Oxyhaemoglobin Dissociation Curve

Source: *Reproduced from Free Access*

It can be seen from the curve that the venous blood (PO_2 = 40mmHg), the haemoglobin is about 75% saturated with O_2.and in the arterial blood (PO_2 = 100mmHg), the saturation is about 100%.

Significance of sigmoid shape of O_2 dissociation curve is such that the Plateau provides an excellent safety factor in supply of O_2 to tissues. A significant drop in PO_2 (e.g. 100 to 60mmHg) will lead to only a small drop (about 10%) of O_2 carried by haemoglobin. Peripheral tissue can withdraw large amount of O_2 with only a small drop in capillary O_2.

Flat upper portion shows that loading of O_2 is little affected even with a fall in alveolar O_2 tension. Shift of the curve to the right or to the left will affect amount of O_2 carried.

Summary of O_2 carriage in the blood:

	Venous blood (PO_2 = 40mmHg)	arterial blood (PO_2 = 100mmHg)
i. Simple solution in plasma:	0.13ml/dL of blood	0.30ml/dL of blood
ii. Combined with haemoglobin:	15ml/dL of blood	19.5ml/dL of blood

1g of haemoglobin will carry 1.34ml O_2 at full saturation

With haemoglobin concentration of 15g/dL, 100ml blood will carry 20ml O_2

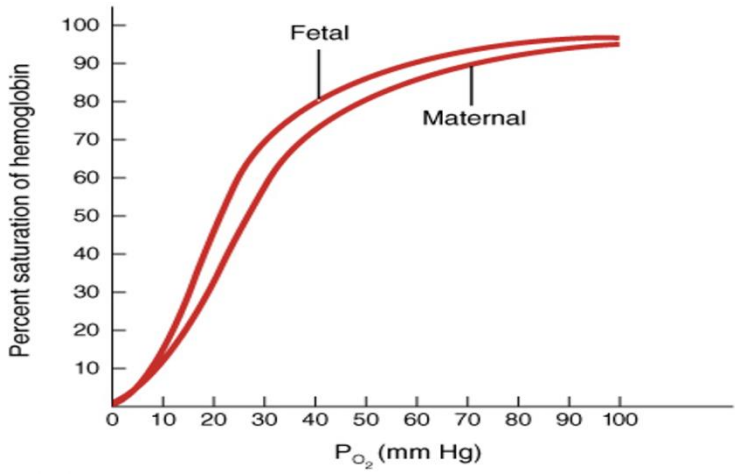
O_2 Capacity of the blood = 20ml

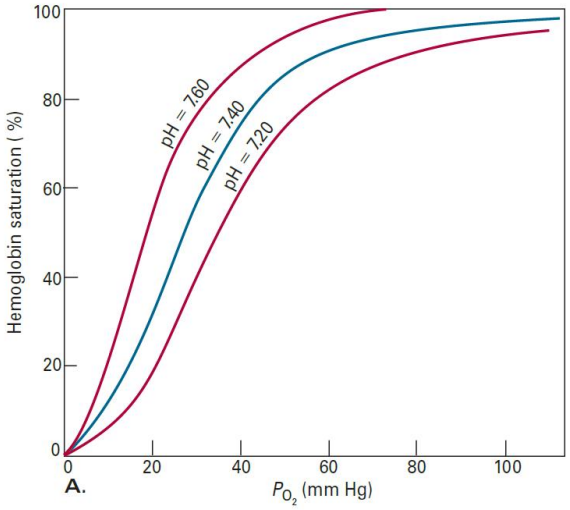
O_2 Content = amount of O_2 carried at a particular O_2 tension.

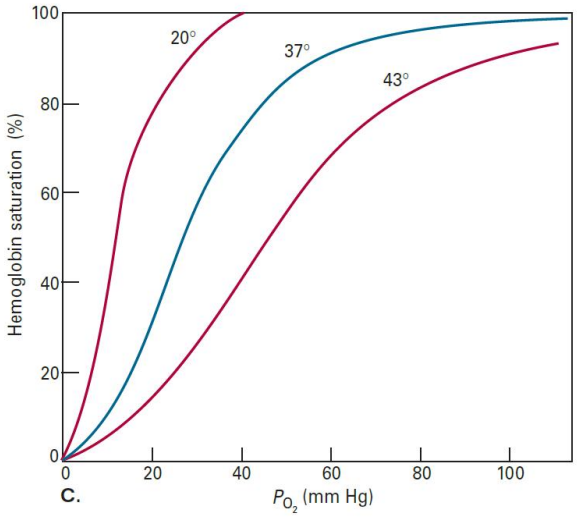
Factors affecting carriage of O_2 by combination with haemoglobin are those that affect the shift of the oxyhaemoglobin dissociation curve. A shift to the right of the curve will reduce amount of O_2 carried, thus increasing delivery of O_2 into the tissue. A shift to the left will result in carriage of more O_2. The factors include Temperature, $[H^+]$ (the Bohr effect), PCO_2, 2,3-DPG (BPG) and Fetal haemoglobin.

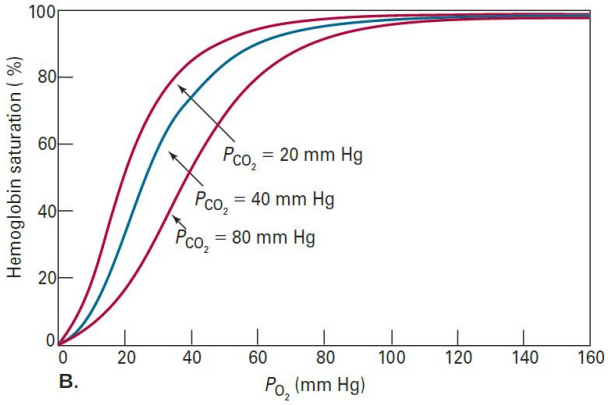
The curve is shifted to the right by increase in temperature, increased in hydrogen ion concentration, increase in PCO_2 and increase in concentration of 2,3-DPG. The effect of hydrogen ion concentration on the oxyhaemoglobin dissociation curve is call the Bohr Effect. These conditions are seen in the skeletal muscle vascular bed during exercise. Thus, muscular exercise will result in greater O_2 delivery to the exercising muscle, partly through the right shift of the oxyhaemoglobin dissociation curve.

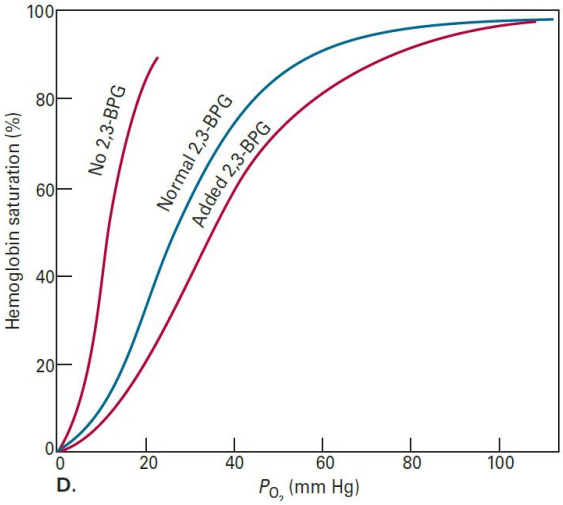
Fetal haemoglobin binds more avidly to 2,3-DPG (reducing effective concentration of 2,3-DPG), and so will bind more to O_2 than adult haemoglobin. This is one of the factors for enhancing adequate O_2 carriage in the fetal blood.


Fetal
Maternal
Percent saturation of hemoglobin
100
90
80
70
60
50
40
30
20
10
0 10 20 30 40 50 60 70 80 90 100
P_{O_2} (mm Hg)


Hemoglobin saturation (%)
pH = 7.60
pH = 7.40
pH = 7.20
0 20 40 60 80 100
A.
P_{O_2} (mm Hg)


Hemoglobin saturation (%)
20°
37°
43°
0 20 40 60 80 100
C.
P_{O_2} (mm Hg)


Hemoglobin saturation (%)
P_{CO_2} = 20 mm Hg
P_{CO_2} = 40 mm Hg
P_{CO_2} = 80 mm Hg
0 20 40 60 80 100 120 140 160
B.
P_{O_2} (mm Hg)


Hemoglobin saturation (%)
No 2,3-BPG
Normal 2,3-BPG
Added 2,3-BPG
0 20 40 60 80 100
D.
P_{O_2} (mm Hg)

Effects of pH, Temperature, PCO2 and 2,3-DPG on Oxyhaemoglobin Dissociation Curve (*Reproduced from Free Access*)

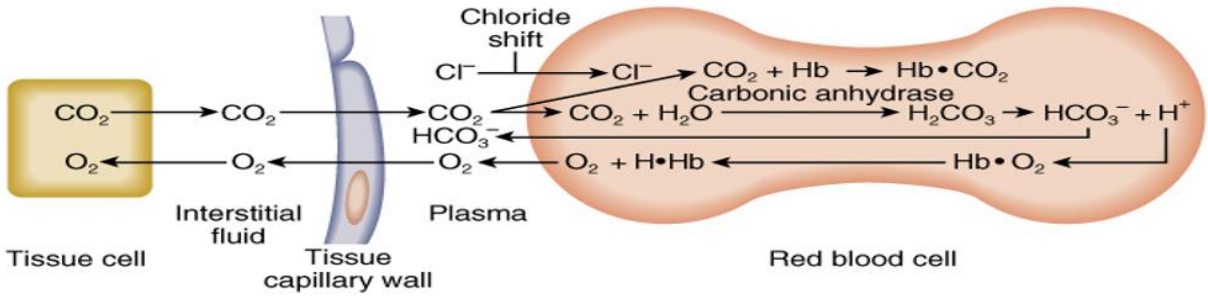
2,3DPG:

Synthesized in RBC from metabolites of the glycolytic pathway and binds tightly to reduced haemoglobin. In the presence of DPG, affinity of haemoglobin for O_2 is reduced. Concentration of 2,3DPG is increased by Thyroxine, Growth Hormone, Testosterone, exercise and hypoxia (anaemic and hypoxic). Concentration of 2,3DPG is also decreased by $\uparrow[H^+]$ ($\downarrow$pH).

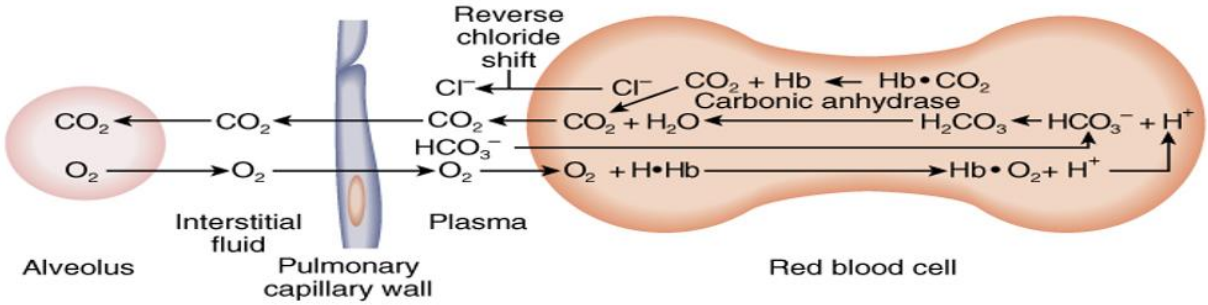
Carriage of Carbon Dioxide (CO_2) in the blood

Carbon dioxide diffuses from the tissues to the blood and it is carried to the lungs for elimination through expiration of air.

CO_2 is carried in the blood in three different forms. It is carried in simple solution, according to Henry's Law. It is also carried combined with haemoglobin as a carbamino compound. Finally, it is carried within the red blood cells as bicarbonate. CO_2 is readily soluble in the plasma but the bulk of its carriage in the blood is in form of bicarbonate, formed inside the red blood cells with the enzyme carbonic anhydrase catalyzing the reaction CO_2 and water to form bicarbonate.



(a) Exchange of O_2 and CO_2 in the tissues (internal respiration)



(b) Exchange of O_2 and CO_2 in the lungs (external respiration)

Location of carbonic anhydrase in the body:

- RBC
- Gastric mucosa cells
- Renal tubular cells
- Pancreatic acinar cells
- Cells lining the choroid plexus

Summary of the carriage of c in the blood is illustrated below:

<u>Carbon Dioxide:</u>	A-V difference	arterial blood
i. Dissolved:	10%	5%
ii. Carbamino compound	30%	5%
iii. Bicarbonate	60%	90%

Amount of CO_2 carried in 100ml of blood:

Arterial (PCO_2 = 40mmHg) Venous (PCO_2 = 40mmHg)

In solution	3ml		3.5ml	
As carbamino compound	3ml		3.7ml	
As bicarbonate		42ml		44.8ml
Total		48ml		52ml

Difference = 4ml of CO_2 per 100ml blood

CO_2 carriage is affected by the level of oxygenation of the blood. The CO_2 dissociation curve is shifted to the right by an increase in oxyhaemoglobin in the blood. This shift to the right is called Haldane Effect.

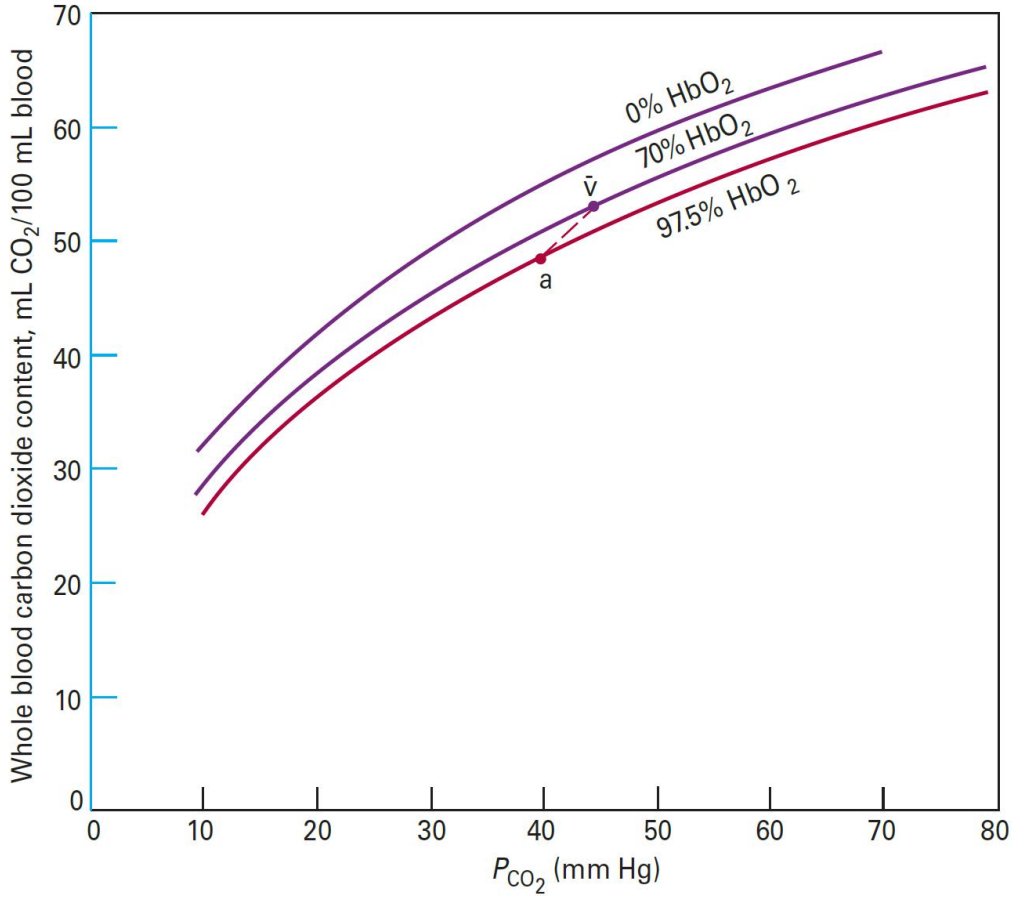


Fig. 4.??: Carbon Dioxide Dissociation Curve.

Measurement of Cardiac Output by the Fick Principle

Cardiac Output (CO) = [O_2 uptake/min] ÷ [(A – V)O_2 difference] x 100.

= [CO_2 given off/min] ÷ [(V – A)CO_2 difference] x 100.

For O_2: CO = 250ml/min ÷ [19 – 14] x 100 = 5000ml per min.

For CO_2: CO = 200ml/min ÷ [52 – 48] x 100 = 5000ml/min.

O_2 uptake and CO_2 output can be measured from timed collection of respiratory air using a Douglas bag.

Arterial blood sample can be taken from a peripheral artery, eg the radial artery.

Mixed venous sample is taken from the pulmonary trunk through a catheter passed in from a vein in the antecubital fossa.

Gas analysis done on the air and blood samples.

Control of Respiration

Remarkable regulation of respiration is due to a very careful control by the three basic elements of respiratory control.

i. Sensors: Gather information and feed it to central controller.
ii. Central controller: Coordination of information and sending signal to effectors.
iii. Effectors: respond to impulses from central controller.

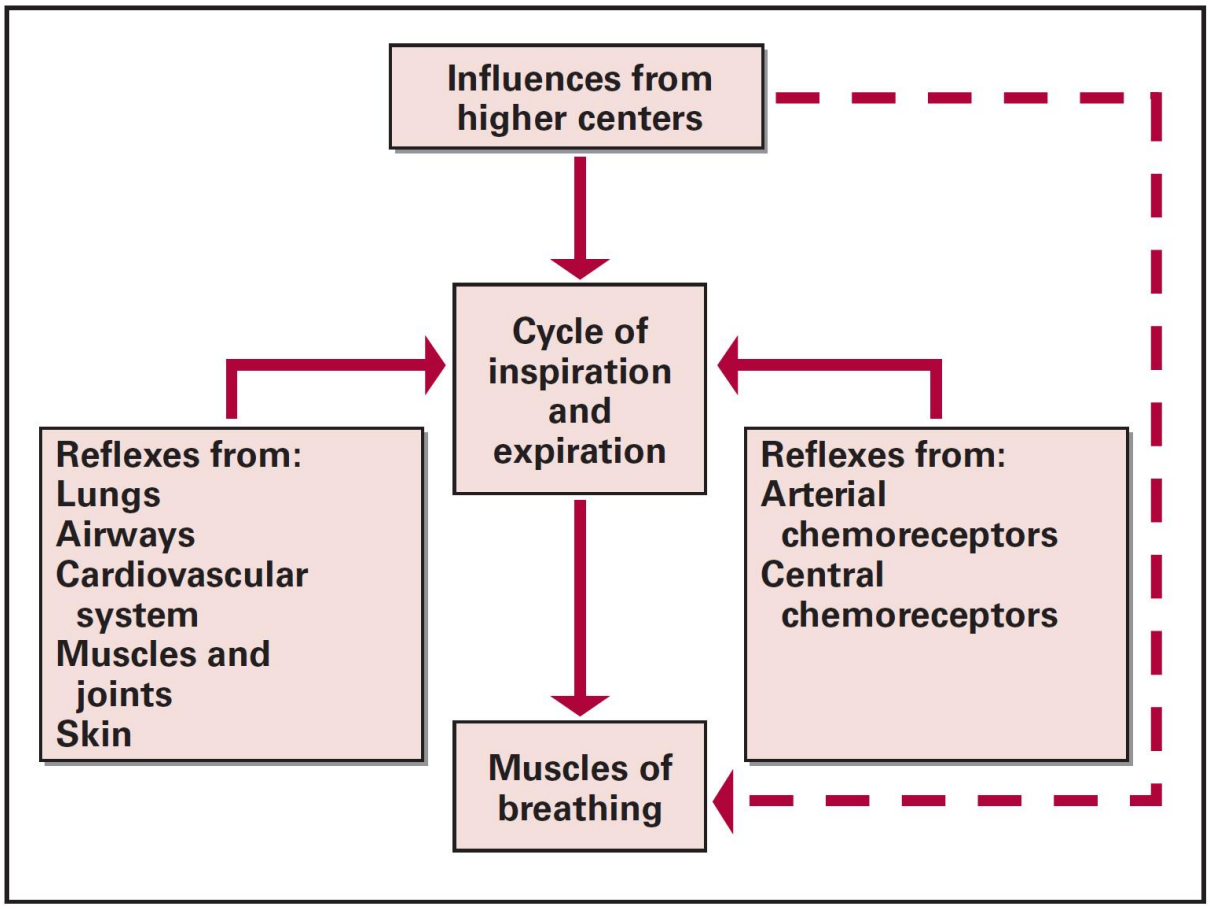


Fig. 4.??: Schematic representation of respiratory control mechanisms.

Ultimate function of the lungs is to replenish the supply of O_2 in the blood, and to

eliminate the CO_2 produced by metabolic activity. Both rate and depth of breathing are regulated to maintain arterial PCO_2 close to 40mmHg.

Mechanisms of respiration

Neural mechanisms comprise Voluntary (used in behavioural activities) and Involuntary (automatic – used to meet metabolic needs of the body).

Chemical mechanisms comprise Responses of breathing to arterial PCO_2 and PO_2. These are intimately associated with automatic neural control of respiration.

Non-Chemical Reflexes are modifiers seen in operation in various day-to-day activities like swallowing and speech. These modify the rate and pattern of respiration.

Voluntary neural mechanisms

Behavioural in nature

Coordinate breathing in relation to volitional motor activities that make use of lungs and chest walls - eg swallowing, speech, breath-holding etc.

Controller may reside in the thalamus and cerebral cortex, and fibre tracts are located in the extrapyramidal path.

Ondine's curse: Typical picture occurs when there is disruption of automatic control of respiration without loss of voluntary control. Seen in patients with bulbar poliomyelitis. disease processes that compress the medulla and surgical procedures with disruption of anterolateral descending fibres in the upper cervical spinal cord.

Role of the BRAINSTEM in control of respiration

Metabolic controller lies in the Pons and Medulla, as diffuse areas surrounding and scattered throughout the reticular activating system (which maintains state of alertness of the brain).

Experimental evidence from observations of patients with neurological disorders,

systematic stimulation of brainstem groups of cells, and selective destruction of brainstem groups of cells have led to the understanding of the brainstem in the control of respiration.

Conclusion of the experimental evidence is such that the brainstem regions that function as intrinsic breathing controllers (Medullary respiratory area) are neuronal groups located in the nucleus tractus solitarius. These are dorsally located and discharge impulses mainly during inspiration. Also, the nucleus retroambiguus, which is ventrally located, is excited during both inspiration and expiration.

Motor fibres from both ventral and dorsal groups direct respiratory activity of muscles of respiration through the common motor pathway. Efferent fibres from both cross over and travel contralaterally as pyramidal tracts to motor neurons of respiratory muscles.

Pontine influencing areas include the pneumotaxic centre which is located in the rostral pons and the apneustic centre located in caudal pons.

The respiratory rhythm generator is located in the Neurons in the area called the **pre-Botzinger complex**, which have been identified as the pacemaker for respiration. This pacemaker has a controlling input from several sources, similar to the pacemaker in the heart. Generation of impulses in the pre-Botzinger complex is what is responsible for the automatic respiratory impulse generation.

Older view of brainstem control

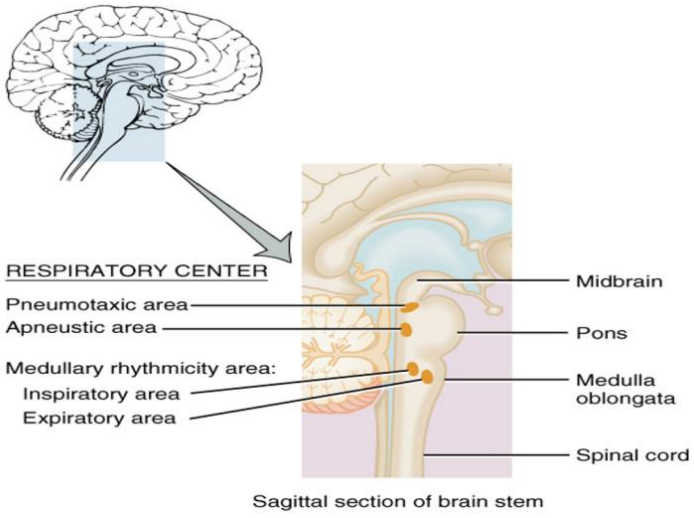
Apneustic centre may have tonic stimulatory discharge inhibited only by pneumotaxic discharge or vagal discharge from lung inflation.

Inspiratory centre in medulla, stimulated by apneustic centre, discharges to stimulate inspiratory muscles, via anterior horn cells and motor nerves, to contract. It also stimulates the pneumotaxic centre - a sort of negative feedback effect.

Pneumotaxic centre stimulates expiratory centre and also inhibits apneustic centre. Lack of pneumotaxic and vagal inhibition on the apneustic centre results in breathing pattern called *APNEUSIS,* a state of sustained inspiration, interspersed by gasps of expiration.

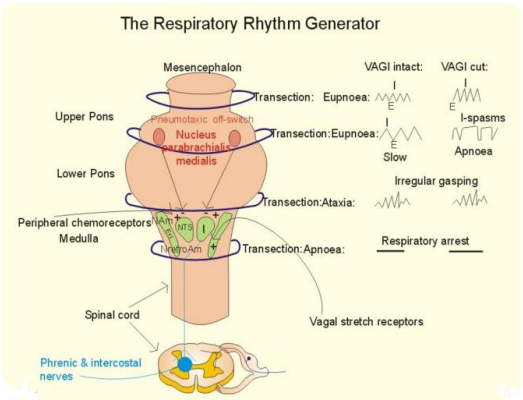
It is believed that some of the assumptions of the older view on the control of respitation are still relevant to the understanding of the role of the brainstem in the control of respiration.

Fig. 4.??.



Sagittal section of brain stem

Sagittal section of brain stem



Chemical control of respiration

Chemoreceptor control of breathing: Chemoreceptors provide an important excitatory input to the medullary inspiratory neurons for automatic control of respiration at rest.

Chemoreceptors are grouped into:

i. Peripheral chemoreceptors located at the carotid bodies (at the bifurcation of right and left common carotid arteries), and the aortic bodies (at the arch of the aorta).
ii. Central chemoreceptors located in the medulla (medullary chemoreceptors)

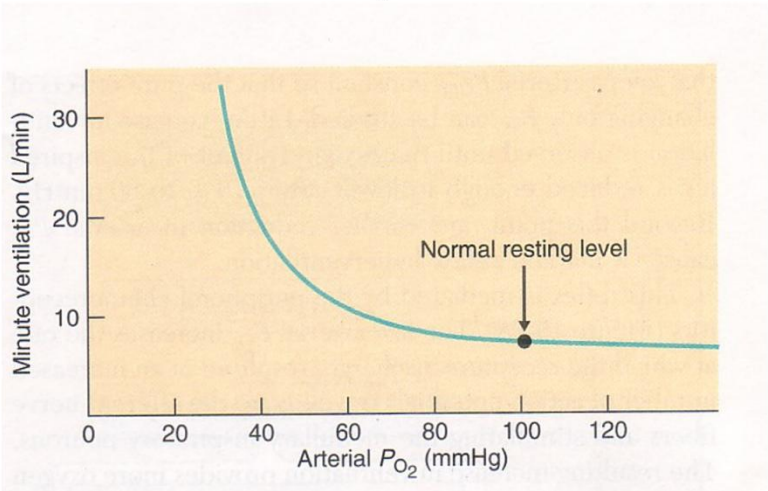
Control by arterial PCO_2: direct effect on peripheral and indirect effect on central chemoreceptors. CO_2 diffuses into brain ECF to form H^+ by hydration. The brain ECF H^+ stimulates central chemoreceptors.

Control by arterial PO_2: reciprocal effect on peripheral chemoreceptors, i.e. reduced arterial PO_2 stimulates peripheral chemoreceptors.

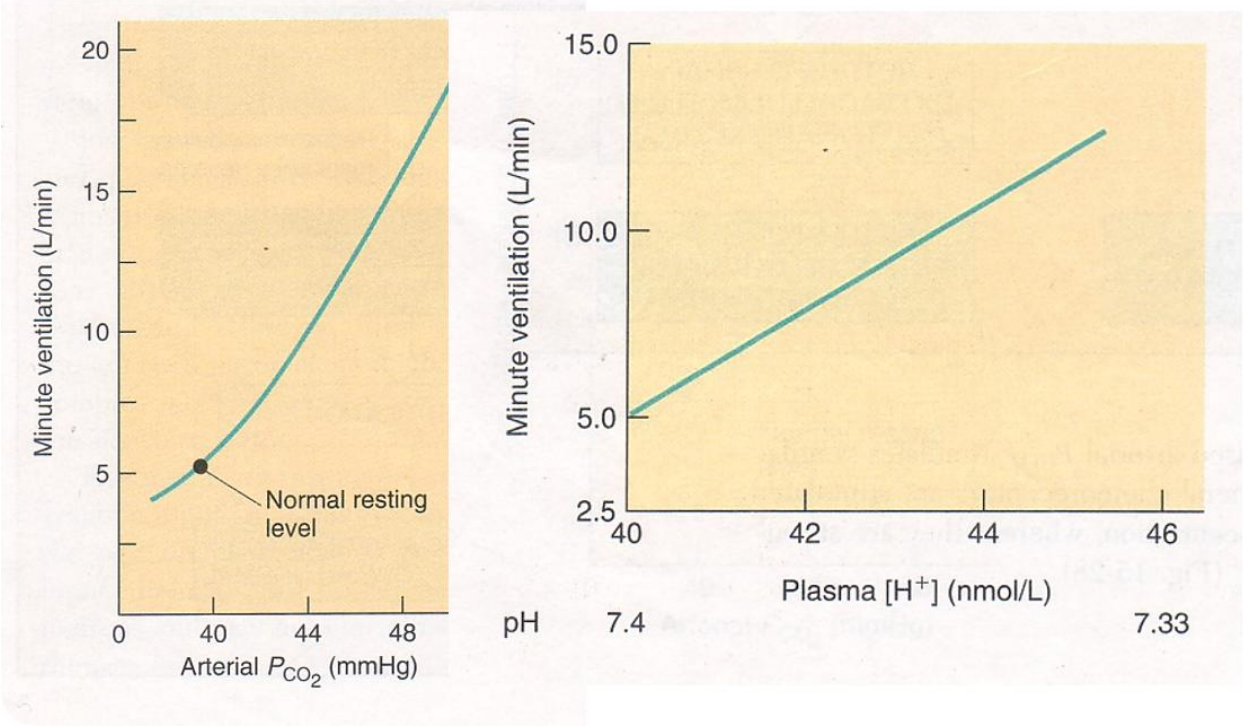
Control by arterial $[H^+]$: direct effect on peripheral chemoreceptors.

Thus, increased arterial PCO_2, decreased PO_2 and increased $[H^+]$ stimulate an increased rate and depth of respiration. The effect of this is to increase arterial oxygen tension and decrease arterial carbon dioxide tension.

Effect of Arterial PO_2 on ventilation



Effects of Arterial PCO_2 & pH on ventilation



Effects of various conditions on alveolar gas pressures

Condition	alveolar PO_2	alveolar PCO_2
Breathing air with low PO_2	↓	N
↑ alveolar vent, unchanged metabolism	↑	↓
↓ alveolar vent, unchanged metabolism	↓	↑
↑ metabolism, unchanged alveolar vent	↓	↑
Proportional ↑ in metabolism and alv. Vent	N	N

Oxygen toxicity: results from hyperbaric O_2 (100% O_2 at increased pressures). Hyperbaric O_2 inhalation can lead to 6-fold increase in alveolar PO_2

Oxygen toxicity leads to airway irritation, lung congestion and loss of surfactant, convulsions, tinnitus, loss of fertility and retrolental fibroplasia, especially in preterm infants.

Carbon dioxide narcosis: results in headache, confusion and coma.

ACID-BASE BALANCE

Blood pH is 7.40. The body can only tolerate minor changes in pH

$pH = -\log[H^+]$

BUFFERS: Chemicals that prevent overt changes in the acidity of solutions, even with the addition of acids and bases. They are made of weak acids and their salts with strong bases, or weak bases and their salts with strong acids

Blood buffers include:

- HCO_3^-/H_2CO_3; pK value = 6.1
- Hb, due to the presence of 38 histidine residues per molecule of Hb
- Plasma proteins
- Phosphates also serve as minor blood buffers; pK = 6.8

Acidosis: Metabolic and Respiratory

Alkalosis: Metabolic and Respiratory

Henderson – Hasselbalch equation: $pH = pK + \log [A^-]/[HA]$

RESPIRATORY SYSTEM AND ACID-BASE BALANCE

Acid-base status of the body is kept within narrow range by interplay of buffer systems in the blood, the respiratory system and the renal system.

Respiratory system responds to metabolic alterations in acid-base status:

Acidosis: $\uparrow [H^+] \rightarrow \uparrow PCO_2$ due to leftward shift in reaction:

$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$

$\uparrow PCO_2 \rightarrow \uparrow$ stimulation of respiration $\rightarrow$ Hyperventilation $\rightarrow \downarrow PCO_2$

The reverse is true for Alkalosis:

where $\downarrow[H^+] \rightarrow \downarrow PCO_2 \rightarrow$ Hypoventilation $\rightarrow \uparrow PCO_2$.

Mechanical Control of Breathing (Non-chemical influences on respiration)

Pulmonary receptors: These are stimulated by mucosal irritation and changes in airway distending pressure. Afferent sensory traffic travels to the brainstem via the vagus nerves.

Types of Pulmonary receptors:

Stretch receptors located within the smooth muscle layer of the extra-pulmonary airways.

Irritant receptors that ramify among airway epithelial cells and whose distribution is similar to that of stretch receptors.

Unmyelinated C-fibres situated in the lung interstitium and alveolar walls.

Stretch receptors serve a regulatory function.

Irritant receptors and unmyelinated C-fibres are protective receptors.

Irritant receptors and C-fibre receptor neurons, however, rapidly adapt when subjected to a sustained stimulus.

Irritant receptors are stimulated chemically by various noxious agents such as - NO_2, SO_2, NH_3, and Pollens (inhaled antigens); and mechanically by lung inflation, changes in airflow, particles impinging on bronchial surfaces, changes in bronchial smooth muscle tone.

Irritant receptor stimulation causes cough, bronchoconstriction, increased mucus secretion, apnea and glottal closure followed by rapid, shallow breathing.

C fibres participate in intrabronchal axon-reflex that releases neuropeptides in the bronchial submucosa and causes localized vasodilatation and increased venular leakiness (vascular congestion and oedema).

Hering-Breuer reflex: Production of apnea in response to large lung inflation and augmentation of expiratory muscle contraction. It is made up of inflation and deflation components.

This is not important in adults, unless in certain situations e.g. hypnosis.

Some reflex responses - nonchemical influences on respiration include lung oedema causing rapid shallow breathing, lung hyperinflation and intravenous and intracardiac administration of some chemicals, stimulating the J-receptors. These produce the pulmonary chemoreflex (apnea followed by rapid breathing, bradycardia and hypotension).

Active and passive joint movements stimulate proprioceptors to increase ventilation. This is the primary respiratory drive in moderate exercise.

Chest wall receptors - joint, tendon, muscle spindle: activity varies with extent and speed of rib movement.

Swallowing reflex: Prevents food going into the trachea, the nose and back into the mouth once the food gets into the oro-pharynx. The reflex is accomplished by closure and elevation of the glottis, elevation of the soft palate, apposition of the fauces of the mouth, and relaxation of the upper oesophageal sphincter.

Muscle spindles in respiratory musles give rise to afferent discharge for monitoring of chest wall volume and adjustment of force of contraction of respiratory muscles to maintain tidal volume.

J – receptors: (Juxta-capillary location) when stimulated, give rise to rapid shallow breathing following lung collapse, oedema or congestion.

Pain and Emotion: reflex results in increase or decrease in respiration.

Proprioceptors: stimulation of respiratory centre by active or passive limb movements. This is especially useful in exercise.

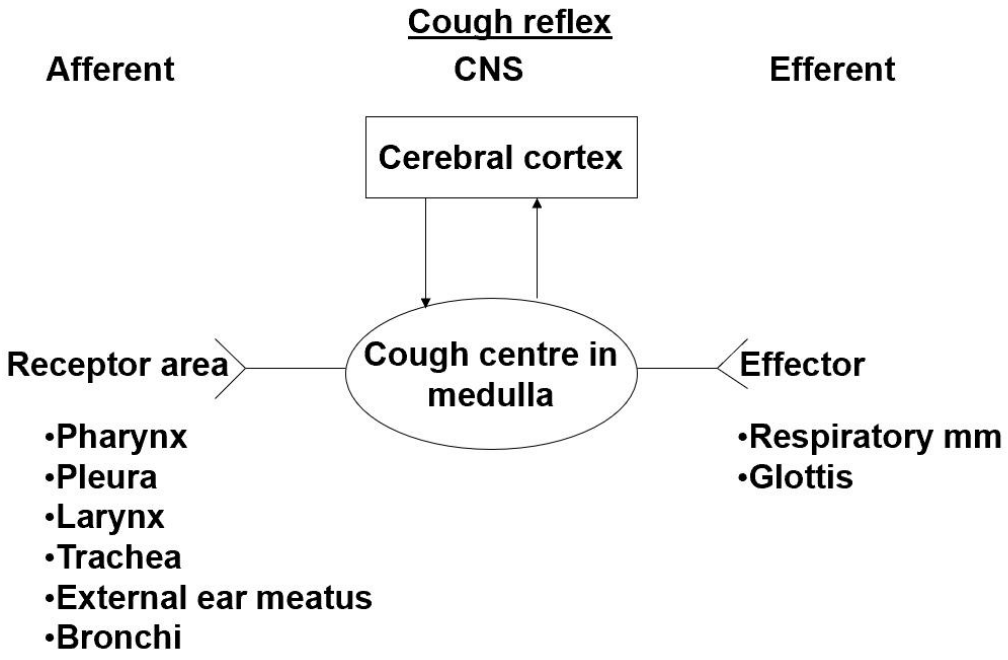
Baroreceptors: sudden rise of pressure in sino-aortic zone elicits a brief reflex decrease in respiratory rate and depth. Also very low BP increases respiration.

Cough:

A protective reflex that can expel secretions and extraneous materials from the respiratory tract. Irritation of the respiratory passage from the pharynx downwards initiates the cough reflex. Sneezing occurs when irritants affect upper parts of the tract up to the nose.

Irritative substances/factors include foreign bodies, airway compression (tumours/allergic bronchoconstriction), cold or very hot air, oedema of the lungs and airways/fluid collection from whatever cause, including intrapleural fluid collections.

The cough centre is in the medulla, and the stimulants of the centre, include ACE inhibitors which cause a characteristic dry cough, without a feeling of airway irritation.



Physiology of cough:

Deep inspiration followed by forced expiration against a closed glottis. Intrapleural pressure increases to 100mmHg or more from pre-inspiration value of - 4mmHg. There is sudden opening of the glottis and this forces air out at high velocities (of up to 1000Km/Hr) with an explosive sound thereby dislodging irritants.

In sneezing, the glottis is persistently open.

It should be noted that irritants in airways cause copious mucus secretion which further causes irritation. Smokers have defective tracheal ciliary action. Diaphragm irritation (e.g. by subdiaphragmatic air) causes cough.

External meatus irritation causes cough through central connections and external ear blockage may lead to otitis media and nasopharyngeal irritation.

Abnormal breathing patterns

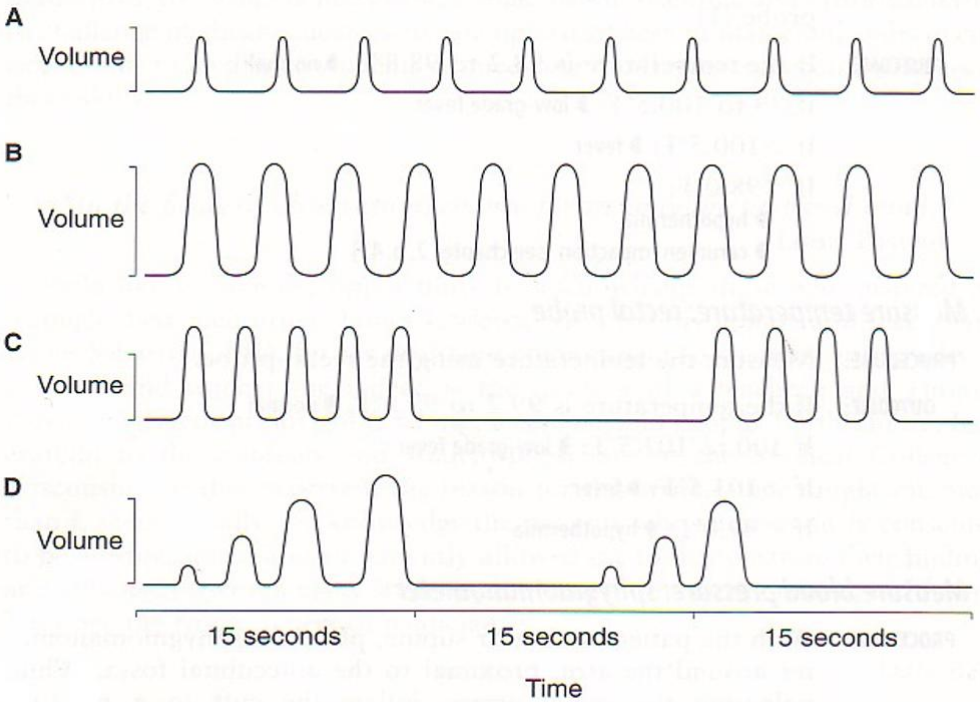
Cheyne-Stokes respiration is seen in advanced heart failure and may be accompanied by periodic breathing with alternate periods of apnea and hyperventilation.

Kussmaul respiration Characteristic increase in ventilation (deep and rapid breathing), especially tidal volume which accompanies fall in pH of metabolic acidosis.

Apneustic breathing Sustained inspiration interspersed by gasps of expiration, seen in brainstem lesions affecting the pneumotaxic area .

Biot's breathing Made up of abrupt, irregular alternating periods of apnea with constant rate and depth of breathing, as that resulting from lesions due to increased intracranial pressure.

Sleep: Decreased sensitivity to CO_2 leads to irregular slow breathing, characteristic of breathing pattern during sleep. Periods of apnea are seen in sleep but this can become a clinical problem in some people (sleep-apnea syndrome).



Breathing patterns. A. Normal. B. Kussmaul's. C. Biot. D. Cheyne-Stokes.

Breath holding

Breaking point in voluntary holding of the breath is due to increasing PCO_2 and decreasing PO_2. Breath can be held longer by prior hyperventilation, prior breathing of 100%O_2, denervation of the carotid bodies, and psychological factors.

Voluntary Hyperventilation (leads to increased PO_2 and decreased PCO_2). This is followed by periodic apnea, until respiration becomes normal, respiratory alkalaemia, renal compensation for the alkalaemia – (incresed loss of Na^+ and HCO_3^-). Other changes include those of cardiovascular changes – (increased Cardiac Output $\rightarrow$ slight $\uparrow$ BP), neurological changes (dizziness, light headedness, paraesthesia, loss of consciousness,

tetany - due to increased excitability of the nerves following decreased Ca^{++} concentrations in blood (increased calcium proteinate formation).

RESPIRATION IN HEALTH AND DISEASE

Hypoxia: Reduced oxygen tension at the tissue level. There are typically four types of hypoxia. **Hypoxic hypoxia** occurring in low oxygen tension environment, airway obstruction or in situations when the diffusion of oxygen int the blood from the alveoli is impeded. **Anaemic hypoxia** occurs in situations of low oxygen-carrying capacity of the blood (all forms of anaemia) and in carbon monoxide (CO) poisoning, in which case, the proper oxygenation of haemoglobin is inhibited by competitive attachment of CO to haem. In **Stagnant hypoxia**, blood flow to the tissues is impeded, causing reduction in the amount of O_2 being delivered to the tissues. This is typically seen in heart failure. In **Histotoxic hypoxia**, mechanism for the transfer of O_2 from the blood to the tissue is inhibited. Poisoning by cyanide can rapidly cause death due to histotoxic hypoxia. The blood of those dying of histotoxic hypoxia appears cherry red due to full oxygenation of the blood.

Cyanosis: Bluish discolouration of the skin and mucous membranes due to increased arterial deoxyhaemoglobin level (>5g/dL). Central cyanosis is seen in cardiac and lung diseases which reduce proper blood circulation and arterial blood oxygenation. In Peripheral cyanosis, blood circulation to the extremities is reduced. It is typically seen in the hands and feet of people with arterial vasoconstriction due to cold exposure. Cyanosis is not seen in patients with anaemia, as the condition would have resulted in death before the deoxyhaemoglobin level could be more than 5mg/dL.

Effect of age on breathing

The newborn: During intra-uterine life, the fetus is exposed to low O_2 tension. Certain mechanisms are put in place by the fetus to cope with the persistent hypoxic intra-uterine condition. These include Fetal haemoglobin (which binds more O_2 than adult haemoglobin), increased heart rate (120 – 160 per min), increased red blood cell

count (typically about 8milliom/mm^3). At birth, the baby is exposed to atmospheric air and the coping strategy for oxygenation is no more needed, leading to reversal of mechanisms for fetal survival in hypoxic condition. There is massive destruction of red blood cells. The liver may not be able to cope with the conjugation process for bilirubin in some of the newborn, especially those that are slightly preterm. These newborn infants then develop jaundice, which is typically physiologic. It could be pathologic in a few cases.

The elderly: The elderly typically present with reduced response to ventilatory drive and reduced lung expansion with some degree of hyperinflation. These result in hypoventilation and increased tendency for respiratory insufficiency.

Respiratory effects of high altitude

The ambient pressure decreases with higher altitude. There is corresponding decrease in partial pressure of oxygen (PO_2) as one ascends up. When the ambient atmospheric pressure reduces to half, the PO_2 would be about 79mmHg. This PO_2 is not capable of ordinarily sustaining life, the subject exposed to this ambient pressure thus experience a state of hypoxic hypoxia.

Rapid ascent to such a height that will bring about rapid development of hypoxic hypoxia leads to a situation referred to as acute mountain sickness. The individual presents with fatigue, nausea, breathlessness, palpitations, headache, impaired vision and judgment, and even death may ensue.

A slow ascent may give the individual opportunity to adjust to the hypoxia in a process called **Acclimatization**. Certain adjustments are made in the body to enhance acclimatization process. These include: hyperventilation (hypoxia is the respiratory drive), increase in heart rate, increased erythropoiesis (due to increased erythropoietin secretion), increase in erythrocyte 2, 3-DPG, increased levels of cytochrome oxidase and oxidative enzymes within the tissues, increased tissue mitochondria, increased muscle myoglobin, and tissue neoangiogenesis. The hyperventilation will result in alkalosis, and there will be renal compensation for the respiratory alkalosis. Pulmonary hypertension and increased blood viscosity are also commonly seen.

DEEP SEA DIVING AND DECOMPRESSION SICKNESS

For every 10m descent below sea level, there is an ambient pressure increase of one atmosphere. When a diver goes to a 20m under the sea, he would be exposed to 3 atmospheres, (i.e. 2280mmHg). PN_2 becomes (3 x 79% of 760, i.e.1800mmHg) and N_2 is soluble at high PN_2. Since elemental nitrogen is practically inert in the body, a rapid rise from the sea bed can cause bubbles of nitrogen to appear in the blood stream. This can cause blockage to flow of blood to essential organs in the body, resulting in **Nitrogen narcosis** – euphoria, impaired performance;

Oxygen toxicity – lung damage, convulsions;

High-pressure nervous syndrome – tremors, somnolence;

Decompression sickness – pain (especially in the joints), muscle stiffness, rigidity and paralysis;

Air embolism – sudden death.

Recompression Procedures: can be performed in Recompression chamber or by the

Use of experienced divers, who will rapidly take the victim to deep sea level and then guide back up through a slow ascent.

EXERCISE

The exercising muscle requires an increase in oxygen delivery to the muscle in order to maintain the metabolic activities required for the exercise. Both the respiratory and cardiovascular systems adjust to provide the necessary increased O_2 delivery. Ventilation is increased 4-fold through joint and muscle proprioceptor activity. Cardiac output is increased 6-fold through increased muscle pump and respiratory pump activities.

O_2 delivery to exercising muscles is also increased through increase in blood supply by opening of more capillaries beds in the muscle. There is dilatation of vessels and diversion of blood flow from splanchnic organs to the exercising muscles. There is a right shift of the O_2 dissociation curve and an increase in muscle concentration of 2,3DPG. Temperature of exercising muscles increase and muscle [H^+] (from the glycolytic pathway) is increased. All of these are factors for increase of O_2 delivery.

Artificial Respiration

The process of restoring or initiating breathing by forcing air into and out of the lungs to establish the rhythm of inspiration and expiration. This will be necessary in states of inadequate respiration, seen in cases of failure of CNS to send impulses in brainstem damage, failure of afferent pathways to send impulses to effectors, failure of effectors – e.g. in paralysis of respiratory muscles, and others such as sudden cessation of breathing due to: drowning, inhalation of poisonous gases, narcotic overdose, electrocution,airway obstruction, rib fracture (resulting in 'Flail chest'), fluid in the pleura – leading to lung compression (air, water, blood, pus).

ABC of Resuscitation:

Airway maintenance

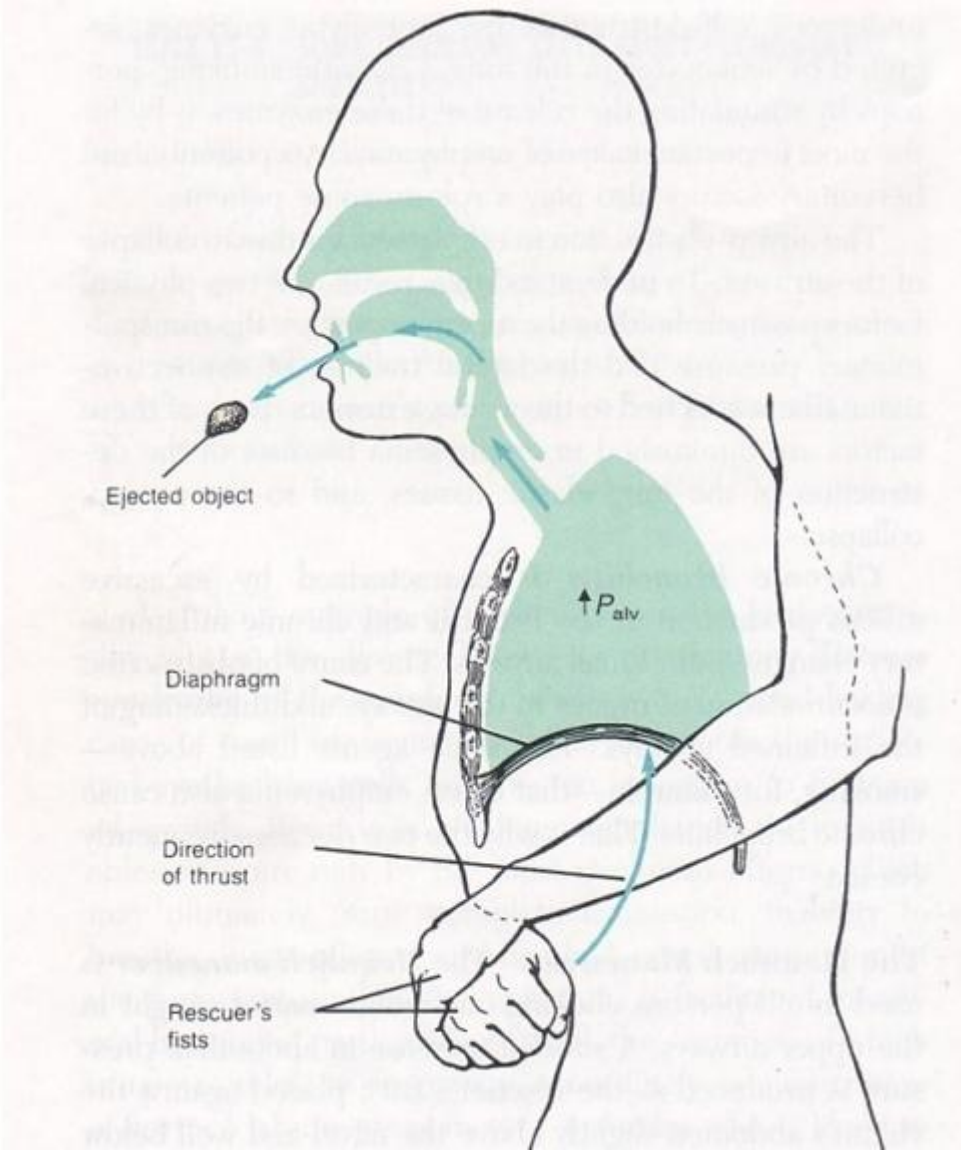
Breathing

Circulation maintenance

Manual methods of artificial Respiration include:

- Mouth-to-mouth (Kiss of Life) with or without Cardiac Massage,
- Schaefer's method: Patient lies prone
- Nielsen's method: Patient lives prone
- Silvester's method: Patient lies supine
- Eve Rocking method: Patient supine – ("see – saw")

Mechanical Method: Drinker's Method, employing negative and positive pressure techniques.



Heimlich hug: is a maneuvre to dislodge large particles from the trachea.

RESPIRATORY FUNCTION TESTS

They are rarely a key factor in making a definitive diagnosis in a patient with lung disease but are useful for follow-up of progress of disease with or without treatment. They are also useful in deciding mode of treatment and may be used in assessing patients for Life Insurance Policies. The following are tests that may be done to assess the functions of the respiratory system:

- Lung volumes and capacities
- Air flow rates
- Ventilation/Perfusion relationships
    - Use of radioactive Xenon
- Blood flow
- Diffusion
- Arterial blood gases and pH.

Summary:

The respiratory system supplies oxygen for the tissue oxidative processes and expels carbon dioxide, produced in the tissues, into the atmosphere. In the course of these activities, there is a balance of control that keeps the processes in perfect order. There are other factors that are involved in the processes.

Exercise:

1. Describe the functional anatomy of the upper and lower respiratory tracts
2. Describe the various Gas Laws that are relevant to the understanding of respiratory processes
3. Write an essay on the transportation of oxygen from the atmosphere into the tissues of the body
4. Describe the ways by which carbon dioxide is carried in the blood
5. Describe the role of the respiratory system in the maintenance of acid-base balance in the body
6. Write short notes on:
    a. Ondine's curse
    b. Oxyhaemoglobin dissociation curve
    c. Carbonic anhydrase
    d. FeV_1
    e. Bohr Effect
    f. Cough reflex
7. Write an essay on neural control of respiration
8. Describe the sequence of events taking place in an individual who is acclimatizing to chronic hypoxia
9. Enumerate the various adjustments made by the body to meet the oxygen demand of exercising muscle
10. Describe the physiological principles involved in the administration of the manual methods of artificial respiration

Chapter 5

PHS 205. CARDIOVASCULAR SYSYTEM

Aliyu Mohammed, Olawadare Ogunlade, Eze K. Nwangwa

OVERVIEW

The Cardiovascular Physiology is a course that initially covers the overall design and functions of the cardiovascular system. It further describes the Physiologic-anatomy of the heart. A definition of cardiac, mechanical as well as electrical events during a cardiac cycle are described. Thereafter, a definition of cardiac output, its determinants and estimation were covered. This section provides insight into the vascular system, cross sectional area of different vascular groups, systolic, diastolic, pulse and mean pressures, exchange of fluids across the capillaries, venous and central venous pressures. It also focuses on integration of C.V.S functions, central control centres and regulation of systemic blood pressure. The cardiovascular system is made up of the heart and a closed system of blood vessels. The vascular system (arteries, arterioles, capillaries, venules and vein) are the conduits through which the blood is distributed round the entire body. The arteries carry blood away from the heart and the largest is the aorta and the smallest division is the arterioles while the veins return blood back to the heart and the smallest division is the venules. The arterioles and venules are connected by the capillaries and it is the site where most functions of the cardiovascular system are subserved. The cardiovascular system operates like a hydraulic pump. The ancient understanding of the heart is as the seat of thought or wisdom where man stores whatever he wants to do. It is also seen as a seat of empowerment- this is why someone who is generous is regarded as being kind-hearted, or having a good heart. The heart is not a seat of emotion or love. However, the physiological role of the heart is that of a muscular pump which is central to the functioning of the cardiovascular system..The cardiovascular system undergo a number of adaptations in health and disease to be able to carry out its functions effectively. It also undergo changes with age, particularly adjustment at the point of change from fetal circulation to that of extra-uterine life.The cardiovascular system adapt to this very demanding functions by changing to the peculiarity of the individual, for instance the size of the heart of an individual is same as his clinched fist. It is therefore imperative that the physiology of the heart and possible deviations from the normal should be taught to potential health care professional, because that man dies when the hearts stop to beat.

OBJECTIVES

At the end of this course, students should be able to:

1. explain the functional organisation of the heart and circulation;
2. enumerate properties of cardiac muscle and conduction system of the heart;
3. explain pace-maker potential and artificial pacemaker;
4. define cardiac cycle and its regulation;
5. state correlate cardiac cycle;
6. discuss electrocardiogram (ECG) and heart sounds;

7. demonstrate ECG-recording and interpretation;
8. explain mechanism of development of arrhythmias;
9. classify blood vessels;
10. explain the mechanism of local control of blood flow;
11. discuss cardiac output measurement and regulation;
12. evaluate arterial pulse;
13. evaluate arterial blood pressure;
14. explain foetal circulation and readjustments at birth; and
15. discuss vascular endothelium in cardiovascular control.
16. Describe the components of the vascular system.
17. Discuss capillary fluid exchange
18. Define systolic blood pressure, diastolic blood pressure and mean arterial pressure.
19. Describe how to assess pulse pressure and state its clinical significance.
20. Describe how to measure blood pressure.
21. Discuss jugular venous pressure and central venous pressure and the clinical significance of their assessment.
22. Describe the mechanisms of blood pressure regulation
23. explain the functional organization of the heart and circulation;
24. acquire basic knowledge of the parts of the cardiovascular system;
25. know the direction of flow of blood in the cardiovascular system;
26. understand the changes in the cardiovascular system in health;
27. discus the heart parameters that improve during exercise;
28. understand the changes in the cardiovascular system in disease;
29. understand special features of the circulation in the brain, skin, kidneys coronary vessels and and how they are regulated;
30. explain foetal circulation and readjustments at birth; and
31. discus vascular endothelium in cardiovascular control.

OVERALL PLAN AND FUNCTIONS OF THE CARDIOVASCULAR SYSTEM

.DEFINATION: The Cardiovascular system is a system composed of the Heart and a closed system of blood vessels inside which the blood circulates. It forms part of circulatory system together with the Lymphatic system. The Cardiovascular system is also broadly divided into types based on the blood flow that passes through the system, namely Systemic circulation and Pulmonary circulation.

1. Systemic circulation: The blood flow starts from the left ventricle by the left ventricular contraction through the aorta, systemic arteries, systemic capillaries, systemic veins, the venae cavae and enters the right atrium.

2. Pulmonary circulation: The blood flow stars from the right ventricle by the right ventricular contraction through the pulmonary arteries, capillaries, pulmonary veins and enters the left atrium.

The Cardiovascular system is schematically represented in the figure below.

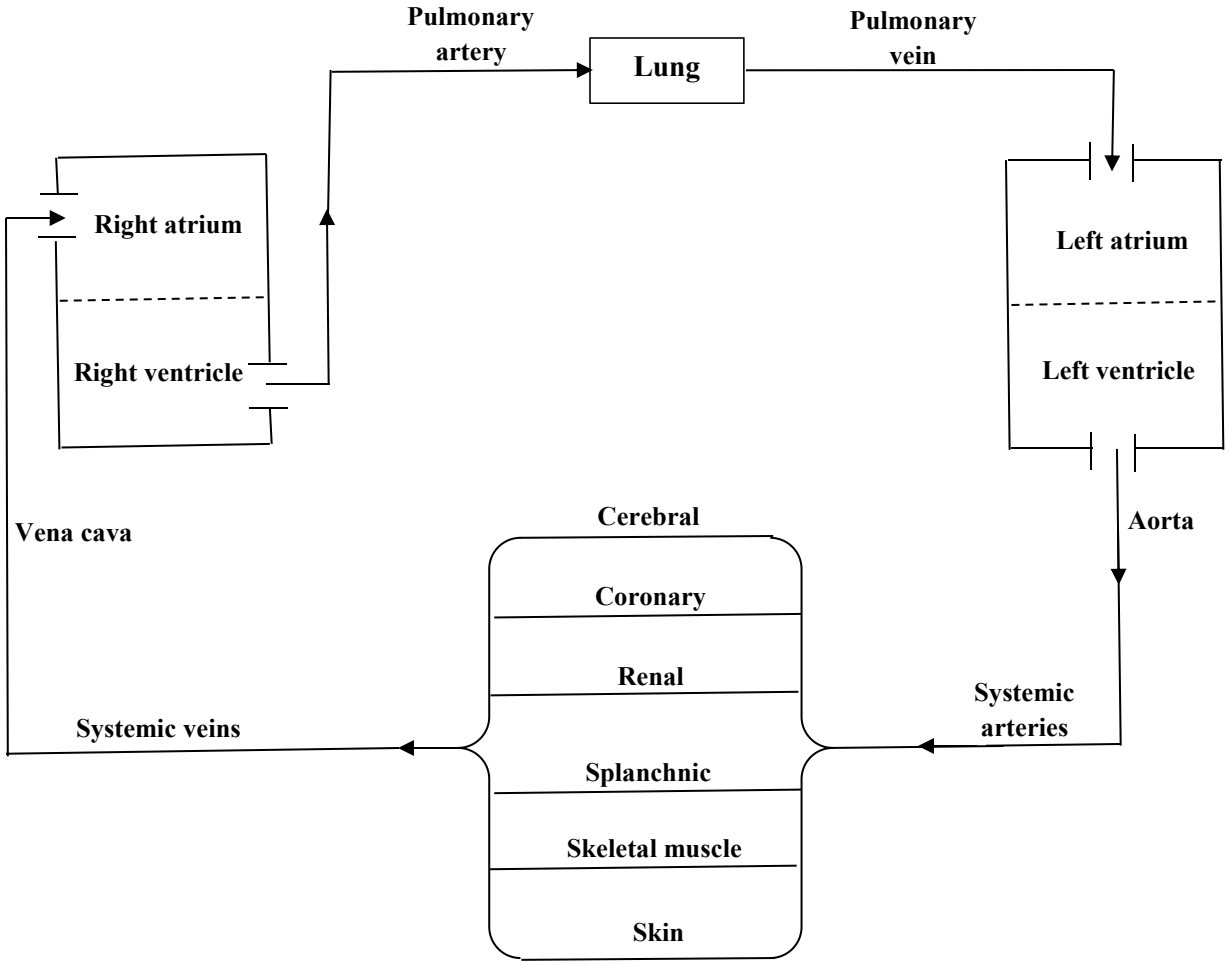


Figure 5.1: Schematic diagram of the Cardiovascular system

FUNCTIONS OF THE CARDIOVASCULAR SYSTEM

The Cardiovascular system performs the following three (3) basic functions, namely-

1. Transport: function (a) It helps in the transport of nutritive products of digestion from the intestines to various tissues (b) transport oxygen from the lungs to the tissues and vice versa with carbon dioxide

2. Homeostatic function: (a) It helps in eliminating waste products through the Kidneys, Lungs and skin (b) It helps in temperature regulation by dissipating heat at the skin and lungs.

3. Endocrine function: In addition to transportation of hormones from the endocrine glands, the Heart also produces arterial natriuretic polypeptide (ANP).

PHYSIOLOGIC ANATOMY OF THE HEART

A*: FUNCTIONAL ANATOMY OF THE HEART*

The heart is located in the thoracic cavity and in a normal adult male it weighs about 300g grams (0.5% of body weight) and in normal adult female it weighs about 200 grams (0.4% of body weight). The heart is muscular organ enclose in a fibrous sac called PERICARDIUM. The inner layer of the pericardium is called the EPICARDIUM. The narrow space between the pericardium and epicardium is filled with a fluid called PERICARDIAL FLUID. The wall of the heart is called MYOCARDIUM that is composed of cardiac muscle cells. The myocardium is located as the middle layer of the wall of the heart. Different types of muscle (myocardium) fibers include the following;

- 1. Those which form contractile unit
- 2. Those which form the pacemaker- the Sino arterial node
- 3. Those which form conductive system

Layer of cells called endothelial cells lines the surface of the cardiac chambers.

The heart is divided into right and left halves, each consisting of an atrium and a ventricle. Right and left atria are separated from one another by a fibrous septum called INTERATRIAL SEPTUM. INTERVENTRICULAR SEPTUM separates right and left ventricles from one another. The Atria are separated from the ventricles by a band of thick fibrous connective tissue called Annulus Fibrosus. Between the atrium and ventricles are the arterio-venous (AV) valves. The right AV valves are called the TRICUSPID VALVES. While the left AV valves are called the BICUSPID VALVES. The opening of the right ventricles into the pulmonary trunk and the left ventricle into the aorta also has valves called SEMILUNAR VALVES. The valves are fastened to muscular projections (PAPILLARY MUSCLE) by fibrous strands called *chordae tendinae*.

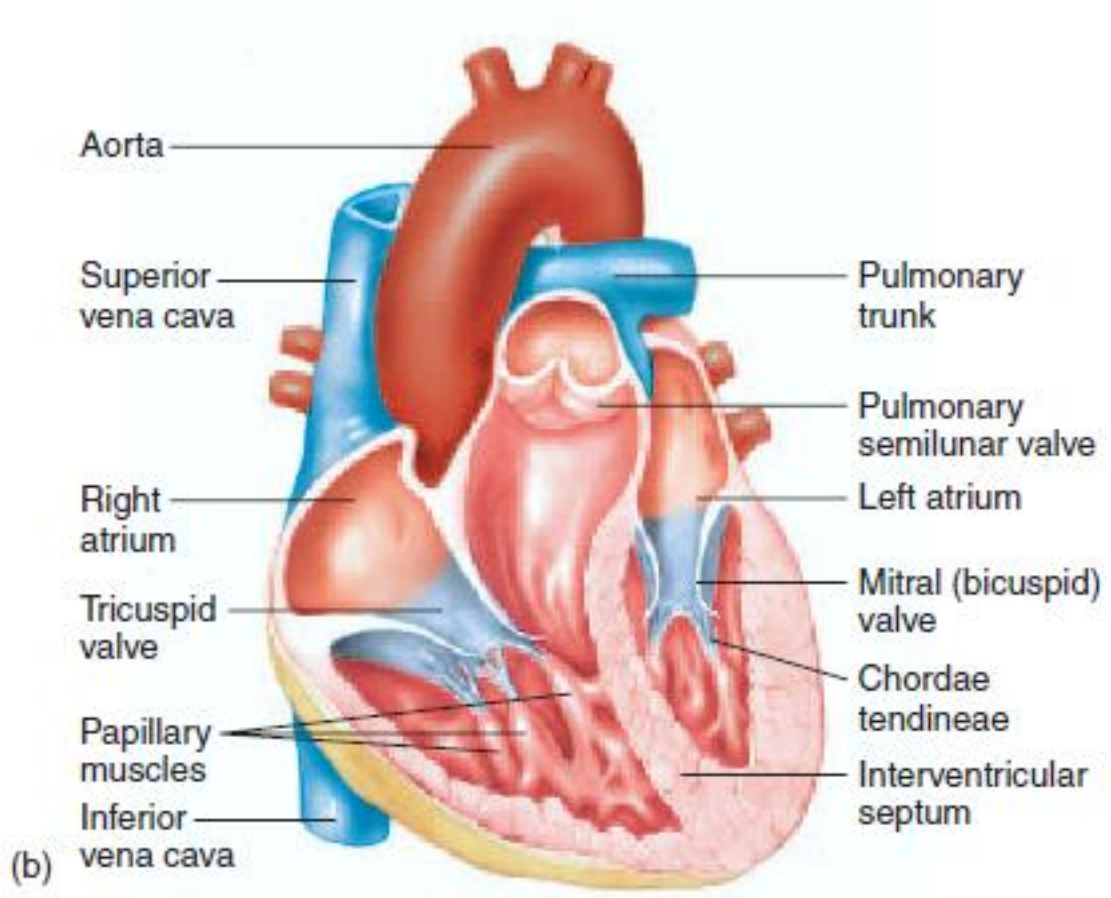


Figure 5.2: Functional Anatomy of the Heart

B: *PHYSIOLOGIC PROPERTIES OF THE HEART:*

The Physiological properties of the heart are the following, namely-

i. Excitability: This is the ability of a tissue to respond to stimuli. The response to stimuli means generation of action potential (AP) followed by a physiological action in the form of contraction. The AP in the cardiac muscle occurs in five phases; (0) Depolarization, (1) Initial repolarization, (2) plateau, (3) Final repolarization and (4) resting membrane potential.

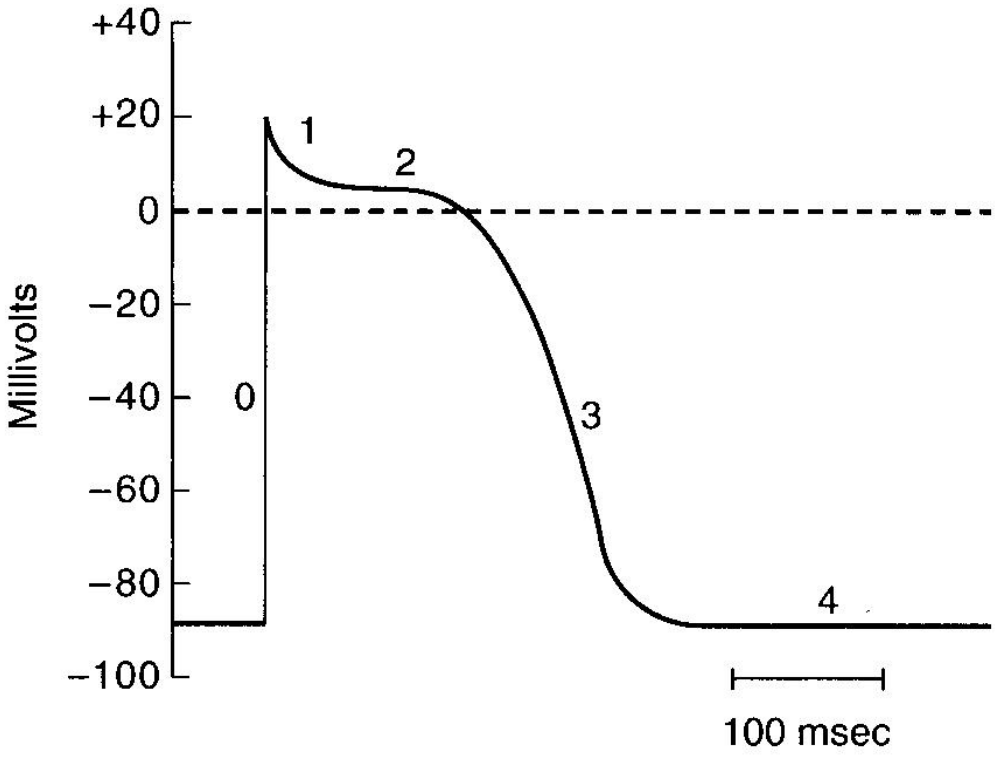


Figure 5.3: Action potential of a cardiac muscle.

ii. Autorhythmicity/Automaticity: Rhythmicity is the ability of a tissue to generate its own impulses regularly. This is the property of all the tissues of the heart. The heart has a specialized excitatory structure from which the discharge of impulse is rapid. This specialized structure is the SA Node and it produces what is called the PACEMAKER POTENTIAL. From this structure impulses spread to other parts through a specialized conducting system. The rhythmicity rates in various parts of the heart are as follows;

SA Node	70-80/min
AV Node	40- 50/min
Arterial muscle	40- 50/min
Purkinje fibres	35- 40/min
Ventricular muscles	20- 40/min

iii. Conductivity: The human heart has a specialized conductive system, through which the impulses from the SA node are transmitted to all other parts of the heart. Conductive system in the human heart includes; SA node, Internodal fibres(Anterior internodal fibers of Bachman, Middle internodal fibers of Wenckebach and Posterior internodal fibers of Thorel:), AV node, The bundle of HIS, Right and left bundle branches and Purkinje fibers

iv. Contractility: This is the ability of the tissue to shorten in length after receiving a stimulus. All or none law- When a stimulus is applied, and the strength is adequate (i.e. not below the threshold level), the cardiac muscle responds by contraction, or if the strength is not adequate, it does not respond at all. Refractory period-It is the period in which the muscle does not show any response to a stimulus. Refractory period is of two types: *Absolute refractory period*- Is period during which the muscle does not show any response at all whatever may be the strength of the stimulus. The absolute RP in cardiac muscle extends throughout the contraction period; *Relative refractory period*- It is the period during which the muscle show response if the strength of stimulus is increased to maximum. RRP extends during the first half of relaxation period. Significance of long refractory period in cardiac muscle-Summation of contractions does not occur, fatigue and tetanus does not occur.

MECHANICAL EVENTS OF CARDIAC CYCLE

Cardiac cycle is the sequence of both mechanically and electro-chemically coordinated events that happens during a heartbeat. Each heartbeat consists of two major periods called systole and diastole. During systole, there is contraction of the cardiac muscle and pumping of blood from the heart. During diastole, there is relaxation of cardiac muscle and filling of blood.

When the heart beats at a normal rate of 72/minute, duration of each cardiac cycle is about 0.8 second. Atrial events are divided into two divisions:

1. Atrial systole = 0.11 (0.1) sec

2. Atrial diastole = 0.69 (0.7) sec

Ventricular events are divided into two divisions:

1. Ventricular systole = 0.27 (0.3) sec

2. Ventricular diastole = 0.53 (0.5) sec

The mechanical events of the heart during both systole and Diastole are further divided as follows:

Atrial Systole: = 0.11 sec

Ventricular Systole:

- 1. Isometric contraction = 0.05
- 2. Ejection period = <u>0.22</u>

0.27 sec

Diastole of the whole Heart:

•	1.	Protodiastole	=	0.04
•	2.	Isometric relaxation	=	0.08
•	3.	Rapid filling	=	0.11
•	4.	Slow filling	=	0.19

0.42 sec

Atrial systole:

Atrial systole is also known as second or last rapid filling phase. It is considered as the last phase of ventricular diastole. During this period, only a small amount i.e. 10% of the blood is forced from atria into ventricles. *Atrial systole is not essential for the maintenance of circulation*. There are slight increases in Intraatrial pressure, intra-ventricular pressure and Ventricular volume. There is also production of the fourth heart sound.

Atrial diastole starts simultaneously with Ventricular systole (about 0.69 secs). Out of 0.7 sec of atrial diastole, first 0.3 sec (0.27 sec accurately) coincides with ventricular systole. Ventricular diastole starts and it lasts for about 0.5 Sec (0.53 sec accurately). Ending part of atrial diastole coincides with ventricular diastole for about 0.4 sec. So, the heart relaxes as a whole for 0.4 sec.

Isovolumetric/Isometric contraction period:

Isometric contraction is the first phase of ventricular systole. It occurs immediately after atrial systole. The ventricles contract as closed cavities in such a way that there is no change in the volume of ventricular chambers or in the length of muscle fibers. Only the tension increases in ventricular musculature. Because of the increased tension in ventricular musculature during isometric contraction, the pressure increases sharply inside the ventricles. The atrioventricular valves are closed due to increase in ventricular pressure. The closure of the Atrioventricular valves at the beginning of the phase produces the first heart sound. The pressure build-up here is responsible for opening of the semi-lunar valves.

Ejection period:

Due to the opening of semilunar valves and the contraction of ventricles, the blood is ejected out of both the ventricle hence this period is called ejection period. Ejection period is of 2 stages, namely-

I. First stage is called the rapid ejection period this occurs immediately after the opening of semilunar valves.

II. Second stage is called the slow ejection period. During this stage, the blood is ejected slowly with much less force.

The semilunar valves open when pressure in the ventricle exceeds that in its respective artery. Note that pulmonary artery pressure (15 mmHg) is considerably less than that in the aorta (80 mmHg).

Protodiastole:

Protodiastole is the first stage of ventricular diastole. Duration of this period is 0.04 seconds. As pressure in aorta and pulmonary artery increases and pressure in ventricles drops. When intraventricular pressure becomes less than the pressure in aorta and pulmonary artery, the semilunar valves close. Closure of the semilunar valves is associated with the Second heart sound. Thus, protodiastole indicates the end of systole and beginning of diastole

Isometric relaxation period:

During this period, all the valves of the heart are closed. Both ventricles are relaxed as closed cavities without any change in volume or length of the muscle fiber, so it is called isometric or isovolumetric relaxation period. The intra-ventricular pressure decreases during this time and the AV valves opens.

Rapid filling phase:

When the AV valves open, there is a sudden rush of blood (which has accumulated in the atria during atrial diastole) from atria into ventricles. This is called the first rapid filling phase and about 70% of filling takes place during this phase. This is also associated with production of the third heart sound.

Slow filling phase (Diastasis):

After the sudden rush of blood, the ventricular filling becomes slow. It is also responsible for 20% of ventricular filling. After slow filling period, the atria contracts, a small amount of blood enters the ventricle from the atria and the cycle is repeated.

ELECTROCARDIOGRAM (E.C.G)

The activity of the cardiac chambers gives rise to electrical potential differences that can be recorded from the body surface. This signal can be amplified and recorded as an electrocardiogram (ECG).

Electrocardiogram:

This is the record or graphical representation of electrical activities of the heart

Electrocardiograph:

This is the instrument by which the electrical activities of the heart are recoded.

Electrocardiography:

It is the techniques used by which electrical activities of the heart are studied.

ECG LEADS

The recording of ECG on the surface of the body is done by connecting the ECG machine to electrodes called ECG leads. The ECG leads are of two types, namely: Unipolar and Bipolar leads.

Bipolar leads:

They are otherwise known as standard limb leads. Two limbs are connected to obtain these leads and both electrodes are active. These standard limb leads are: Limb lead I, II and III. The electrodes are fixed on the right arm, left arm and left leg respectively. The heart is said to be in the centre of an imaginary equilateral triangle drawn by connecting the roots of these three limbs. This triangle is called Einthoven's image.

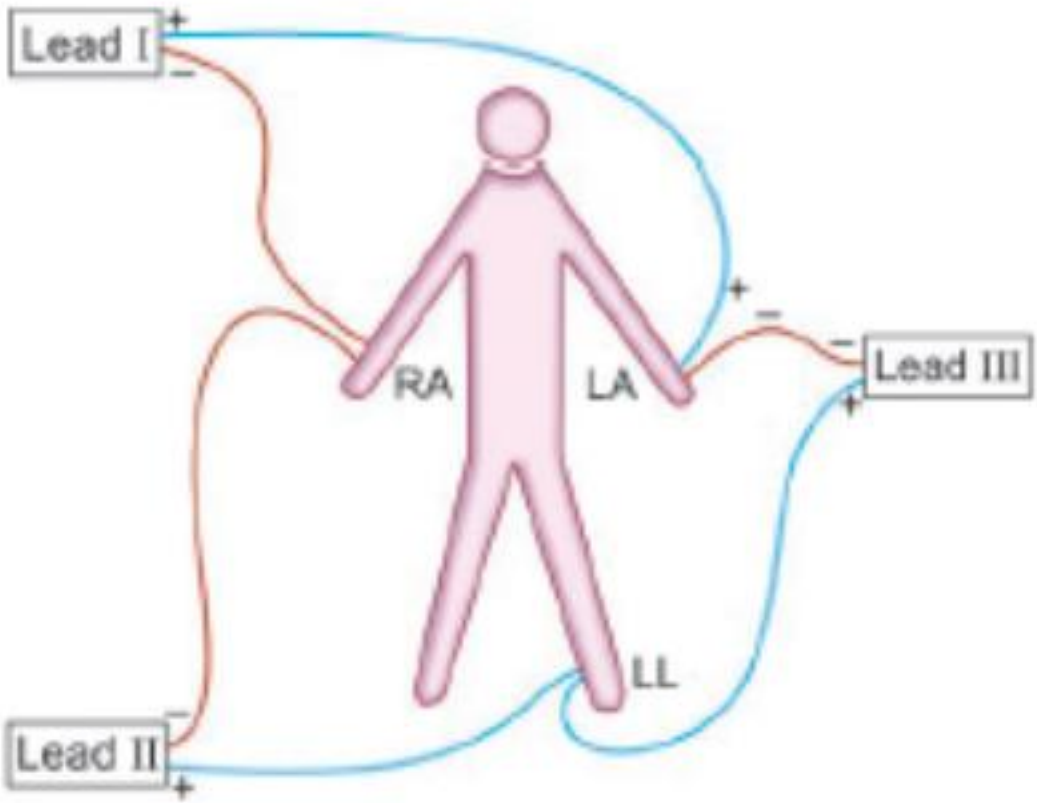


Figure 5.4: Diagram of the standard Limb Leads.

Unipolar leads:

One electrode is active and the other is indifferent or exploring electrode. The unipolar leads are of two types: Unipolar Limb leads and Unipolar Chest leads.

I. Unipolar limb leads: They are also referred to as augmented limb leads. The active electrode is connected to one of the limbs, while the indifferent electrode is obtained by connecting the other two limbs through a resistance. Unipolar limb leads are of 3 types, namely: aV_R , aV_L and aV_F

II. Unipolar chest leads: These electrodes are known as chest electrodes, and the positions over the chest are denoted as V_1, V_2, V_3, V_4, V_5, V_6.

- V_1 - 4th intercostal space near the right sternal margin
- V_2 - 4th intercostal space near the left sternal margin

- V_3 - In-between V_2 and V_4
- V_4 - left 5th intercostal space mid-clavicular line
- V_5 - 5th intercostals space anterior auxiliary line
- V_6 - 5th intercostals space mid auxiliary line

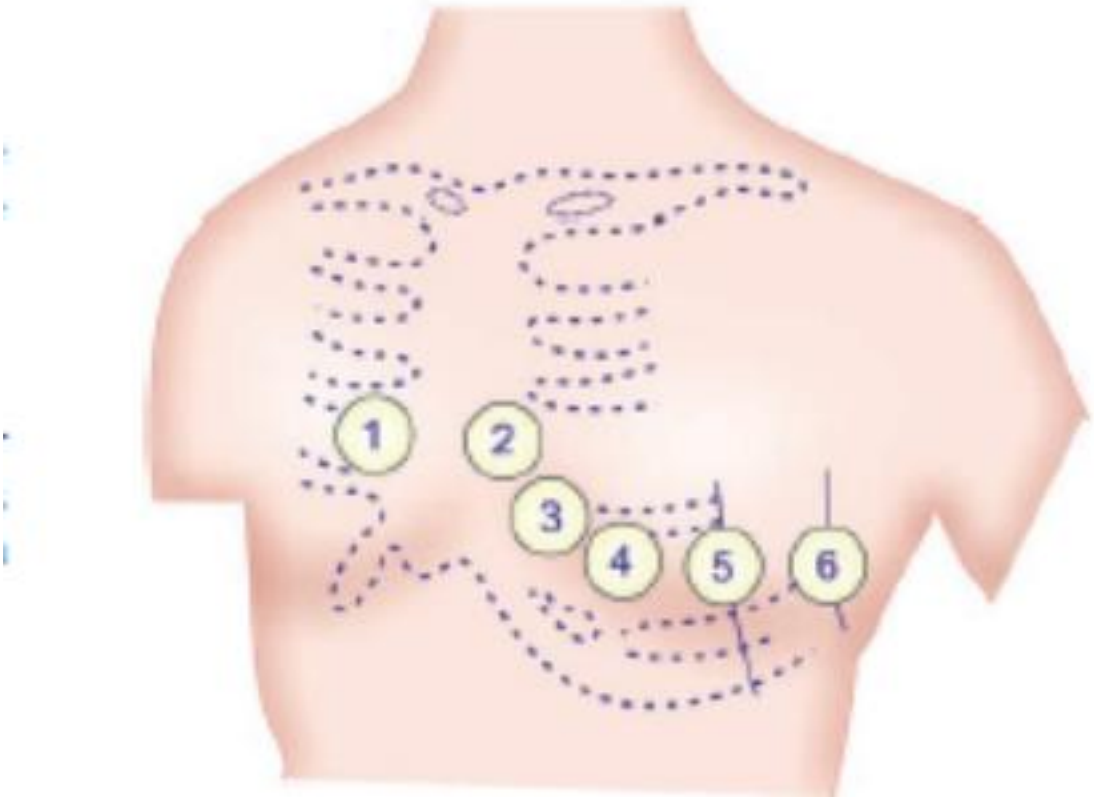


Figure 5.5: Diagrammatic representation of the Chest leads.

NORMAL ELECTROCARDIOGRAM (ECG) WAVES

The normal ECG consists of 5 main waves called P, Q, R, S, T wave and sometimes the U-wave. These waves are separated by segments that starts and ends on the isoelectric line.

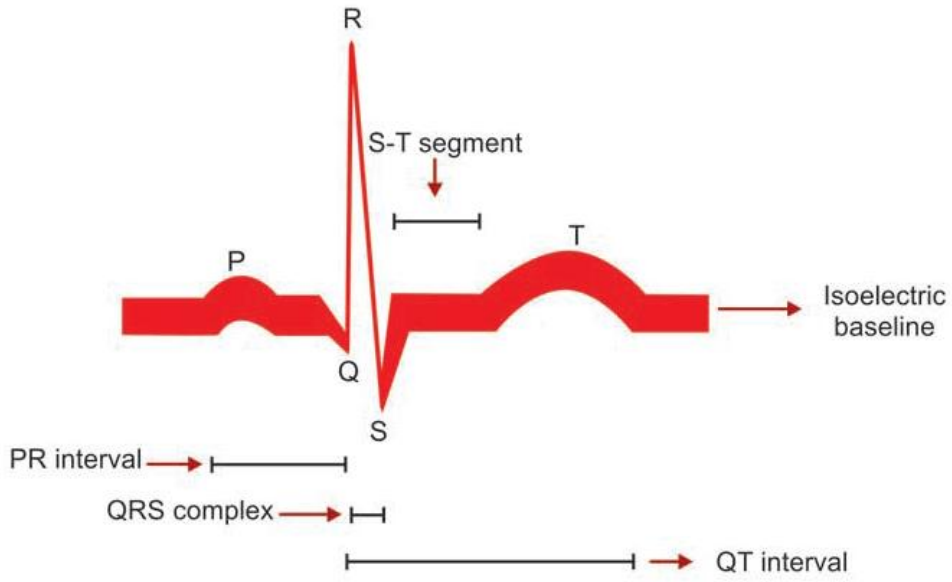


Figure 5.6: Diagram of a normal ECG tracing

P wave

It is a positive wave, which is produced by the electrical activity due to atrial depolarization. It last for 0.1 seconds.

QRS complex

The Q is a small negative wave, which is continued by a tall positive R wave, then it is followed by a small negative, the S wave. The QRS complex is obtained due to ventricular depolarization. It last between 0.08 -0.10 seconds.

The Q wave is due to depolarization of the basal portion of the interventricular septum. The R wave is due to the depolarization of the apex and ventricular wall.

The S is due to depolarization of the posterior basal part of the left ventricle and the pulmonary conus.

T wave

It is a positive wave and occurs as a result of ventricular repolarization. It lasts for 0.2 seconds.

U wave

It is supposed to be due to repolarization of the papillary muscles, but is rarely seen on the ECG.

ECG INTERVALS AND SEGMENTS

P – R Interval

This is the interval between the onset of p wave and the onset of Q wave or QRS complex. It signifies the atrial depolarization and the conduction of impulses through AV node. Normal duration is 0.12 – 0.21 seconds

Q – T interval

It is the interval between the onset of Q wave and the end of T wave. The Q-T interval indicates the ventricular depolarization and repolarization (i.e. electrical activity in the ventricle). Normal duration is 0.4 seconds

R – R interval

This is the time interval between the consecutive R waves. The R – R interval signifies the duration of one cardiac cycle. it lasts for about 0.8 seconds.

S-T segment

The time interval between the end of S wave and the onset of T wave is called the S-T segment. Normal duration is 0.12 seconds

CARDIAC ARRHYTHMIAS

These are abnormal heart rhythms that can be detected by ECG. The following are some arrhythmias, namely-

BRADYCARDIA: A cardiac rate slower than 60 beats per minute

TACHYCARDIA: A cardiac rate faster than 100 beats per minute

FLUTTER: The contractions of the myocardial cells are very rapid (200 to 300 per minute) but are coordinated

FIBRILLATION: The contractions of different groups of myocardial cells occur at different times, so that a coordinated pumping action of the chambers is impossible.

First-degree AV nodal block: This occurs when the rate of impulse conduction through the AV node (as reflected by the P-R interval) exceeds 0.20 seconds.

Second-degree AV nodal block: This occurs when the AV node is damaged so severely that only one out of every two, three, or four atrial electrical waves can pass through to the ventricles. This is indicated in an ECG by the presence of P waves without associated QRS waves.

Third-degree, or complete, AV nodal block: This occurs when none of the atrial waves can pass through the AV node to the ventricles. The atria are paced by the SA node (follow a normal "sinus rhythm"), but in complete AV node block a secondary pacemaker in the Purkinje fibers paces the ventricles

Artificial pacemaker: This is a battery- powered device, about the size of a locket, which may be placed in permanent position under the skin. The electrodes from the pacemaker are guided through a vein to the right atrium, through the tricuspid valve, and into the right ventricle. The electrodes are fixed to the trabeculae carnae and are in contact with the wall of the ventricle. When these electrodes deliver shocks—either at a continuous pace or on demand (when the heart's own impulse doesn't arrive on time)—both ventricles are depolarized and contract, and then repolarize and relax, just as they do in response to endogenous stimulation.

CARDIAC OUTPUT AND ITS ESTIMATION

DEFINATIONS:

Cardiac output: It is the amount of blood pumped out by each ventricle in one minute. Usually, it refers to the left ventricular output through aorta into various organs of the body. It is the product of stroke volume and heart rate.

Stroke volume: It is the amount of blood pumped out by each ventricle during each heartbeat. Its normal value is 70ml (60-80 ml) when the heart rate is normal (72/minute)

VARIATIONS IN CARDIAC OUTPUT

Physiological variations

1. Age:- Is higher in newborn and decreases gradually with age
2. Sex: - Is higher in females than males of the same age.
3. Body build: directly proportional to the body mass index
4. Diurnal variation: Is lowest in the morning and highest in the evening
5. Environmental temperature: Directly proportional to the environmental temperature

6. Emotional conditions: Varies with the emotional state of the individual
7. After meals: tends to be higher after meals
8. Exercise: Athletes tends to have lower heart rates
9. High altitude: tends to be higher with increasing altitude
10. Posture: Increases on standing
11. Pregnancy: tends to increase during pregnancy
12. Sleep: lower during rest or sleep

Pathological variations

Factors that increase cardiac output include:

- Fever – due to increased oxidative processes
- Anemia – due to hypoxia
- Hyperthyroidism

Factors that decrease cardiac output:

- Cardiac output decreases in the following conditions:
- Hypothroidism due to the decreased basal metabolism rate
- Atrial fibrillation because of incomplete filling
- Shock due to poor pumping and circulation
- Hemorrhage because of decreased blood volume

DISTRIBUTION OF CARDIAC OUPUT

The fraction of cardiac output distributed to a particular region or organ depends upon the metabolic activities of that region or organ. The distribution of blood pumped out of the left ventricle is as follows:

- Liver 1500ml = 30%
- Kidneys 1300ml = 26%
- Skeletal muscle 900ml = 18%
- Brain 800ml = 16%

•	Skin, bone and GIT	300ml	=	6%
•	Heart	200ml	=	4%
•	Total	5000ml	100%	

DETERMINANTS OF CARDIAC OUTPUT

Cardiac output is maintained/determined by main four factors:

1. Venous return

It is the amount of blood, which is returned to the heart from different parts of the body. When it increases, the ventricular filling and cardiac output are increased. Thus, the cardiac output is direct proportional to venous return provided other factors remain constant. Venous return in turn depends on five factors:

a. Respiratory pump

b. Muscle pump

c. Gravity

d. Venous pressure

e. Sympathetic tone

2. Force of contraction

The cardiac output is directly proportional to the force of contraction *provided the other three factors remain constant.* According to Frank Starling's law, the energy liberated by the heart when it contracts is a function of length of its muscle fibers at the end of diastole (i.e. the force of contraction of heart is directly proportional to the initial length of muscle fibers before the onset of contraction.

Preload:

During diastolic period due to ventricular filling, the muscle fibers are stretched resulting in increase in the length of muscle fibers. This increases the end diastolic pressure in the ventricle, which is called preload. It therefore determines the force of contraction.

Afterload:

At the end of isometric contraction phase, the semilunar valves are opened and blood is ejected into the aorta and pulmonary artery. So the pressure increases in these two vessels. Now, the ventricules have to work against this pressure for further ejection. This pressure in aorta and pulmonary artery is called afterload.

3. Heart rate

Cardiac output is directly proportional to heart rate provided the other three factors remain constant. Moderate changes in heart rate does not alter the cardiac output, but if there is a marked increase in heart rate, cardiac output is increased if there is marked decreases in heart rate, cardiac output is decreased.

4. Peripheral resistance

This is the resistance against which the heart has to pump blood. So the cardiac output is inversely proportional to peripheral resistance.

DETRMINATION OF CARDIAC OUTPUT

The most commonly used methods for measuring the cardiac output in humans using the Fick's principle are as follows;

1. Respiratory or Direct Fick's method

The oxygen (mL/min) uptake in the lungs is determined using Spirometry. Thereafter, the oxygen content in arterial and mixed venous blood is determined separately. The difference in the arteriovenous values will determine the volume of oxygen taken by each 100 mL of blood that passes through the lungs. Thus by knowing the total volume of oxygen taken per minute and the arteriovenous oxygen (mL/d) difference, the total volume of blood flowing through the lungs can be calculated. This volume is equal to the pulmonary blood flow per minute that represents the output from the right ventricle (cardiac output).

2. Indicator Dye dilutions or Indirect Fick's method

The commonly used dyes are indocyanine green or Evan's blue. Radioactive active isotopes can also be used. A known quantity of the indicator is injected in the antecubital vein. Thereafter, serial arterial blood samples are taken and determine the concentration of the indicator. A graph of the concentrations are then plotted against time . The curve does not drop back to zero because the indicator recirculates. Using semi-logarithmic extrapolation of the curve, the time taken from the appearance to the disappearance of the indicator can be determined that will represents the time of a single circulation. The mean concentration of the indicator in the blood samples can be determined by integrating the concentrations with the time of a single circulation. Thus from the data obtained, the cardiac output can be calculated.

3. Thermodilution method

The method uses a double-lumen catheter that is guided into the right atrium. The outer lumen is used for injecting the indicator that is usually about 5 mL of normal saline at room temperature into the right atrium. The inner lumen of the catheter contains a wired thermistor that is used to monitor the temperature of the blood flowing through the pulmonary artery. As the injected saline is pumped from the atrium into the right ventricle and pulmonary artery, the changes in he temperature of blood flowing is detected by the thermistor. The data are fed into a computer that will analyses and compute the cardiac output.

VASCULAR SYSTEM

The vascular system is otherwise known as the circulatory system. It consists of network of vessels and organs that distributes blood or lymph around the body. It is classified into two types. The vascular system that carries blood through the body is called the cardiovascular system. So, blood is the fluid within the cardiovascular system. The vascular system that carries lymph is called the lymphatic system. So, lymph is the fluid within the lymphatic system. There are two types of communication between the cardiovascular and lymphatic systems; anatomical and functional. The cardiovascular system is linked with the lymphatic system anatomically through the connection between subclavian vein and thoracic duct. Functionally, the cardiovascular system is linked with the lymphatic system through the capillary fluid exchange.

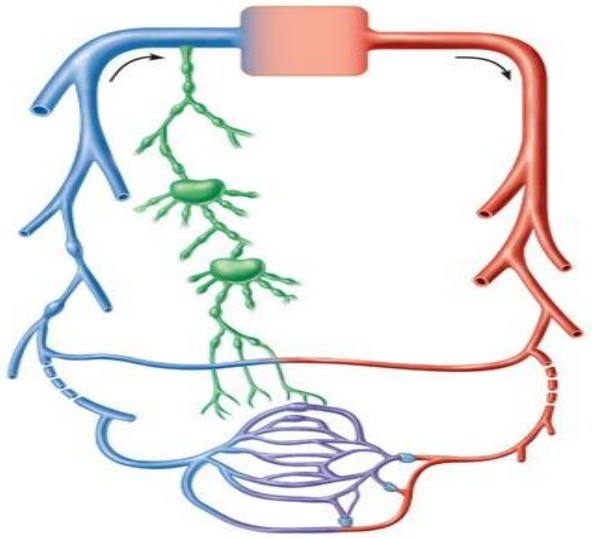


Fig. 5.7:. Vascular System

Cardiovascular System

The cardiovascular system consists of the heart and network of blood vessels (aorta, arteries, arterioles, capillaries, venules, veins and vena cava). The cardiovascular system has two main divisions;

1. Systemic circulation (major division)

2. Pulmonary circulation (minor division)

Divisions of Cardiovascular System

Systemic Circulation

Systemic circulation involves transportation of blood and its constituents from the left side of the heart to the body tissues and back to the right side of the heart. The systemic circulation is called the major circulation and it is a high pressure driven system. The pump for the systemic circulation is the left ventricle. The feeding venous system to the systemic circulation is the pulmonary venous system.

Box 1. Systemic circulation

Left Atrium→ Left Ventricle→ Aorta→ Arteries→ Arterioles→ Capillaries→ Venules →Veins→ Vena Cava → Right Atrium

Pulmonary Circulation

Pulmonary circulation involves transportation of blood and its constituents from the right side of the heart to lung and back to the left side of the heart. It is a low pressure driven system compared with systemic circulation. The pump for the pulmonary circulation is the right ventricle. The feeding venous system to the pulmonary circulation is the systemic venous system.

Box 2. Pulmonary circulation

right atrium→ right ventricle→ pulmonary trunk→ pulmonary arteries→ lung capillaries→ pulmonary veins→ left atrium

Arteries

The *arteries* are the blood vessels that deliver oxygen-rich blood from the heart to the tissues of the body. Exception of this are pulmonary and umbilical arteries which transport de-oxygenated blood. Based on their position in the arterial tree, arteries can be divided into;

1. *Conducting arteries*: largest arteries with a large amount of elastic tissue to expand and recoil response to the oscillatory pressure changes accompanying by intermittent ventricular ejection. Examples include aorta, carotid arteries and pulmonary artery.

2. *Conduit arteries*: branches of conducting arteries which are responsible for distributing blood into specific regions e.g radial and femoral arteries.

3. *Resistance arteries*: branches of conduit arteries characterized by large amount of smooth muscle with rich sympathetic innervations. Resistance arteries maintain blood flow to the tissues.

Veins

Veins are low pressure vessels that transport blood to the heart. All veins transport de-oxygenated blood except pulmonary and umbilical veins. Veins are capacitance vessels, serving as a 'reservoir' containing 60% of blood volume in human body. Veins possess one-directional valves to ensure that blood flow into the heart under low pressure. Venous return is aided by muscular pump and thoracic pump associated with negative intrathoracic pressure during inspiratory phase of respiration.

Microcirculation

The microcirculation refers to the smallest blood vessels in the body. It includes the following;

1. arterioles
2. metarterioles
3. precapillary sphincters
4. capillaries
5. venules

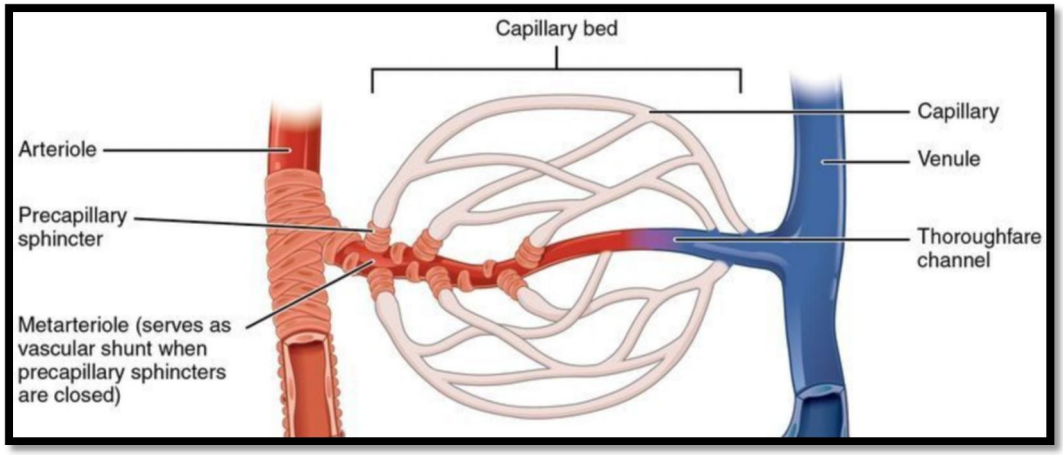


Fig.5.8:. Microcirculation

Arterioles

Arterioles are small precapillary resistance vessels which are composed of an endothelium surrounded by one or more layers of smooth muscle cells. They are innervated by sympathetic adrenergic fibres. Sympathetic stimulation results in vasoconstriction. Arterioles are the major site for regulating systemic vascular resistance. The primary function of arterioles within an organ is blood flow regulation.

Capillaries

Capillaries are small exchange vessels composed of endothelial cells surrounded by basement membrane. The capillaries have large surface area. Capillaries are classified as continuous, fenestrated and discontinuous with different degrees of vascular permeability at various vascular beds; lowest permeability, relatively high permeability and extremely high permeability respectively (Fig 3). Capillaries are the primary site for of exchange for electrolyte, fluid, gases and macromolecules.

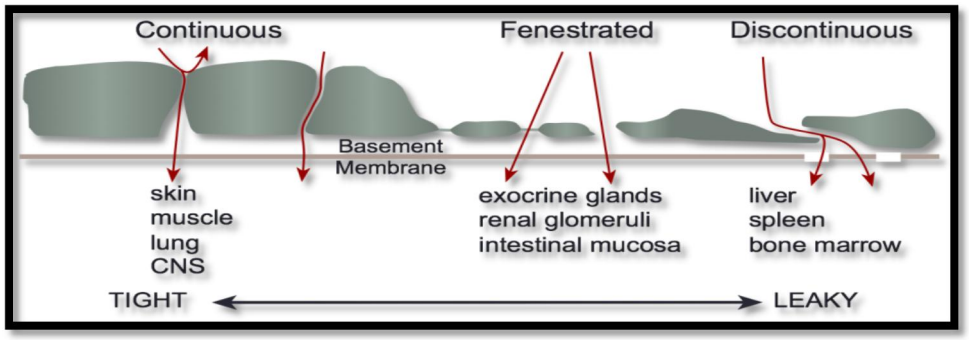


Fig. 5.9:. Categories of capillaries

Venules

Venules are small exchange vessels (10-200 μ) composed of endothelial cells surrounded by basement membrane (smallest postcapillary venules) and smooth muscle (larger venules). Fluid and macromolecular exchange occur at small postcapillary venular junctions. Sympathetic innervation of larger venules can alter venular tone, which plays a role in regulating capillary hydrostatic pressure.

Total Cross-sectional Area of Vascular Groups

The arterial portion of the vascular system consists of branching network of vessels with progressive reduction in the radius of the vessels from aorta to the capillaries. As capillaries form venules and venules forms veins, the internal diameter progressively increases, though with reduction in the number of vessels. The cross-sectional area of a vessel can be calculated from its internal radius (r) using the formular; πr^2. The total cross-sectional area (A) of a particular segment of vessels , N, is calculated from product of the average cross-sectional area of the vessels and the total number of the vessels in the segment.

Total cross-sectional area (TA) = $N \pi r^2$

The cross-sectional area of aorta is the same as the total sectional area of aorta since, it is the only vessel but with increasing branching the total cross-sectional area of the arteries increases towards the capillaries which has the largest total cross-sectional area. At the venous side, although, there is increase in individual vessel cross-sectional area, the total cross-sectional area declines with the progressive decrease in number of vessels as tributaries unite to form veins. Generally, the total cross-sectional area of the arteries is less that of total cross-sectional area of the corresponding veins (Fig.4)

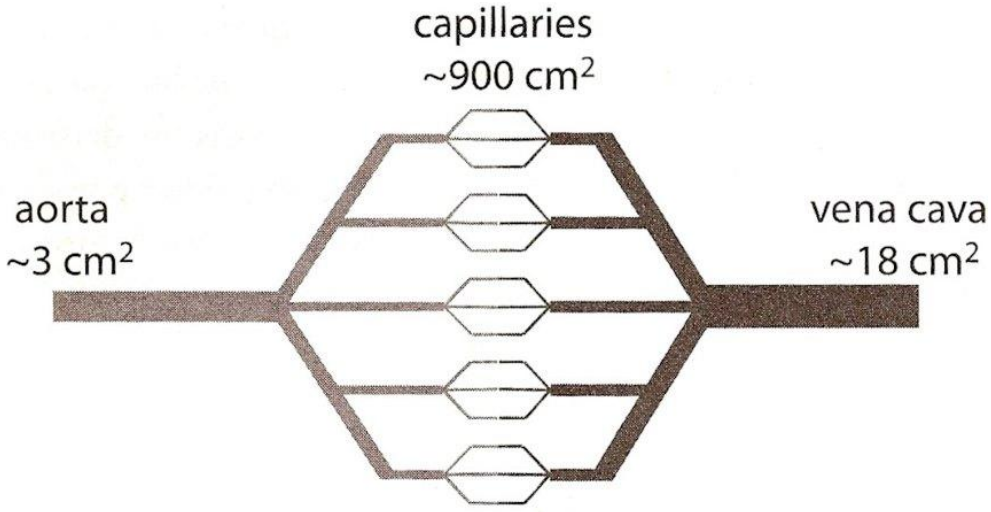


Fig. 5.10:. Total cross-sectional area of vascular groups

Lymphatic System

The lymphatic system consists of lymphoid tissues and organs interconnected by network of vessels that drain excess tissue fluid called lymph. The vessels include; lymphatic vessels (lymphatics), lymph capillaries, lymphatic collecting vessels, right lymphatic duct and thoracic duct (Fig. 1). Minivalves are present to ensure unidirectional flow of lymph to the right and left subclavian veins through the right thoracic duct and thoracic duct respectively. The lymphatic systems also include lymph nodes through which lymph enters and exit via afferent and efferent lymphatic vessels, cells such as macrophages, T and lymphocytes and other lymphoid organs such as the spleen and thymus. Together, the components of the lymphatic system are involved in immunity.

CAPILLARY FLUID EXCHANGE

Capillary fluid exchange refers to the movement of fluid between capillary and interstitium (tissue). This depends on pressure gradients between the capillary and the tissue at arteriolar and venular ends of the capillary as illustrated by Starling equation.

Starling Equation

In 1896, Ernest H. Starling, a British Physiologist derived an equation that shows relationship among forces that govern movement of fluid in and out of capillary. The Starling hypothesis states that fluid flux at the capillary level is controlled by a balance between hydrostatic pressure and osmotic pressure gradients between the capillaries and interstitial space.

$$J_v = K_{fc}\,[(P_c - P_i) - \sigma(\pi_p - \pi_i)]$$

J_v = Net rate of capillary filtration

K_{fc} = Capillary filtration coefficient (a product of capillary surface area and capillary hydraulic conductance)

P_c = Capillary hydrostatic pressure

P_i = Interstitial hydrostatic pressure

σ = Osmotic reflection coefficient

π_p = Plasma oncotic pressure

π_i = Interstitial oncotic pressure

Determinants of Capillary Fluid Exchange

Capillary fluid exchange is determined by four forces;

1. *Capillary oncotic pressure (COP):* osmotic pressure generated by plasma proteins. It draws fluid from interstitium into the capillary.

2. *Capillary hydrostatic pressure (CHP)*: force generated by fluid within the capillary. It pushes fluid out of the capillary into the interstitium.

3. *Tissue oncotic pressure (TOP):* force generated by interstitial proteins. It draws fluid from capillary into interstitium.

4. *Tissue hydrostatic pressure (THP)*: force generated by interstitial fluid. It pushes fluid out of interstitium into the capillary.

CHP and TOP drive fluid out of the capillary while COP and THP drive fluid into the capillary (Fig.5).

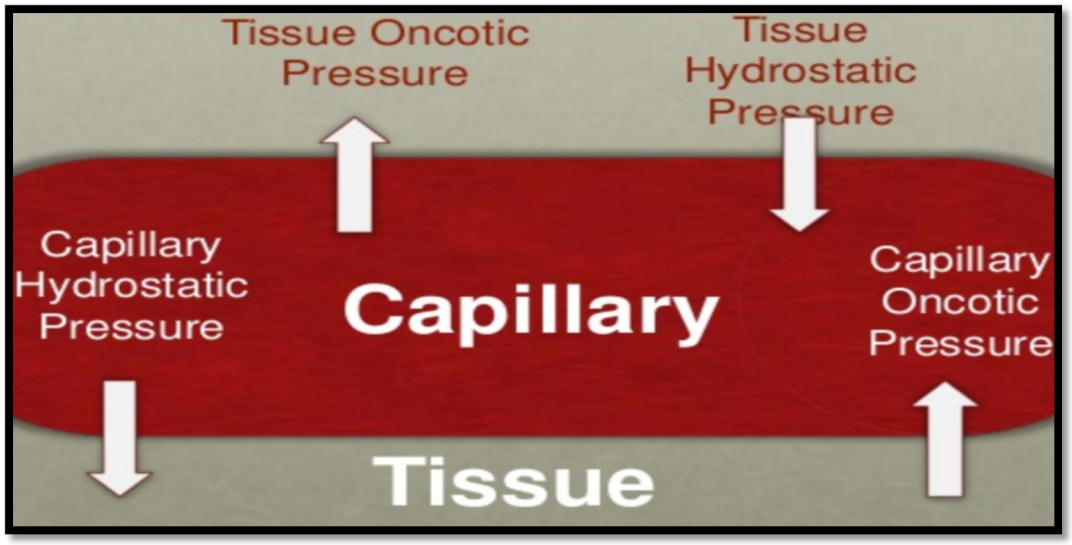


Fig. 5.11: Forces controlling movement of fluid in and out of capillary

Capillary Filtration Pressure (CFP) = (CHP+TOP) - (COP + THP)

= CHP + TOP - COP - THP

= CHP-THP - COP + TOP

= (CHP - THP) - (COP - TOP)

CHP-Capillary hydrostatic pressure, THP-Tissue hydrostatic pressure

COP-Capillary oncotic pressure, TOP-Tissue oncotic pressure

CHP-THP = Net hydrostatic pressure

COP-TOP = Net oncotic pressure

CFP = Net hydrostatic pressure - net oncotic pressure

Table 1. Variables of Forces determining capillary fluid exchange

Capillary Exchange Forces	Capillary	
	Arteriolar End	Venular End
Capillary hydrostatic pressure (CHP)	35mmHg	17mmHg
Tissue hydrostatic pressure (THP)	0	0
Capillary oncotic pressure (COP)	26mmHg	1mmHg
Tissue oncotic pressure (TOP)	1mmHg	1mmHg

Capillary Filtration Pressure (CFP) = (CHP - THP) - (COP - TOP)

At arteriolar end of capillary

CFP = (35-0)- (26-1) = +10mmHg, this results in filtration at the arteriolar end of capillary.

At venular end of capillary

CFP = (17 - 0) - (26 - 1) = - 8mmHg, this results in reabsorption of fluid at venular end of the capillary.

Fluid Filtration and Reabsorption

Due to pressure gradients between the arteriolar and venular ends of capillary, filtration occurs at the arteriolar end while fluid reabsorption takes place at the venular end. Excess fluid within the interstitium is absorbed by the lymphatic vessels which drain such fluid into the cardiovascular system (Fig. 6).

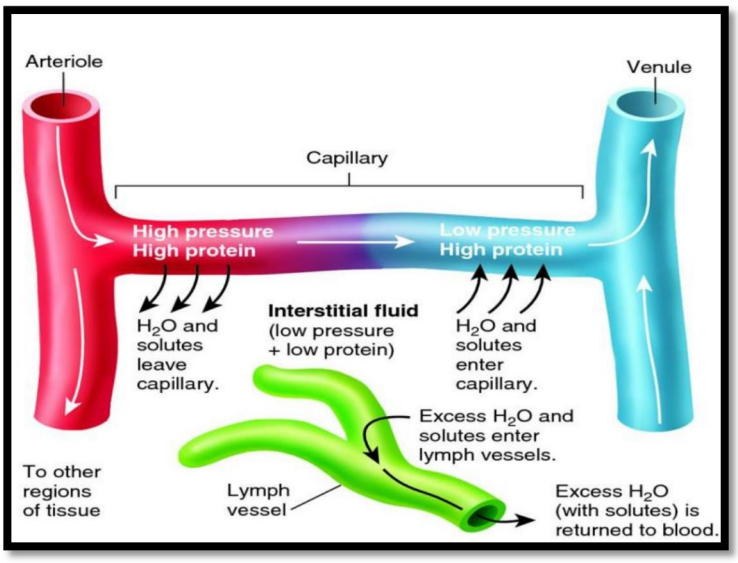


Fig. 5.12:. Capillary Fluid Exchange

Clinical Applications

Oedema: This is swelling of a tissue resulting from excessive accumulation of fluid within the tissue. It is associated with imbalance of forces governing capillary fluid exchange with resultant fluid accumulation in the interstitium.

The pathophysiological mechanisms involved in oedema include;

1. Decrease plasma oncotic pressure e.g., hypoalbuminaemia, liver cirrhosis, nephrotic syndrome
2. Increase capillary hydrostatic pressure e.g., congestive heart failure
3. Increase capillary permeability e.g., sepsis, allergy
4. Lymphatic obstruction e.g., filariasis

BLOOD PRESSURE

Blood Pressure is the force of circulating blood on the wall of the blood vessels.

Systemic arterial blood pressure is the force of circulating blood on the wall of the systemic arteries. Determinants of blood pressure include; stroke volume, heart rate, vascular structure and function (Fig.7).

Haemodynamically, Blood Pressure (BP) = CO X PVR

CO = Cardiac output, PVR = Peripheral Vascular Resistance

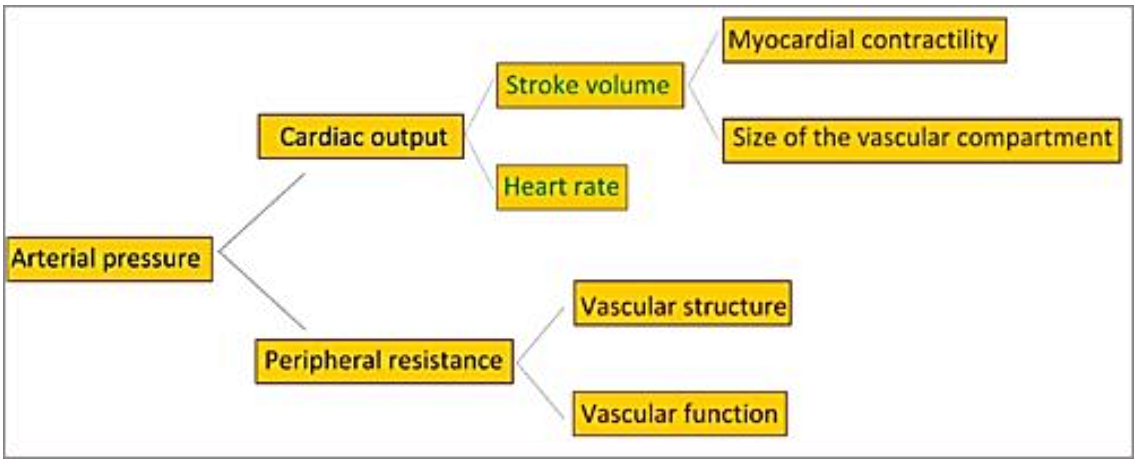


Fig.5.13: Determinants of Blood Pressure

Systolic and Diastolic Blood Pressure

Blood pressure is classified based on phases of cardiac cycle during which the measurement. It is classified into systolic blood pressure, diastolic blood pressure and mean arterial blood pressure. Blood pressure is recorded as x/y mmHg,

where *x = Systolic Blood Pressure*

y= Diastolic blood pressure

Normal BP: 120/80mmHg

1. *Systolic Blood Pressure (SBP):* maximum arterial pressure during ventricular systole.
2. *Diastolic Blood Pressure (DBP):* minimum arterial pressure during ventricular diastole.
3. *Mean Arterial Pressure (MAP):* average blood pressure during a cardiac cycle.

Pulse Pressure

Pulse Pressure refers to the difference between the systolic and diastolic blood pressures. Pulse pressure is dependent on stroke volume and arterial wall elastic properties.

Pulse Pressure = SBP- DBP

If blood pressure = 120/80mmHg, the pulse pressure will be 120-80mmHg = 40mmHg

The resting pulse pressure range in healthy adults in sitting position is 40-60mmHg. During exercise, the pulse pressure rises up to 100mmHg and return to normal within about 10 minutes. The exercise-induced rise in blood pressure is due to reduction in total peripheral resistance accompanying exercise. Pulse pressure may be low (narrow) or high (wide). Both narrow and wide pulse pressure are detrimental to well- being. A high resting pulse pressure tends to accelerate the aging process of the body organs especially the kidneys, heart and brain. A high pulse pressure is an important risk factor for heart disease.

Determinants of Pulse Pressure

The major determinants of pulse pressure include;

1. Stroke volume: pulse pressure is directly proportional to the stroke volume
2. Rate of ventricular ejection
3. Arterial compliance: pulse pressure is inversely proportional to arterial compliance. This explains age-dependent increase in pulse pressure due to decreasing arterial compliance (increasing arterial stiffness) with advancing age.

Abnormalities of Pulse Pressure

Causes of Narrow Pulse Pressure

1. Dehydration
2. Shock
3. Heart Failure

Causes of Wide Pulse Pressure

1. Exercise
2. Pregnancy
3. Fever
4. Anxiety
5. Anaemia
6. Aortic regurgitation
7. Atherosclerosis
8. Arteriovenous malformation
9. Thyrotoxicosis
10. Heart block
11. Beriberi [Vitamin B1(thiamine) Deficiency]
12. Raised intracranial pressure
13. Patent ductus arteriosus

Mean Arterial Pressure (MAP)

Mean arterial Pressure (MAP) refers to the average blood pressure during a cardiac cycle.

$$MAP = (CO \times PVR) + CVP$$

where CO = cardiac output, PVR=peripheral vascular resistance,

CVP= central venous pressure

Normal range of MAP: 70-110mmHg

The two major determinants of mean arterial pressure are the cardiac output and peripheral vascular resistance.

Estimation of MAP

In cardiac cycle, the duration of ventricular diastole (2/3) is more than duration of ventricular systole (1/3). As such, MAP is not equal to the mean of SBP and DBP. It is closer to DBP than SBP. MAP is estimated from SBP and DBP using either of the formulae below;

1. MAP = (2/3 DBP) + (1/3 SBP)

2. MAP = $\frac{2DBP + SBP}{3}$

3. MAP = DBP + 1/3 (PP)

If the BP = 120/80mmHg, therefore, MAP = 80 + 1/3 (40) = 93mmHg

Physiological Significance of MAP

Mean arterial pressure plays a prominent role in maintaining tissue perfusion.

Methods of Measurement of Blood Pressure

Non-invasive method: indirect methods of BP measurement. These methods include palpation, auscultatory and oscillometric methods.

Invasive method: direct measurement of BP through intra-arterial line that is connected to pressure sensor.

Non-Invasive Method of Blood Pressure Measurement

1. *Palpation Method*: by palpation and use of sphygmomanometer

2. *Auscultatory method*: by use of stethoscope and sphygmomanometer

3. *Oscillometric method*: utilizes sphygmomanometer with special pressure sensor that detects cuff pressure oscillations. The result is recorded digitally.

Types of Sphygmomanometer

1. Mercury sphygmomanometer
2. Aneroid sphygmomanometer
3. Digital sphygmomanometer

Fig. 5.14a Digital Sphygmomanometer

Fig.5.14b. Aneroid Sphygmomanometer

Fig.5.14c. Digital Sphygmomanometer

Auscultatory Method

Auscultatory method involve the use of *mercury* or *anaeroid sphygmomanometer* with stethoscope. An appropriate size inflatable sphygmomanometer cuff is placed around the arm and then inflated until the brachial artery is completely occluded. While listening with the stethoscope at the elbow, the examiner slowly releases the pressure in the cuff. When blood just starts to flow in the artery, the turbulent flow creates a tapping sound (first Korotkoff sound). The cuff size should be appropriate for the arm to get an accurate reading.

Korotkoff Sounds

Korotkoff Sounds are the sounds that are heard over the brachial artery when taking blood pressure using a non-invasive procedure. They are named after *Dr Nikolai Korotkoff*, a Russian physician who described them in 1905. Korotkoff sounds occurs in five phases(I-V).

Phases of Korotkoff Sound

Phase I: tapping sound

Phase II: murmur

Phase III: tapping sound

Phase IV: muffling sound

Phase V: silence

Systolic blood pressure is taken to be the pressure at the beginning of phase I

Diastolic blood pressure *is taken at the beginning of phase V*

Cases in which DBP is taken at Phase IV

Cases in which DBP is taken at phase IV because there is no phase V include the following;

1. Children
2. Pregnancy
3. Hyperthyroidism
4. Aortic Regurgitation

Self-Measured Blood Pressure Monitoring

Self-measured blood pressure (BP) monitoring at home or in the office is an essential part of heart care. It is an easy, stress-free and cost-effective process. It encourages BP drug compliance with resultant BP control. Self-measured BP monitoring is facilitated by the use of *Digital BP Monitor or Sphygmomanometer.* The medical device is an electronic instrument made up of a monitor connected to a cuff by a tube (Fig. 8c). The monitor component displays the following parameters; Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Pulse Rate (PR).

A Note on Digital BP Monitor Cuff: Upper Arm or Wrist Cuff?

The cuff is the component of the digital BP monitor that is fixable to upper limb for measurement of the blood pressure (Fig. 8cAn individual with normal body build should use the digital BP monitor with an upper arm cuff. It is more accurate than digital BP monitor with wrist cuff. However, digital BP monitor with wrist cuff is recommended for individuals with extra-large arm size which cannot fit into the upper arm cuff of the device.

A*ppropriate Size of the Cuff of BP Monitor*

In monitoring BP, it is essential that the cuff size of the BP monitor should be appropriate for the body build of the individual (Table 2). This is important because of the following;

1. The use of cuff size small for the body build results in overestimation of blood pressure.
2. The use of cuff size large for body build results in underestimation of blood pressure.

Table 2 Appropriate cuff size based on body build and mid-upper arm circumference

Mid-Arm Circumference (cm)	Body Build Class	Range of BP monitor Cuff Size (cm)
22-26	Small adult	22-30
27-34	Adult	22-36
35-44	Large Adult	*

** A wrist cuff may be suitable than arm cuff.*

N.B. A cuff size of 22-42cm accommodates a wide range of body build (small adult and adult)

BP Cuff: Bladder Size

The bladder is the inflatable portion of the BP cuff. The bladder size should be appropriate so that the BP monitor can function effectively. The width and length of the bladder of the cuff should be at least 40% and 80% of the mid-arm circumference respectively.

Home Blood Pressure Assessment

Why Measuring Blood Pressure?

Measurement of blood pressure is the diagnostic test for persistently elevated blood pressure, also called hypertension, the silent killer. Hypertension occurs asymptomatically in most cases but it often presents with deadly complications such as *stroke*, *heart attack, heart failure*, *pulmonary oedema (fluid in lungs), arrhythmia, kidney failure, eye damage* and *sudden death*. Hence, the need to measure blood pressure periodically in order to detect dangerous fluctuations which may put an individual in danger.

When to Measure Blood Pressure?

1. BP should be measured around the same time of the day since BP fluctuates with time.
2. Monitor the BP in the morning and evening and keep the record.
3. BP may also be monitored more frequently according to Physician's advice, if need be.
4. Measure the BP before exercise, food or drug intake.

How to Measure Blood Pressure in Sitting Position

1. Sit up, with your back straight and relax.
2. Ensure that the BP monitor is placed on a platform at the level of the heart.
3. Ensure that your legs are uncrossed and the feet are placed on the ground.
4. Rest for at least five minutes before BP measurement.
5. There should be no smoking nor intake of drug, alcohol, energy drink nor caffeinated tea thirty minutes before measuring BP.
6. Ensure that the BP monitor cuff size is appropriate for your body build.
7. If battery-powered, ensure that the batteries are in good condition, belonging to same set (don't mix batteries).
8. Roll up the sleeve on your left arm for insertion of the BP cuff if you are right-handed except you are instructed otherwise by your physician.
9. Wear the cuff of the BP monitor and ensure that its lower end is about 1inch (2.5cm) above the bend of your elbow (Fig.9).

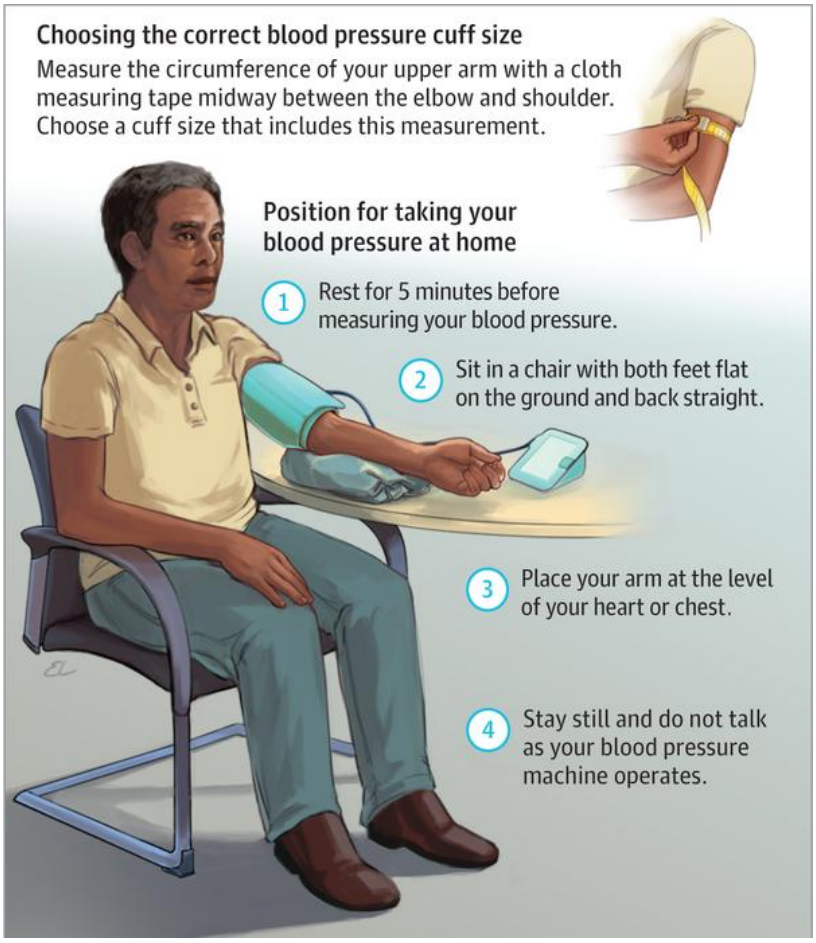


Fig. 5.15. Measurement of Blood Pressure using BP monitor

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10. The cuff should be snugged around the bare arm but not too tight.

11. Rest the forearm on the plane bearing the BP monitor and ensure that the palm faces upwards while the fingers are relaxed.

12. Avoid distractions such as conversation, phone usage, watching television or reading news items when measuring the BP

13. When you are ready, turn on the BP monitor and press start button.

14. Stay still as measurement continues.

15. The BP monitor will display three figures; the upper figure is the SBP, the middle figure is the DBP while the lower figure is the Pulse Rate (PR)

16. Take three measures at least 2 minutes apart and document the figures

17. Remove the cuff from your arm and keep the BP monitor is a safe location.

18. Get the average of the last two sets of BP readings (*the first set of BP figures are documented but are not used in the estimation of the mean BP)*.

19. At first, measure the blood pressure at both sides of the body and compare the figures.

20. Subsequent blood pressure measurement should be done at the side with higher mean arterial blood pressure.

Blood Pressure Classification According to Established Guidelines

Blood pressure figures are classified into categories based on the level of the variables. Various

guidelines exist and they are reviewed from time to time. Below are examples of blood pressure classification guides.

Table 5.3. WHO/ISH Classification of Blood Pressure, 1999 and 2003

Category		SBP(mmHg)	DBP(mmHg)
Optimal Blood Pressure		< 120	<80
Normal Blood Pressure		120-129	80-84
High-Normal Blood Pressure		130-139	85-89
Hypertension	Grade 1	140-159	90-99
	Grade 2	160-179	100-109
	Grade 3	≥180	≥110

WHO- World Health Organization, ISH-International Society for Hypertension

Hypertension is diagnosed when SBP ≥ 140mmHg and or DBP ≥ 90mmHg on two or more occasions.

Table 5.4. JNC VII Classification of Blood Pressure, 2013

Category	SBP (mmHg)	DBP (mmHg)
Normal Blood Pressure	< 120	< 80

Prehypertension		120-139	80-89
Hypertension	Stage 1	140-159	90-99
	Stage 2	≥ 160	≥ 100

JNC VII: Seventh Report of the Joint National Committee on Prevention,

Detection, Evaluation and Treatment of High Blood Pressure

Hypertension is diagnosed when SBP ≥ 140mmHg and or DBP ≥ 90mmHg on two or more occasions.

Table 5.5. ACC/AHA Classification of Blood Pressure, 2017

Category	SBP(mmHg)	DBP(mmHg)
Normal Blood Pressure	< 120	< 80
Elevated Blood Pressure	120-129	< 80
*Hypertension Stage 1	130-139	80-89
Hypertension stage 2	≥ 140	≥ 90

ACC- American College Cardiology; AHA-American Heart Association

**Hypertension is diagnosed when SBP ≥ 130mmg and or DBP ≥ 80mmHg on two or more occasions.*

Factors Affecting Blood Pressure (BP)

1. *Age*: BP increases with age

2. *Gender*: BP is higher in male than female before the age of menopause (a female attribute). After menopause BP of both gender of same age should be equal.

3. *Posture*: In some individuals, rising from supine to erect position, systolic blood pressure falls while diastolic blood pressure slightly rises, however, in some young individuals especially of Black descent, there is a slight increase in both systolic and diastolic components of blood pressure upon rising from supine to erect position.

4. *Emotion*: Anxiety increases BP due to release of sympathomimetic hormone such as adrenaline.

5. *Sleep:* Sleep is a restorative to the cardiovascular system. Blood pressure decreases during sleep. This is referred to as *nocturnal dipping*. Blood pressure rises during the dream. Sleeping for less than six hours a day can activate two major stress systems; hypothalamo-pituitary-adrenal system and sympathomedullary system

resulting in release of stress-promoting substances such as cortisol and adrenaline which increases blood pressure. *Sleep deprivation* is a risk factor for elevation of blood pressure.

6. *Circadian rhythm:* BP increases early morning but decreases at night.

7. *Obesity*: Facilitates increase in blood pressure

8. *Temperature:* Exposure to cold increases blood pressure but exposure to hot weather decreases blood pressure.

JUGULAR VENOUS PULSATION AND PRESSURE

Jugular venous pulsation reflects the phasic pressure changes in the right atrium during the cardiac cycle. It is assessed at right side of the neck by observing the multiphasic pulsatile changes of the internal jugular vein. Jugular venous (Fig.10) has three peaks (a, c and v waves) and two troughs (x and y descents).

Description of Jugular Venous Waveforms

a wave: Represents a rise in right atrial pressure accompanying atrial contraction(systole).

c wave: Represents a slight rise in right atrial pressure associated with closure of tricuspid valve.

x descent: Represents a fall in right atrial pressure accompanying atrial relaxation.

v wave: Represents a rise in right atrial pressure accompanying atrial filling during ventricular systole

y descent: Represents a fall in right atrial pressure accompanying emptying of blood from the right atrium.

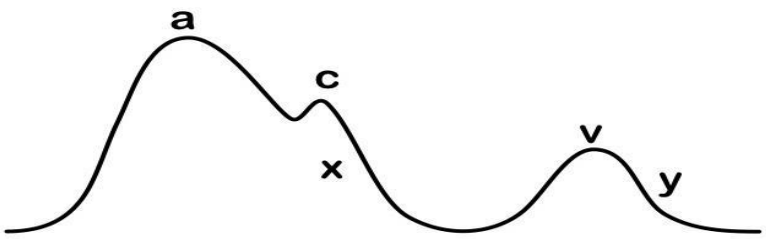


Fig. 5.16. Jugular venous pulsation waveforms

Clinical Utility of Jugular Venous Pulsations and Pressure

Jugular venous pulsations can be observed on the right side of the neck. Jugular venous pressure (JVP) is a measure of central venous pressure. JVP can also be measured non-invasively at bed-side. The normal upper limit of JVP is <4cm H_2O above the manubrosternal angle or < 9cmH_2O above the centre of the right atrium (to convert pressure from cmH_2O to mmHg, multiply by a factor of 1.36). Jugular venous pulsations and pressure are important diagnostic parameters in the assessment of cardiovascular diseases such as heart failure and valvular diseases.

Measurement of Jugular Venous Pressure

In the medical practice, non-invasive measurement of jugular venous pressure (JVP) is almost becoming a neglected procedure especially in developing countries due to non-availability of a standard device for its assessment. Traditionally, two rulers strategically placed at right angle to each other in which the lower end of the vertical ruler is placed at the manubrosternal angle are used for the measurement of jugular venous pressure. However, this method has improved by the use of jugulometer (Fig. 11).

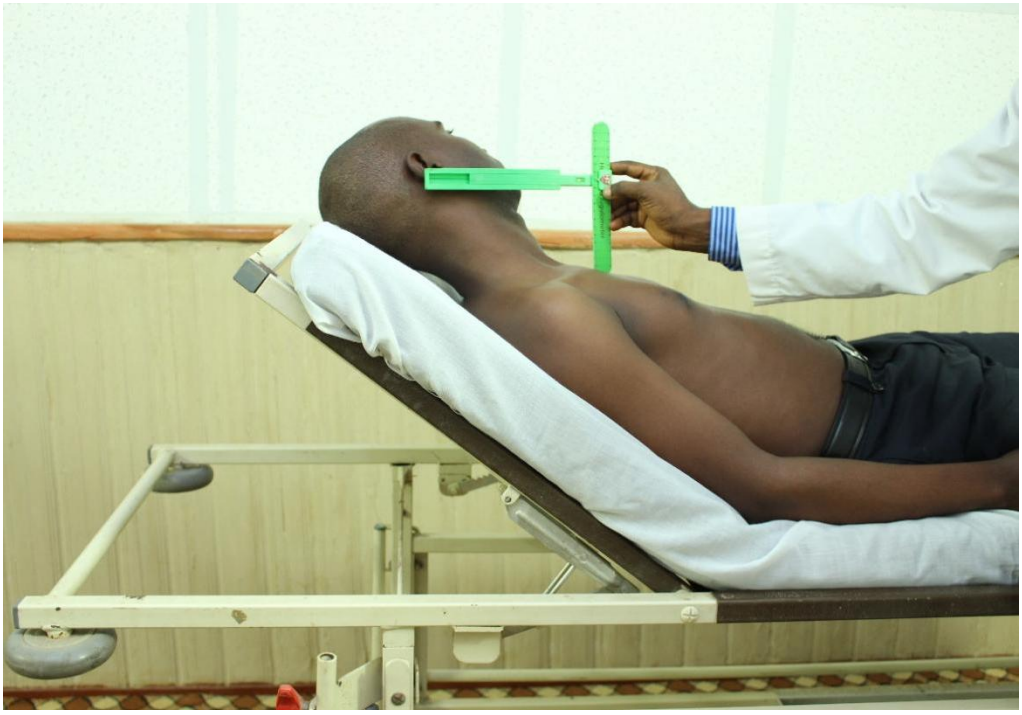
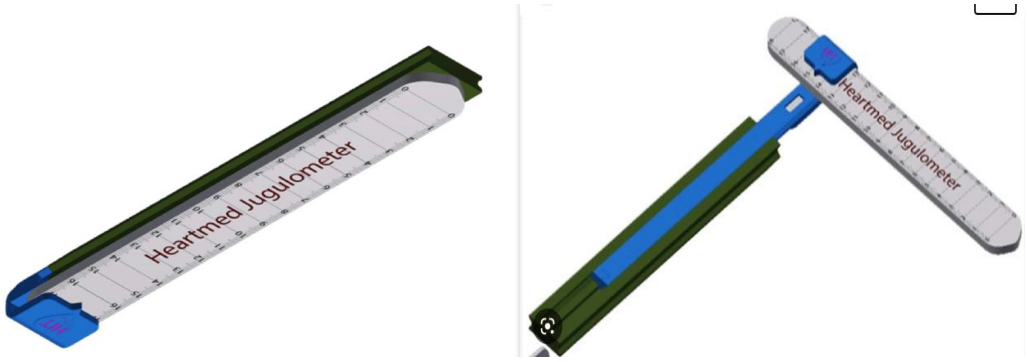


Fig.5.17. Measurement of Jugular Venous Pressure using jugulometer

Source: https://youtu.be/T_bn2rCQXHc&t=0 (Retrieved ……)

Jugulometer

Jugulometer is a medical device for non-invasive assessment of jugular venous pressure at bed-side. In 2005, Professor Oluwadare Ogunlade, a physician and physiologist pioneered an innovative idea which gave birth to jugulometer at Obafemi Awolowo University Teaching Hospital Complex (OAUTHC), Ile-Ife, Nigeria. He subsequently obtained a patent for this device. Jugulometer is made up of two perpendicular bars that can slide over each other. The vertical bar is graduated in centimeter; for easy measurement of JVP in cmH_2O. This device improves the technique of bed-side assessment of JVP. The Heartmed model of the device(Fig.12aandb) was developed at Obafemi Awolowo University, Ile-Ife with collaboration with colleagues at the Department of Mechanical Engineering of the University.



a b

Fig 5.18 a and b. Heartmed Jugulometer; a model of jugulometer (https://youtu.be/SVTJGspLUsA&t=0)

Central Venous Pressure

Central venous pressure (CVP) is a measure of the pressure within the vena cava and right atrium.

It is used for the estimation of preload and right atrial pressure. The normal is CVP < $9cmH_2O$.

Factors affecting CVP includes total blood volume, cardiac output and posture.

Measurement of CVP

CVP can be measured through a central venous catheter inserted to the subclavian vein or internal jugular vein. A transducer or amplifier can be used to monitor the pressure. Another method of monitoring CVP is ultrasonography.

The variables that can be assessed to reflect CVP includes;

1. Maximal inferior vena cava diameter (a value <2cm, indicates low CVP and a value >2cm indicates elevated CVP).

2. Inspiratory inferior vena cava collapse

3. Inferior vena cava/internal jugular vein ratio

Clinical Significance of CVP

1. Low CVP indicates hypovolaemia and decrease venous tone

2. Elevated CVP indicates fluid overload, right heart failure or congestive heart failure

INTEGRATION OF CARDIOVASCULAR SYSTEM FUNCTION

Various components of the brain regulate the heart through sympathetic and parasympathetic outflow of the autonomic system. The cardiovascular functions can be altered significantly by reflex activation of the autonomic outflow in response to varieties of inputs from baroreceptors and chemoreceptors coupled with central command from cortical, subcortical and midbrain regions of the brain in association with stress, emotion, arousal, sleep and physical activity (Fig.13)

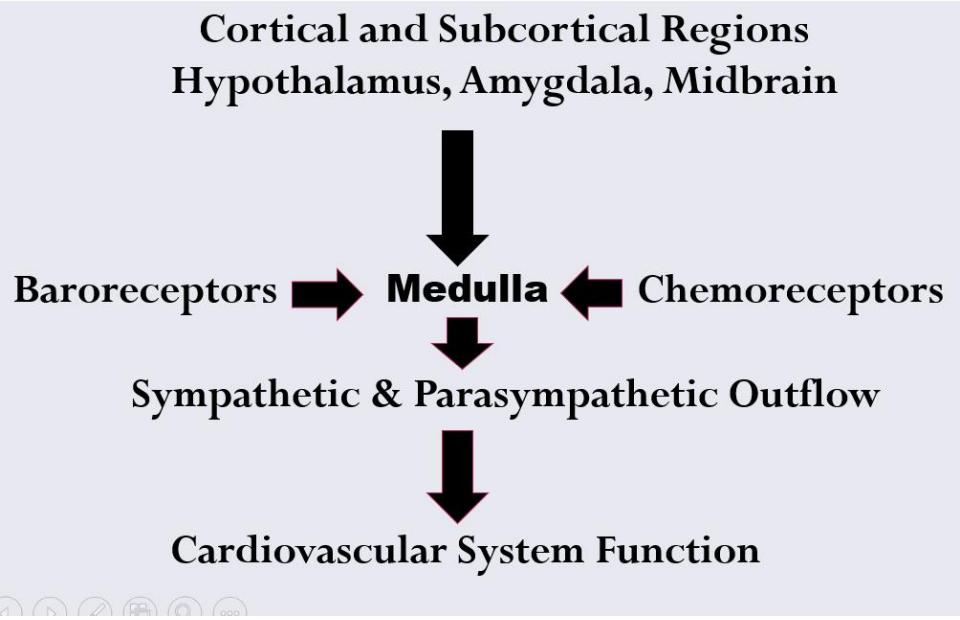


Fig. 5.19. Heart-Brain Interaction for Cardiovascular Function

REGULATION OF SYSTEMIC ARTERIAL BLOOD PRESSURE

The blood pressure is regulated in such a way to maintain mean value for effective tissue perfusion. Failure of the regulatory mechanisms may result in alteration in blood pressure. Blood pressure above or below the physiological range is counterproductive to the cardiovascular systems and other vital systems in the body.

Mechanisms of BP Regulation

The mechanisms for regulation of blood pressure include;

1. Neural Mechanism
2. Renal mechanism
3. Humoral Mechanism

Neural Mechanism

Neural mechanism refers to regulation of the blood pressure by the nervous system

The neural mechanism is for short term blood pressure control.

Components of the Neural Mechanism

1. Brain

Brain stem: Medulla

Cortex and Hypothalamus

2. Receptors

Baroreceptors: carotid sinus baroreceptors and aortic arch baroreceptor

Chemoreceptors: carotid body and aortic body

3. Autonomic nerves

Sympathetic fibres

Parasympathetic fibres

Central Neural Mechanism

The medulla in the brainstem is the primary site in the brain for regulating *sympathetic* and *parasympathetic (vagal) outflow* to the heart and blood vessels. The medulla contains *nucleus of tractus solitarius (NTS)* which receives sensory input from baroreceptors and chemoreceptors. The medulla also receives information from other brain regions e.g cortex and hypothalamus to modulate blood pressure. Autonomic outflow from the

medulla is divided principally into sympathetic and parasympathetic (vagal) branches which innervates the heart and blood vessels.

Vasomotor Centre in the Medulla

The vasomotor centre is located in the medulla. It consists of three areas; sensory, vasoconstrictor and vasodilator areas.

1. Sensory area: nucleus of tractus solitarius which inhibits/stimulates the vasoconstrictor or vasodilator area depending on blood pressure signal received from the baroreceptors or chemoreceptors.

2. Vasoconstrictor area: the pressor or cardioaccelerator area and is located in the lateral portion of vasomotor centre. Its stimulation causes vasoconstriction.

3. Vasodilator area: the depressor or cardioinhibitory area and is located in the medial portion of vasomotor centre. Its stimulation causes vasodilatation.

Baroreceptors

Baroreceptors are a type of mechanoreceptors that detect fluctuation in blood pressure within the vessels.

Types of Baroreceptors

1. *Carotic Sinus Baroreceptor*

The carotid sinus baroreceptors are situated in the carotid sinus of the internal carotid artery near the bifurcation of the common carotid artery. The region is innervated by Hering's nerve, a branch of glossopharyngeal nerve.

2. *Aortic Baroreceptor*

The aortic baroreceptors are situated in the wall of the arch of aorta. The region is innervated

by aortic branch of vagus nerve.

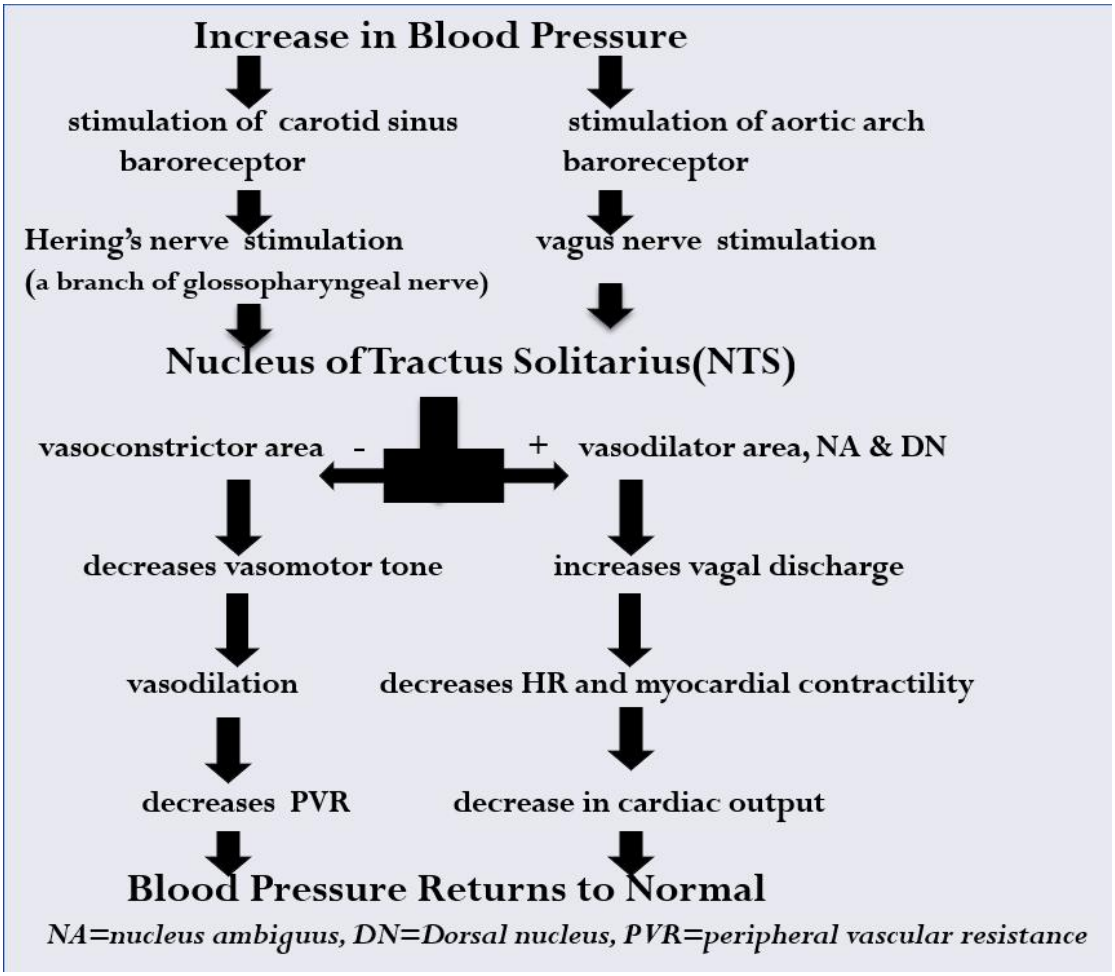


Fig. 5.20: Neural mechanism of blood pressure regulation

Chemoreceptors

Chemoreceptors are special sensors that detect changes in chemical composition of the blood. They located in the carotid body and aortic body. The chemoreceptors in the carotid body are supplied by glossopharyngeal nerve while the chemoreceptors in the aortic body are supplied by vagus nerve. The chemoreceptors are sensitive to hypoxia, hypercapnia and increase in hydrogen ion concentration.

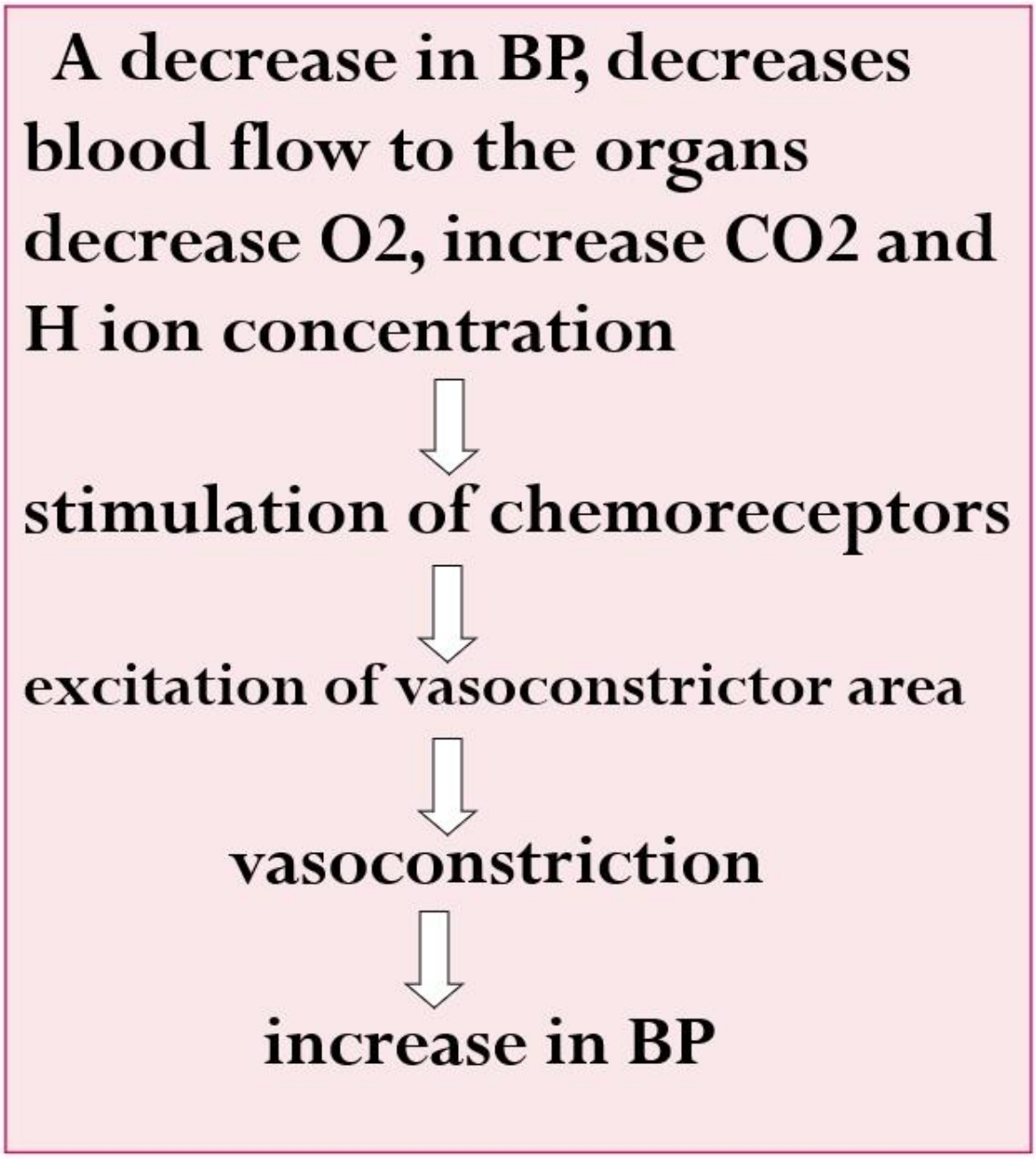


Fig. 5.21: Role of chemoreceptor in blood pressure regulation

Renal Mechanism

Renal mechanism refers to the role of the kidneys in blood pressure control. It is a long-term blood pressure control. Decrease tissue perfusion or reduction in extracellular fluid results in release of renin from the juxtaglomerular apparatus of the kidney. Renin cleaves angiotensinogen (produced by the liver) to angiotensin I,

thus triggering the classical and alternative pathways of renin-angiotensin-aldosterone system (RAAS) for blood volume and blood pressure regulation. Angiotensin Converting Enzyme (ACE) produced in the lung cleaves angiotensin I to angiotensin II in the classical pathway. On the other side, Angiotensin Converting Enzyme 2(ACE2) mainly produced by the endothelial cells of the heart and kidney metabolizes angiotensin I to angiotensin-(1-9), which in turn is converted to angiotensin-(1-7) by ACE. ACE2 also metabolizes angiotensin II to angiotensin-(1-7). Angiotensin II increases total peripheral vascular resistance by facilitating vasoconstriction. It stimulates adrenal cortex to release aldosterone, thereby promoting salt and water retention. Angiotensin II promotes release of antidiuretic hormone by the posterior pituitary, thereby decreasing water excretion by the kidney. It also promotes fibrosis, thrombosis and myocardial hypertrophy. Angiotensin-(1-7) is a vasodilator. It is also anti-inflammatory and anti-proliferative, thereby modulating the effects of angiotensin II(Fig.16).

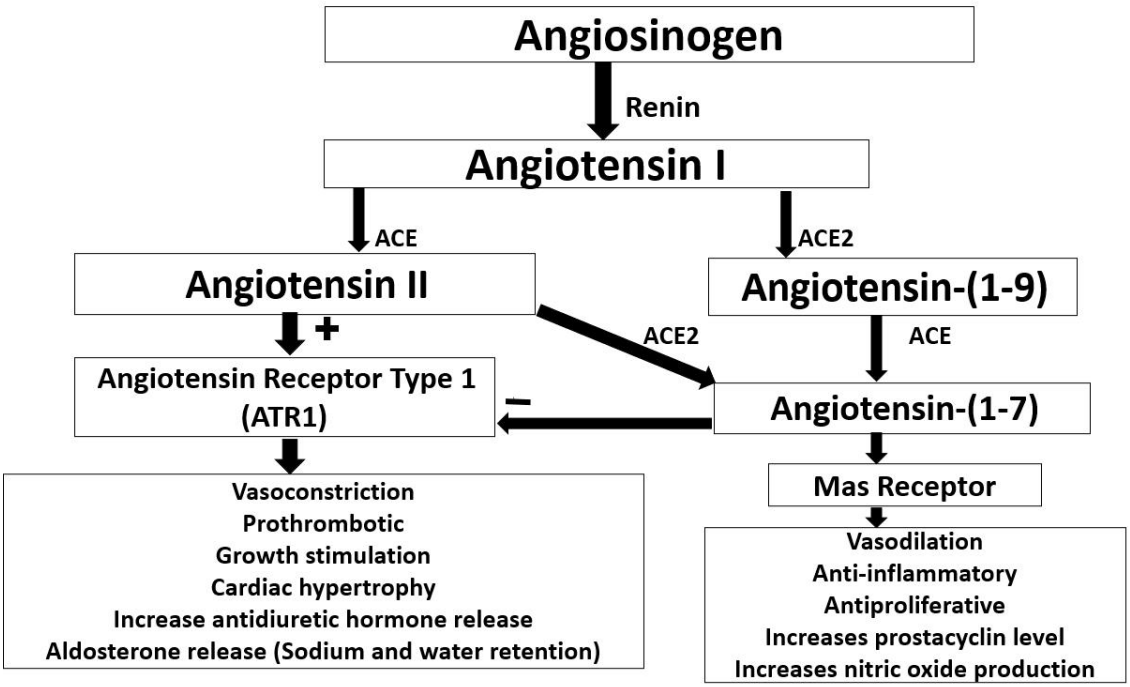


Fig.5.22:. Pathways of Renin Angiotensin Aldosterone System Activation

Humoral Mechanisms

Humoral mechanisms refer to regulation of blood pressure by vasoactive substances; hormones and non-hormones. The substances can be classified as vasoconstrictors or vasodilators. The vasoconstrictors increase the blood pressure while the vasodilators decrease the blood pressure. The effects of the substances could be systemic or local. Systemic vasoconstrictors include; vasopressin, epinephrine, norepinephrine, angiotensin II and urotensin II while local vasoconstrictors include; serotonin, thromboxane A2 and endothelin. Systemic vasodilators include; kinins, Vasoactive intestinal peptide (VIP), atrial natriuretic peptide (ANP) and brain

natriuretic peptide (BNP) while local vasodilators include; histamine, adenosine, lactate, prostacyclin, nitric oxide, decrease PaO_2, decrease PH and increase $PaCO_2$.

Cardiovascular Adaptation in Health and Diseases

The vascular circulatory system consist of the:

•The pulmonary circulation (low pressure system), supplies the lungs and for gas exchange, and

•The systemic circulation, also called greater circulation or peripheral circulation, which delivers blood to specific organs, matching supply to metabolic needs. It supplies all other organs except the lungs. The heart is largely controlled by the autonomic nervous system, that is why it is impossible to voluntarily stop the heart from beating while the individual can withhold the breathe.

Difference between systemic circulation and pulmonary circulation

	Systemic circulation	Pulmonary circulation
i.	High Pressure	low pressure
ii.	High resistance	low resistance
iii.	Supply many tissues and organs	supply the lungs
iv.	Long hydrostatic column	Short hydrostatic column
v.	Many controls	little control

Different Parts of the cardiovascular system and their functions

The Heart

This consist of two (2) pumps: the left pump and the right pumps

Left Pump- made up of the left atria and the left ventricle- which pumps blood to the systemic circulation. The left ventricle is 4x thicker than the right ventricle because it pumps blood at a higher pressure with more work done but same output/volume. It makes up about 75% of the mass of the heart.

Right pump- made up of the right atria and the right ventricle. It provides circulation to the pulmonary system.

The heart is made up of four (4) chambers- right atria, left atria, right ventricle and left ventricle.

The circulatory system can be likened to the plumbing system in a building which is in a closed circuitry supplying different parts of the house. The sumo pump (likened to the heart) with the responsibility of pumping the water (blood) and the pipes of different sizes (vessels) connects the different points where the water is needed.

The early embryonic heart activity is said to start at 35-37 gestational days (about 6 weeks) and expected to continue till death. The muscles of the heart must therefore, have special properties to carry out this continuous function and to prevent tetany, unlike other types of muscles in the body. The heart rate for a physiological normal man is about 72 beats/min (normal range is 60-100 beats/min). That means the heart beats for about 103,680 times/day and over 2.6 billion times at the age of 70 years.

To calculate the maximum heart rate (MHR) of an individual, this formula is used:

Maximum heart rate (MHR)= [220-Age in years]

For a 40 years old man,

MHR=220- 40 = 180 bpm., therefore the individuals heart rate is not expected to exceed this rate.

Heart Rate Reserved (HRR) = [MHR- RHR]

RHR= Resting Heart Rate.

If the resting heart rate of the 40 years old man is 68 bpm

HRR= 180 – 68 =112bpm.

These values are very important to note in prescribing and monitoring the intensity of exercise for individuals.

Cardiovascular Adaptations in Health

The cardiovascular adaptations of importance include:

i. Enlargement and strengthening of the dimensions of cardiac muscle

ii. Improvement in the contractility of the heart

iii. Increased blood volume

iv. Improved ventricular filling

v. Increased stroke volume

vi. Improved cardiac output

The ultimate aim of cardiac adaptation is to improve the functioning efficiency and cardiac output of the individual through increased stroke volume.

Cardiac output is the volume of blood pumped out by the ventricle of the heart per unit time (per minute). It is a volumetric flow rate. The value is about 5L/min. It determines the quantity of blood that is delivered to the various organs and tissues of the body. The efficiency of the heart to meet the metabolic and perfusion needs of the body is determined by the cardiac output.

Stroke Volume (SV) is the volume of blood pumped from the left ventricle per beat.

Therefore,

Cardiac output (CO) =Stroke volume (SV) x Heart Rate (HR)

Also, $C.O = \frac{\text{Blood pressure}}{\text{Total Peripheral Resistance}}$

In health cardiac output= venous returns.

There is always a balance in cardiac output of the two pumps of the heart due to the inherent property of the myocardium called heterometric auto-regulation

There is also homeometric auto-regulation which explains the ability of the heart to increase contractility in order to restore stroke volume when after-load increases.

Afterload-the amount of pressure that the heart must work against to eject blood during systole. The change in after load affects stroke volume, end systolic volume and end diastolic volume.

The causes of increased afterload are:

- ✓ Peripheral vascular resistance
- ✓ Systemic hypertension
- ✓ Aortic stenosis
- ✓ Aortic regurgitation
- ✓ Coarctation of the aorta

Preload- is the end-diastolic volume or the stretch experienced by the myocardium.

Physiological Variations in Cardiac Output

i. Age- maximum cardiac output reduce with age

ii. Sex- female have 10-20% lower values

iii. Body size- CO increases directly with body surface area (BSA)

iv. Exercise- in an untrained individual, CO may increase up to 23 L/min, while in trained athletes it increases to 30 L/min

v. Pregnancy- increases CO by about 1.5 L/min throughout pregnancy

vi. Posture-CO falls on changing from supine to sitting or standing position up to 30%. this may explain the dizziness some individuals feel on rising suddenly from supine position.

Stroke volume- this is the quantity of blood pumped out by the ventricles per beat. Its value is usually about 70ml. Obesity is known to cause a compensatory increase in stroke volume.

Stroke volume = End diastolic volume (EDV) minus End systolic volume (ESV)

This shows that if the stroke volume increases as a result of good cardiovascular adaptation, individuals will require fewer number of heart rate (HR) to get the desired cardiac output. Also, if the ESV decreases due to improved contractility of the ventricular muscles, the stroke volume will also improve. This explains why athletes tend to have lower heart rate, as exercise is known to improve the strength of the cardiac muscles.

Stroke volume is determined by:

i. Heart size

ii. Gender

iii. Duration of contraction

iv. Physical fitness

v. Preload (End diastolic volume)

vi. Afterload (peripheral resistance)

vii. Contractility of the heart

Heart rate is affected by:

i. Age

ii. Drugs

iii. Hormones

iv. Excitements and anxiety

v. Sleep/ Rest

vi. Autonomic innervation (sick sinus syndrome

vii. Temperature

viii. Exercise

Cardiac index (CI) is an assessment of the value of cardiac output as a function of the patients size. This means obesity and stature may affect the value.

CI= CO divided by the body surface area (BSA). Body surface area can be calculated using a nomogram. This means as the BSA increases the cardiac index decreases. The factors that affect BSA are height, weight, age and gender. The normal value is taken as $1.7m^2$, while that of adult male is about $1.9m^2$.

The normal range for cardiac index is 2.5 - 4 $L/min/m^2$

Cardiac Reserve- This refers to the maximum percentage that the cardiac output can increase above the normal value. In a normal adult, the value is 300-400%, while in trained athletes it is 500-600%. this is a predictor of the cardiac health and explains why untrained athletes gets easily fatigue during exercise.

Cardiovascular Adaptations in Exercise

Regular exercise or physical activity leads to improved anatomical (structural) and physiological (functional) changes that reduce the incidences of heart disease and improve spirometric parameters (Godsday *et al*., 2021a). Exercise is known to induce physiological cardiac hypertrophy which is known to improve stroke volume and cardiac output unlike the compensatory pathological cardiac hypertrophy which leads to heart failure. Heart failure results when the heart is not able to pump enough blood to meet the metabolic needs of the body.

During exercise, the stroke volume increases so also the heart rate, this enables an increase in cardiac output to compensate for increased demand from the active muscle mass to deliver the required oxygen. It is also known that there is a transient increase in the systemic vascular resistance (peripheral resistance) which will cause an increase in blood pressure.

Blood pressure= Cardiac output x Total peripheral resistance (TPR)

The acute increase in blood pressure especially in untrained athletes is the reason for crisis experienced in hypertensives who engage in an exercise without the prescription of a doctor. However, long term exercise promotes a reduction in blood pressure which is the reason it is encouraged for a healthy cardiovascular system.

Exercise-induced cardiac remodeling is associated with cellular signaling pathways and gene regulatory mechanisms underlying cellular, molecular, and metabolic adaptations for the maximum efficiency of the heart functioning during isometric exercise (Ogbutor *et al.,* 2022a)

The heart as the primary pump, circulates blood to the entire body during exercise when there is increased demand for oxygen and nutrients. There is also the need for the re-distribution of blood flow to the regions of the body where it is most need by cutting off supply to the metabolically inactive regions of the body. Serving many important functions in the body exercise training therefore, promotes mitochondrial biogenesis and oxidative capacity leading to a decrease in cardiovascular disease in physically active persons

Circulatory Response during Exercise

- Increase in heart rate up to 160 beats/min due to increased sympathetic activity.
- Increase in cardiac output (up to 30 L/min) due to increased venous return as the muscle pump activity increase.
- Increase in blood pressure especially the systolic BP up to 200mmHg, but with little change in diastolic BP as a result of increased cardiac output.

These acute effects may change to a more enduring cardiovascular parameters due to exercise in elite athletes as shown in the changes below.

Cardiovascular Adaptation with Exercise

- Decreased heart rate.
- Increase in stroke volume up to 50% of maximal workload.
- Increase in myocardial contractility and increase in ventricular volume

Local adaptation in the exercising muscles also occurs due to accumulation of products from anaerobic metabolism like lactic acid, adenosine, hypercapnia and existing hypoxia cause vasodilatation in the vessels that supply the muscles This will ultimately increase the blood flow to the muscle and reduce muscle cramps.

Cardiovascular Adaptations in Disease

Cardiomyocytes stop differentiation soon after birth. Therefore, the number of cardiomyocytes does not increase after birth but rather they increase in size. This increase in size leads to myocardial hypertrophy which help to maintain function and efficiency of the heart in response to increased workload. This initial adaptation is necessary because it leads to a reduction in the ventricular wall stress. The cardiac cells can also undergo atrophy though not common.

Hypertrophy could be either physiological (which may be reversible as seen in athletes and pregnant women) or pathological (due to response to chronic pressure or volume overload). It is usually an adaptive response to changes in stimuli which could be physiological or pathological. If the pathological adaptation is not managed, the heart may deteriorate and result to heart failure. Recent advances in therapeutics suggest a strategy for the prevention or reversal of pathological hypertrophy through metabolic remodeling, immune responses, proliferation, epigenetic modification and cellular maladaptive mechanisms.

Aging and Cardiovascular Changes

Cardiovascular changes that occur with aging are a slow but life-long process which vary in rate of progression and it involves all of the structural components in the heart and vasculature. Aging process also causes myocardial fibrosis and arterial stiffness. This may be affected by genetic or environmental conditions. Changes in the cardiovascular system lead to alterations in overall cardiac physiology and function. Cardiac output decreases with increasing age.

Circulation Through Special Areas/ Regional Circulations

Regional circulation refers to the distribution of cardiac output to various parts of the body in a normal man at rest. It involves circulation to different organs, examples

i. Brain- cerebral circulation

ii. Heart- coronary circulation

iii. Lungs- pulmonary circulation

iv. Skin- cutaneous circulation

v. GIT- splanchnic circulation

vi. Kidney- renal circulation

vii. Liver -hepatic circulation

An organ may be supplied by two blood inflows: - the nutrient circulation and the functional circulation. Therefore, there are various ways of anatomical and functional adaptation of an organ-specific circulation to provide the optimal function of the organ. The cardiac output of 5L/min is distributed to various parts of the body at rest in a normal man. This value varies depending on the circulatory needs of the body at any time. The vascular supplies of many organs have additional special features that are important to the normal functioning and physiology of that specific organ. Special circulations have additional features of intrinsic blood flow control, allowing auto-regulation.

The objective of this topic is to explain the special circulations to the brain, the heart, lungs, kidney, skin and the placenta and fetus.

Table 1 shows the approximate values of the blood flow to organs as it relates to the size of the organ and percentage of the cardiac output. It is important to note that the percentage of the CO that supplies an organ is an indicator of the importance the body attach to that particular organ.

Table 1- Blood Flow to Various Organs

	Blood Flow

Region	Mass (kg)	mL/min	Percentage of CO	mL/100g /min
Liver	2.6	1500	27.8	57.7
Kidneys	0.3	1260	23.3	420.0
Brain	1.4	750	13.9	54.0
Skin	3.6	462	8.6	12.8
Skeletal muscle	31.0	840	15.6	2.7
Heart muscle	0.3	250	4.7	84.0
Rest of body	23.8	336	6.2	1.4
Whole body	63.0	5400	100.0	8.6

Adapted from Ganong´s Review of Medical Physiology.

The mL/100g/min supplies to the specific organs is and indicator of blood supply to the organ in relation of the size of the organ. It is important to note that in terms of mL/100g/min the kidney is the most vascularized organ.

Cerebral Circulation

The major arteries to the brain are two internal carotid (very important and significant) and two vertebral arteries (which unite to form the basilar artery). The circle of willis is formed below the hypothalamus from the basilar artery and the carotid artery which gives origin to the six large vessels supplying the cerebral cortex. No crossing over occurs in the two hemispheres of the cerebral cortex probably because of equal pressure on both sides. There is presence of anastomotic channel which help as alternative supply but generally insufficient to maintain the circulation and prevent infarction when a cerebral artery is occluded. The vessels are very thin (hence prone to rupture to cause haemorrahagic stroke), the veins have no valves and blood flow reduce by 15% in the erect posture. Variations in blood flow to the brain occur in sleep, wakefulness, talking and cognitive activities. There is increased flow in some selected areas premotor and frontal cortex during cognitive activities. Decreased blood flow occur in some disease conditions such as Alzheimer's disease, Huntington's disease, maniac depression, epilepsy etc.

The brain is encapsulated in the cranium which is a rigid structure resulting in adverse effects, if there is an increased intracranial pressure (ICP).

An increase in intracranial pressure resulting from increased level of cerebrospinal fluid will cause compression of the vessels thereby decreasing cerebral blood flows and this may lead to ischaemia. There may be a

compensatory stimulation of the vasomotor centre leading to increased blood pressure in order to cause an increased blood flow in an attempt to maintain the cerebral blood flow. This is called Cushing's Reflex.

Special physical conditions of cerebral circulation known as Monro-Kelli theory- flow may be increased only by acceleration of the blood flow, not by an increase of capacity of the bloodstream. This help in protecting the brain. Other factors that are very important in cerebral circulation include the level of systemic pressure due to anti-gravity direction of the cerebral flow which help protect from orthostatic reaction and postural syncope, hypercapnia and hypoxia.

Head Injuries

The brain is protected by spinal fluid and the meninges. The trauma to the brain, even the minor traumas of everyday living, would probably be with severe consequence but for such protection. Therefore, cerebral damage can only result from a severe trauma. Fracture to the skull (depressed skull fracture), a severe blow or a penetrative injury affecting the neural tissues may cause a brain damage. When a moving head (brain) strikes a stationary object, like a car hit one from behind it results in contrecoup injury.

The Blood-Brain Barrier

The blood-brain barrier (BBB) is a dynamic physiological structure that constitutes an interface between the vascular system and the neural tissues. It helps to maintain the constancy of the environment of the neurons in the CNS (similar barrier exists in the testes and placenta. Cerebral capillaries – have tight inter-endothelial connections which uniquely regulates the exchange of substances, prevent proteins from entering the brain in adults and slow the penetration of some smaller molecules. The BBB also help in the protection of the brain from exogenous and endogenous toxins in the blood and prevents the escape of neurotransmitters produced in the brain from entering into the general circulation. This is particularly important in newborn who may be exposed to some forms of infection and toxic substances to the brain because the BBB is not developed. This is important to note in the choice of drugs to be administered for the treatment of ailments involving the brain because not all drugs can penetrate the BBB.

Coronary Blood Flow

The coronary blood flow is phasic on the left coronary vascular bed. Flow occurs during the diastolic phase of cardiac contraction, and the flow approaches zero during the systole as a result of the strong contraction of the left ventricle. However, on the right coronary bed the flow is continuous. The coronary circulation is unique in that O_2 extraction is almost maximal already at rest, capillaries are open. The only possible way of increasing O_2 supply (due to increased demand during exercise) is the coronary vasodilation (sympathetic stimulation). Coronary blood flow is linked to myocardial oxygen consumption by metabolic mechanisms, where increased metabolism releases vasodilator metabolites.

Coronary Flow Reserve (CFR)

Coronary reserve is the maximum increase in blood flow through the coronary arteries above the normal resting volume. It increases with exertion compared to rest. A decreased CFR is an early sign of heart failure.

Ability of coronary vessels to adapt blood flow to the actual cardiac work (ergometry- which is the measurement and quantification of human physical performance. It is a measure of endurance capacity of an individual.

• the maximal blood flow / the resting blood flow

Reduction of the coronary reserve result from

- relative coronary insufficiency

- absolute coronary insufficiency (coronary heart disease)

Reduced coronary reserve is a limiting factor of the cardiac output, thus, also of the effort of organism

Measurement of coronary flow reserve is used in the treatment of conditions affecting the coronary arteries and to determine the efficacy of treatment.

Pulmonary Circulation

The volume of blood flow through the lungs is expected to be equal to the blood flow through all other organs in a healthy man. The functions of the pulmonary blood flow are to provide the exchange of gas, serve as blood reservoir and act as a mechanical, chemical and immunological filter. The vessels of the pulmonary circulation have peculiar characteristics to enable it perform its function. The arteries have bigger total cross-section, smaller thickness of the vessel walls and have high compliance.The capillaries are wide with abundant anastomoses forming a net surrounding alveoles, which improves the time of passage and area of perfused capillaries at rest and severe exertion while the veins have high compliance making it a reservoir of blood.

Blood flow in the lungs is regulated through three (3) mechanisms

i. The systemic mechanisms- neural (sympathetic and parasympathetic) and humoral (due to circulating substances relating to body fluids)

ii. Local mechanisms- which consist of chemical or metabolic auto-regulation which act in opposition to the systemic mechanisms leading to vasoconstriction.

iii. Passive factors- this is related to the cardiac output and the effect of gravity on blood distribution in the lungs.

The ratio of the perfusion versus ventilation is kept relatively constant by local metabolic autoregulation where the non-ventilated alveolus causes vasoconstriction and the non-perfused alveolus leads to vasoconstriction.

Cutaneous circulation

The blood flow through the skin varies considerably from as low as 0.02 L/min to as much as 5L/min. The function is to maintain heat balance especially as heat can diffuse through all vessels. It is one of the organs with compromised blood flow when there is low blood volume. This is why the colour of the skin could be used to

detect anaemia. It helps to maintain the metabolic needs of the skin, maintenance of body temperature (arteriovenous anastomoses), protection against the environment and maintenance of mean blood pressure.

The blood flow through the skin is controlled mainly by temperature changes initiated by the hypothalamic temperature control centre. This have direct effect of a temperature change on the vessel tone, excitation of skin thermoreceptors and excitation of thermoreceptors in brain. Warm temperature stimulates the anterior hypothalamus which leads to cutaneous vasodilatation with subsequent heat loss. This is the bases of tepid sponging to control fever particularly in children. However, cold leads to stimulation of the posterior hypothalamus with cutaneous vasoconstriction leading to heat conservation. In cold environment, the countercurrent heat exchange occurs between the arteries (containing warm blood) and the deep veins (were the cold blood flows).

Muscle circulation

The skeletal muscle makes up about 40% of the body weight. The resting blood flow to the muscles is about 15% of the cardiac output and it may increase by over 20x, that is, up to 90% during intensive and isometric handgrip exercise (Ogbutor *et al.*, 2022c). The muscle bloodstream makes a significant impact in the peripheral resistance of the body hence contributes in the regulation of the blood pressure. The flow during muscle activity is intermittent and may be near zero during tetanic contraction which explains the muscle cramp observed during intense exercise. The muscle blood flow is regulated by neural mechanism which dominates at rest causing vasoconstriction through sympathetic nerve activation and local chemical mechanism which dominate during physical activity causing metabolic vasodilatation. The flow is measured by venous occlusion plethysmography.

Splanchnic circulation

This refers to blood flow through the walls of the intestine (mesenteric bed), pancreas, spleen (splenic bed) and vessels of the liver (hepatic bed). It drains via hepatic vein into the inferior vena cava. The importance is for metabolic function of GIT, blood reservoir (at rest up to 20% of total blood volume) and other special functions such as the spleen acting to remove and degrade old/damaged erythrocytes)

The liver receives portal blood from the GIT and the spleen (which constitutes about 75% of the inflow to the liver) and oxygenated blood from the hepatic artery. Depending on the metabolic needs/ activity of the part of the GIT-secretion, absorption or muscle contraction during digestion and absorption of food, splanchnic circulation may increase by up to 50%

The regulation of hepatic blood flow is via neural mechanisms involving sympathetic stimulation which activates the vasoconstrictive fibres, metabolic with the release of adenosine - a vasodilator and passively by increase in blood pressure leading to passive dilatation of the portal veins radicles and increased liver blood amount.

Renal Circulation

The body considers the kidney as a very important organ due to the high filtration rate and increased vascularization as it contributes 0.3% of the body weight yet receives about 23.3% of the cardiac output (420mL/100g/min). The highest of any other organ in the body. The distribution of blood flow is irregular, the most flows through cortex, therefore decrease renal blood flow will affect the medulla more than the cortex.

The regulation of renal blood flow is via

i. Myogenic autoregulation- this dominates and help to maintain a stable renal filtration activity by ensuring stable blood flow at varying systemic blood pressure

ii. Neural mechanism- which responds to the demands of the systemic circulation. Increased sympathetic tone leads to decreased renal blood flow without a decrease in glomerular filtration rate (GFR).

iii. Humoral- contributes to regulation of systemic blood pressure and regulation of body fluids, Norepinephrine and epinephrine (from the adrenal medulla) causes constriction of affarent and efferent arterioles leading to decrease renal blood flow and GFR. Continual basal production of nitric oxide (NO) which is a vasodilator leads to stable renal blood flow and GFR same also with the production of prostaglandins (PGE2, PGI2), bradykinin which are vasodilators. They have minor impact under physiological conditions but important as non-steroidal anti-inflammatory agents during stress.

Foetal Circulation

In an adult life, oxygenated blood leaving the lungs has a haemoglobin saturation (HbO_2) of about 97.5% while that of mixed venous blood returning back to the heart has HbO_2 of about 70%. The fetus exists in a hypoxic environment in utero, which is responsible for their very high PCV level as hypoxia stimulates erythropoeisis. In foetal circulation the HbO_2 is below that of mixed venous blood.

The peculiarity of the foetal circulation include

i. The placenta serves the function of the lungs, for nutrient supply and for excretion of waste. The supplies from placenta to the foetus is via umbilical vein (which carries oxygenated blood) and send blood to it through the umbilical artery.

ii. The lungs are in collapsed form with the blood vessels compressed

iii. There is presence of foramen ovale also called foramen Botalli or the ostium secondum of Born (interatrial septal opening) which allow for the flow of blood from right atrium to the left atrium bypassing the lungs

iv. There is ductus arteriosus (vascular connection between pulmonary artery and aorta) and ductus venosus (which conveys blood from the umbilical vein and hepatic vein to the inferior vena cava). This bypasses the liver.

v. Foetal red blood cell contains foetal haemoglobin (HbF) which has higher affinity for oxygen hence easily extract oxygen from the placenta.

Changes after Birth

i. Closure of umbilical vein with a sudden increase in peripheral resistance and blood pressure, then contraction of musculature of *ductus venosus* and its closure

ii. The first inspiration which starts with the cry of the baby (due to asphyxia and cooling of the body) leads to decreased resistance of the lung bloodstream and subsequently, much more blood flows into lungs.

iii. Decrease of pressure in right atrium and its increase in left atrium due to:

- increased filling of left atrium by the blood from lungs
- decreased venous return to right atrium due to closure of umbilical vein
- left ventricle works against increased pressure in aorta

iv. Closure of foramen *ovale*

v. Closure of *ductus arteriosus*

vi. Closure of *ductus venosus*

Vascular Endothelium in Cardiovascular Control

Arteries and veins have 3 basic layers or tunics that surround a central blood-containing space, the lumen.

i. An innermost tunica intima

ii. A middle tunica media

iii. An outermost tunica externa /adventitia.

Capillaries contain only the tunica intima

The endothelium is a single layer of squamous endothelial cells that line the interior surface of blood vessels and lymphatic vessels. The endothelium forms an interface between circulating blood or lymph in the lumen and the rest of the vessel wall. Endothelial cells form the barrier between vessels and tissue and control the flow of substances and fluid into and out of a tissue

Endothelial cells are important constituents of blood vessels that play critical roles in cardiovascular homeostasis by regulating blood fluidity and fibrinolysis, vascular tone, angiogenesis, monocyte/leukocyte adhesion, and platelet aggregation which have important haemostatic significance.

The vascular endothelium is a key regulator of blood flow thus blood pressure. Endothelial cells play a major role in vascular biology by modulating both vasodilation and vasoconstriction through autocrine, paracrine and hormonal-like mechanisms and molecules such as nitric oxide, prostacyclin, endothelin, and thromboxane

In healthy blood vessels, the endothelial cell lining of blood vessels (the endothelium) controls vascular reactivity including blood pressure by releasing paracrine signaling molecules, such as nitric oxide (NO) and prostacyclin. Some components of human diet for example cabbage (*Brassica oleracea*) juice is known to down-regulate pro inflammatory cytokines involved in endothelial dysfunctions hence exhibit protective potentials to the endothelium (Asiwe et al., 2022).

A healthy vascular endothelium has a tightly regulated balance between pro- and antioxidants, vasodilators and vasoconstrictors, pro- and anti-inflammatory molecules, pro and anti-proliferative factors, and pro- and anti-thrombotic signals and substances during exercise (Ogbutor et al 2022c). Alterations in these balances induce changes leading to a diseased or dysfunctional endothelium that has lost its tightly regulated balances and displays pro-oxidant, vasoconstrictor, pro-inflammatory and pro-thrombotic properties.

Blood flow is regulated by

a. Acute (short term) factors

b. Long term factors

Short Term Factor- this explains that reduced oxygen availability to the tissues causes reactionary increased blood flow. This is explained by two (2) theories

i. Vasodilator theory

ii. Oxygen lack theory

Vasodilator Theory- this postulates that vasodilator substances are released in response to increased metabolism. Example is adenosine (very important in coronary flow) dilates the arterioles and cause increased flow. Others are lactic acid, CO_2, K^+, H^+ and histamine.

Oxygen Lack Theory-It explains that oxygen is required for the contraction of the vascular smooth muscles. At the arteriolar level there is low oxygen hence rather than contraction, dilatation occurs leading to increased blood flow.

Autoregulation help to maintain constant blood flow even in changing arterial pressure. Increased blood pressure stretches the vascular smooth muscle, this leads to the release of EDRF (nitric oxide) from the vascular endothelial cells, this relaxes the vessels causing vasodilatation and increased flow.

Long Term Factor- this involves changes in physical structure of the vessels, increased vascularization, oxygen and angiogenesis (development of new blood vessels)

Long term changes is in response to:

i. Ischaemia

ii. Rapid tissue growth (as in tumours)

iii. High tissue metabolism

Angiogenic factors include:

i. Angiogenin

ii. Endothelial cell growth Factor (ECGF)

iii. Fibroblast Growth factor

Endothelium Derived Relaxing Factor (EDRF) is a powerful vasodilator secreted by the endothelium. Many substances act through the releasing of EDRF for example acetylcholine, bradykinins, substance P and vasoactive intestinal peptide (VIP).

Substances released by vascular endothelium include:

i. EDRF

ii. Endothelin

iii. Prostacyclin

iv. Thrombomodulin

v. Interleukins

vi. Platelet derived growth factor (PDGF)

vii. Endothelial cell growth factor (ECGF)

viii. von willbrand factor (vWF)

The endothelium of blood vessels secretes these hormones that regulate blood vessel tone and protect against atherosclerosis and thrombosis. However, damage to endothelial cells, as well as disturbance of endothelial cell activities are the most critical events in the pathophysiology of cardiovascular disease. Endothelial cell dysfunction is characterized by anomalies in the production or bioavailability of endothelial-derived vasodilators, as well as excessive production of endothelial-derived vasoactive proteins (vasoconstrictors) which lead to negative alterations in vascular physiology which consequently result to cardiovascular dysfunctions and complications. It is established that some dietary supplements like *Ginkgo biloba* modulates the activities of the endothelium via oxidative and inflammatory mechanisms (Asiwe *et al*., 2023).

SUMMARY

The Cardiovascular system is a system composed of the Heart and a closed system of blood vessels inside which the blood circulates inside which the blood circulates. The functions of the cardiovascular system are mainly for transportation of nutrients and homoeostatic activity. The right and left sides of the heart pump blood through the pulmonary and systemic circulations, respectively.

The heart contains two pairs of one-way valves (atrioventricular and semilunar). The closing of the AV valves produces the first heart sound, or "lub," at systole. The closing of the semilunar valves produces the second heart sound, or "dub," at diastole The heart is a two-step pump. The atria contract first, and then the ventricles. When the ventricles contract at systole, the pressure within them first rises sufficiently to close the AV valves and then rises sufficiently to open the semilunar valves.

In the normal heart, action potentials originate in the SA node as a result of spontaneous depolarization called the pacemaker potential. The impulse then excites the atrioventricular node, from which it is conducted by the bundle of His into the ventricles. The Purkinje fibers transmit the impulse into the ventricular muscle and cause it to contract. The recording of this changing pattern caused by the heart's electrical activity is called an electrocardiogram (ECG). The P wave is caused by depolarization of the atria; the QRS wave is caused by depolarization of the ventricles; and the T wave is produced by repolarization of the ventricles. The ECG can be used to detect abnormal cardiac rates, abnormal conduction between the atria and ventricles, and other abnormal patterns of electrical conduction in the heart.

Cardiac output is a product of heart rate and stroke volume. There are physiological variations in cardiac output depending on the factors affecting either the heart rate or stroke volume. There are also pathological conditions that can affect the cardiac output. In humans, the determination of cardiac output is carried out using the Fick's principle.

Before 1900 infectious diseases and malnutrition were the most common cause of death particularly in sub Saharan Africa, but due to the westernization of our diet and sedentary life style As a result, new diseases have been imported which hitherto, was considered almost nonexistent in this environment. Cardiovascular diseases emerged as dominant chronic disease in Nigeria and other parts of the world. It is predicted to become the main cause of mortality and morbidity worldwide. One of the most recognized preventive measure to protect from this epidemiological transition is to avoid sedentary lifestyle and be involved in exercise and physical activity. This chapter affords one of adequate knowledge on the cardiovascular adaptations in health, exercise and disease geared towards a healthy life and optimal cardiovascular physiology. The knowledge and understanding of the distribution of the cardiac output to the various organs of the body and the circulatory changes of a newborn to the extra uterine life. Finally, this chapter explained succinctly the role of vascular endothelium through the release of vasodilators and vasoconstrictors in the control of the vascular reactivity in health and disease and associated vascular dysfunction

EXERCISES

1. Discuss the Physiological properties of he heart.
2. Write a concise on the mechanical events during a cardiac cycle.

3. With the aid of well-labeled diagram, describe the electrical events during a cardiac cycle.

4. Define cardiac output. Discuss the factors affecting cardiac output.

5. Describe the components of the vascular system and state their functions

6. Discuss capillary fluid exchange and its clinical significance

7. Classify systemic arterial blood pressure.

8. State the determinants of blood pressure.

9. Describe how to assess pulse pressure and state its clinical significance.

10. Describe how to measure blood pressure and state precautions to ensure accuracy of blood pressure figures.

11. Discuss jugular venous pressure and central venous pressure and the clinical significance of their assessment.

12. Describe renal and neural mechanisms of blood pressure control.

13. Explain the different parts of the heart and the direction of blood flow in the cardiovascular system?

14. What are the cardiovascular adaptations in Exercise and disease?

15. Discus the circulatory changes in a new born?

16. Explain the peculiarities in cerebral and coronary circulation?

17. Explain the role of the endothelium in the control of the cardiovascular system?

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Chapter 6

PHS 206. NEUROSCIENCE I

Victor D. Dapper, Jude N. Egwurugwu, Alhassan Abdulwahab

DEVELOPMENT AND GENERAL PLAN OF THE CENTRAL NERVOUS SYSTEM

Overview

The central nervous system (CNS) consists of the brain and the spinal cord. It is the part of the nervous system that integrates the information that it receives from, and coordinates the activity of, all parts of the body. The nervous tissue is extremely delicate and can suffer damage by the smallest amount of force. In addition, it has a blood-brain barrier preventing the brain from any harmful substance that could be floating in the blood. The nervous system has two main types of cells, namely neurones(nerve cells) and neuroglia or glial cells. The neurones are the functional and structural units of the nervous system. The glial cells are the supporting cells of the nervous system, they fill the spaces between the neurones, and play significant roles in maintaining the nervous structure. The cell membranes of the cells in the body have difference in electrical charges called membrane potential. We have three types of membrane potential: resting membrane potential, receptor potential and action potential. Resting membrane potential occurs in a cell at rest, not excited. Receptor potential occurs when a cell is excited but the stimulation is localized and the change in potential is decremental. Action potential occurs when the cell is excited, leading to generation of a propagated nerve impulse that travels along the entire length of the excitable tissue, The central nervous system gets information from the internal and external environments via sensory receptors. They are biological transducers. The reticular formation is a complex network of nuclei dispersed throughout the brainstem. Though anatomically not completely defined, it extends from the mesencephalon, through the medulla oblongata into the cervical spinal cord. For lack of clear boundaries of the its numerous nuclei, the reticular formation difficult fully delineate. It functions in motor control, cardiovascular control, modulation of pain, maintenance of consciousness, arousal and sleep and habituation. The Thalamus area pair of large ovoid organs that form most of the lateral walls of the third ventricle of the brain. It functions mainly to relay neural impulses from various peripheral receptors to the cerebral cortex.

The thalamus serves multiple functions including acting as a sensory relay station relaying visual, olfactory, auditory, sensory and proprioceptive information to cerebral cortex. It also regulates arousal sleep and wakefulness along with the reticular formation. It also acts to support of motor systems and processes sensory impulses necessary for motor control particularly at a subcortical level.

Objectives

The objectives of this section are to:

1. Describe the development and general plan of the central nervous system
2. State the divisions of the brain
3. Explain the generation of action potential in a nerve or muscle
4. Understand the types of membrane potential
5. Describe the conduction of action potential along a nerve fiber
6. Draw and label a typical motor neuron
7. Describe the main parts of a neuron and their respective functions

8. Describe the pathways that sensory systems follow into the CNS
9. Differentiate between the two major ascending pathways in the spinal cord
10. Describe the pathway of somatosensory input from the face and compare it to the ascending in the spinal cord
11. Explain the topographical representations of sensory information in at least two systems.
12. Explain what a sensory receptor is
13. Classify sensory receptors based structure, function, location, adaptation, and type of stimulus detected.
14. Describe at least five general properties of receptors
15. Outline general senses and special senses.
16. Understand the physiologic anatomy of the reticular formation
17. Understand the functional importance of the reticular formation
18. Describe the effects of lessons of the reticular formation
19. Understand the physiologic anatomy of the thalamus
20. Understand the functional importance of the thalamus
21. Describe the effects of lessons of the thalamus

Introduction

The CNS system involves 3 germinal layers: ectoderm, mesoderm, and endoderm.

The ectoderm is the key initiating player in the embryogenesis of the CNS. The ectodermis further sub-specialized as the

(1) surface ectoderm, which differentiates into the epidermis, nails, and hair. The ectoderm is also sub-specialized to form the

(2) neural ectoderm, which gives rise to the neural tube and neural crest, which subsequently give rise to the brain, spinal cord, and peripheral nerves.

The mesoderm is differentiated into 3 parts:

Paraxial mesoderm: This part of the mesoderm contains mostly somites which give rise to the axial skeleton, dermis, and muscle.

Intermediate mesoderm: This part of the mesoderm gives rise to the gonads, kidneys, andurogenital structures.

Lateral plate mesoderm is further classified into parietal mesoderm and visceral mesoderm, which give rise to the limb skeleton and muscular wall of the gut tube, respectively.

Development of the central nervous system

During 2 to 8 weeks of gestation, beginning with the trilaminar germ disc, which refers to the epiblast and hypoblast, the epiblast cells undergo an epithelial-mesenchymal transition that replaces the hypoblast. They also proliferate in the middle layer to form the mesoderm. The primitive streak then starts to appear superiorly from the thickened region of the ectoderm. It grows caudal to the cranial and induces notochord formation. The ectoderm then invaginates as cells migrate to form the primitive node and primitive pit where the notochordal process is formed.

The primitive pit is a depression at the center of the primitive node, which is an opening in the notochordal canal. The neural plate folds, via induction from the notochord, into the neural tube, which then becomes the neuroectoderm, which finally forms the CNS, namely the brain and spinal cord. The brain from cranial two-thirds of the segment and spinal cord from caudal one-third of the segment). Neural Crest cells form dorsal root ganglia and connective tissue in the head and neck.

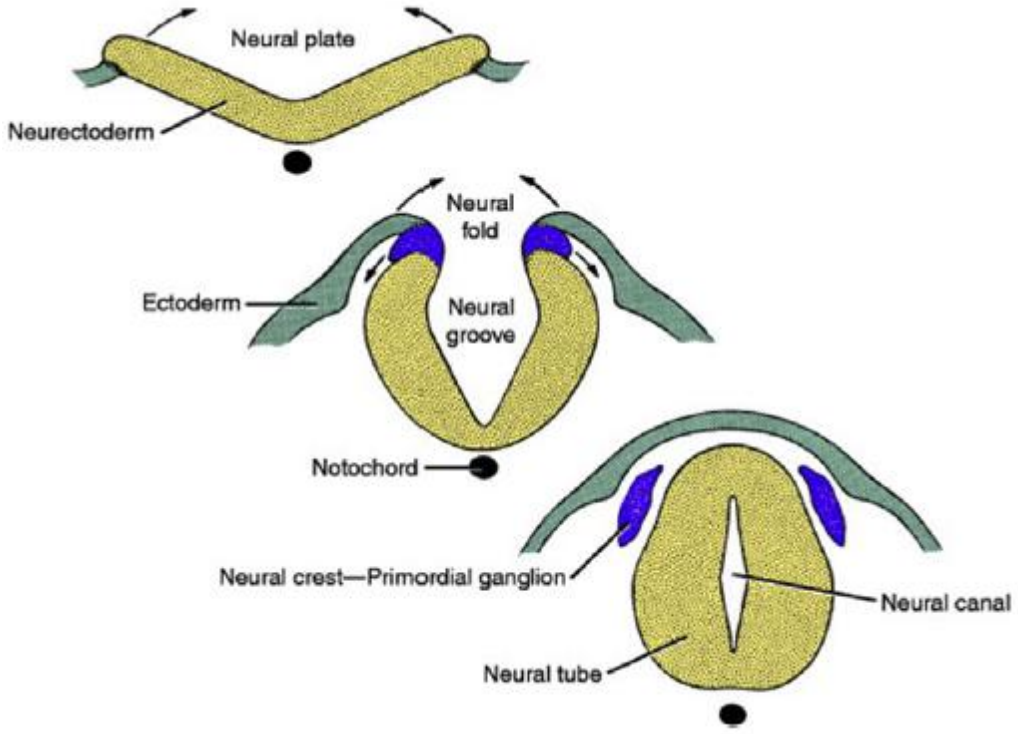

Figure 6.1: Development of the neural tube.

The notochord defines longitudinal axis, it forms parts of the intervertebral discs. The notochordal process formed on top of the primitive node and elongation of the notochordal process occurs caudally and goes upward to the cranial end.
The CNS is derived from the neuroectoderm: notochord induces the formation of the neural plate (thickening of the ectodermal layer), which further differentiates to form neural folds with aneural groove in between, leading to the formation of the neural tube (via neurulation).
The neural tube gets separated into an anterior and posterior end. The anterior end forms the primary brain vesicles, prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain), while the posterior end becomes the spinal cord. The primary brain vesicles continue to differentiate, creating secondary brain vesicles. The forebrain separates to form the telencephalon and diencephalon, and the hindbrain splits to form the metencephalon and the myelencephalon (spinal brain). The midbrain does not divide and stays the mesencephalon. The development of the secondary brain vesicles produces the adult brain structures
Telencephalon to cerebrum
Diencephalon to hypothalamus, thalamus, retina
Mesencephalon to the brain stem (midbrain)
Metencephalon to the brain stem (pons), cerebellum
Myelencephalon to the brain stem (medulla oblongata)
The central part of the neural tube forms continuous, hollow cavities known as ventricles.
The spinal cord, formed from the caudal portion of the neural tube, is composed of both gray and white matter. At 6 weeks of gestation, the gray matter begins to aggregate, forming the dorsal alar plate and ventral basal plate. Interneurons form from the alar plate, while motor neurons form from the basal plate. The dorsal root ganglia, which bring information from the periphery to the spinal cord, arise for the neural crest cells.

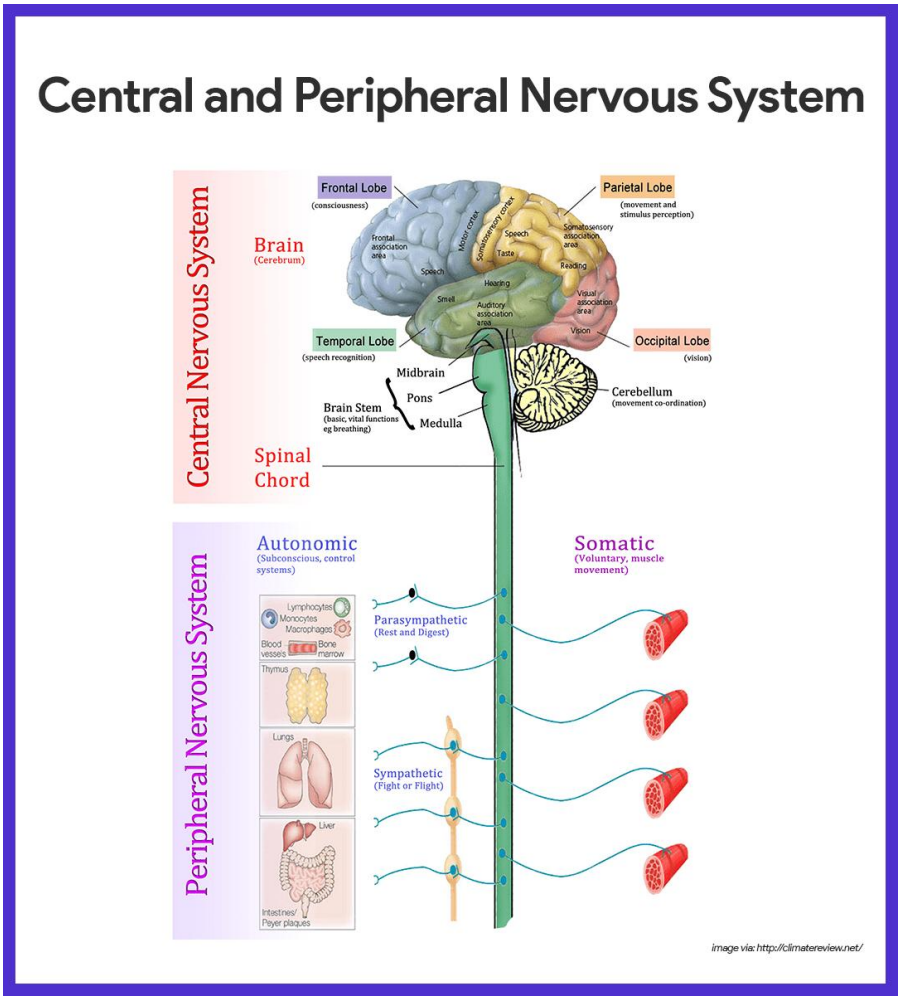

Figure 6. 2: Nervous system.

Between the vertebrae are the discs (intervertebral discs).

General plan of the central nervous system

During brain formation, there are 3 primary brain vesicles that differentiate into 5 secondary brain vesicles.

Prosencephalon, which becomes the forebrain: This later develops into the telencephalon (cerebral hemispheres, basal ganglia, hippocampus and amygdaloid nucleus) and diencephalon (thalamus, hypothalamus, epithalamus and subthalamus).

Mesencephalon, becomes the midbrain: This part of the brain undergoes little structure reorganization compared to the spinal cord and other brain vesicles.

Rhombencephalon, becomes the hindbrain: This part can be further divided into 3 segments:

Metencephalon: The dorsal growth of the cerebellum (integrates sensory information to fine-tune output) and pons.

Caudal myelencephalon: Similar to the structure of the spinal cord with “closed” central canal of Medulla.

Rostral myelencephalon: “Open part” of medulla; cerebrospinal fluid (CNF) is produced via choroid plexus and leaks into the subarachnoid space.

1. NERVE MORPHOLOGY

The nerve cell is one of the two main cells in the nervous system, the other being the glial cells. A neurone has varied shapes and sizes depending on their function and location. All neurones have three common parts: cell body, dendrites and axon.. The dendrites, axon and axon terminals make up the cell processes.

Functionally, there are three classes of neurones: afferent neurones, efferent neurones and interneurones.

Afferent neurons convey information from the tissues and organs of the body into the central nervous system.

Efferent neurons convey information from the central nervous system out to effector cells (particularly muscle or gland cells or other neurons).

Interneurons connect neurons within the central nervous system. They function as integrators and signal changers, integrate groups of afferent and efferent neurons into reflex circuits; lie entirely within the central nervous system and they account for 99 percent of all neuron. A typical motor neurone with myelinated axon is shown in Fig… below.

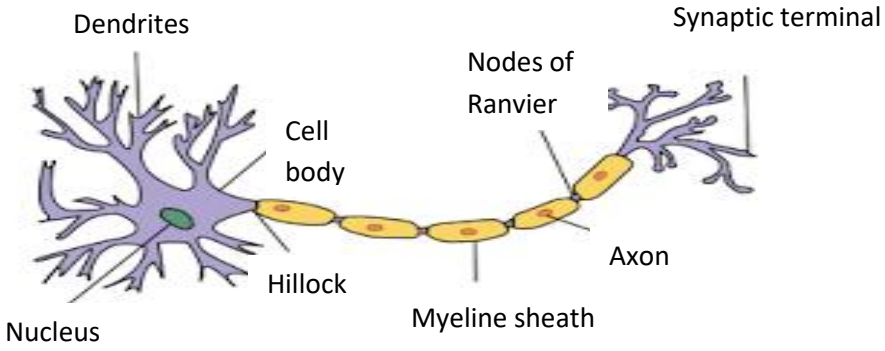

Fig 6.3: A motor neurone with myelinated axon

Dendrites

These are cytoplasmic projections or processes from the surface of cell body and they arborize extensively. Dendrites, especially in cerebral and cerebellar cortex, have smaller projections called dendritic spines, which are points of contact with other axons (neurone-neurones) or muscles(neuromuscular junction). Functions of dendrites include:

1. Receive and process information from another cell and transmit the message to cell body.
2. Contribute to neural functions, for example, action potential has been recorded in dendrites.
3. Can contribute to protein synthesis. Protein is usually synthesized in the cell body within the nucleus. However, some strands of mRNA can migrate into the dendrites, become associated with ribosomes in dendritic spines and produce proteins.

4. dendrites increase a cell's capacity to receive signals from many other neurons
5. Can contribute to learning and memory. Selective changes in dendritic spines can mediate one form of learning and long-term potentiation.

Cell body

The cell body, also called soma or perikyaryon contain nucleus, mitochondria, Golgi apparatus, Nissl bodies, neurofibrils and other organelles. Nissl bodies contain ribosomes and are concerned with protein synthesis in neurones. Golgi apparatus process and package proteins into granules.

Axon

The axon, also called nerve fiber is a single, slender, longer process that originates from a thickened portion of the cell body called axon hillock or initial segment, carries output to its target cells, ends as axon or synaptic terminals() where neurotransmitters are released. The initial segment is the "trigger zone"where electrical signals are generated if electrochemical events in the dendrites and/or cell body reach a threshold level.

These nerve impulses are propagated away from the cell body along the axon or sometimes back along the dendrites.

Its length ranges from a few micrometer to over a meter. Axons may have branches, called collaterals. The main axon and its collateral can undergo further branching, this increases the cell's sphere of influence.

Axons contain mitochondria, microtubules, neurofilaments and smooth endoplasmic reticulum.

Axon has two types: myelinated and unmyelinated. Myelinated axons are wrapped severally by myeline sheaths (a protein-lipid complex) at regular intervals. Nodes of Ranvier are areas along the axon where myeline sheaths are absent. Myelin sheaths insulates the axons, conserves energy and facilitates propagation of action potentials. In the PNS, myelin sheaths are formed by Schwann cells while oligodendrocytes form those in the CNS.

The functions of axons include:

a. Conducts electrical impulses away from neurone's cell body
b. As a long extension part of the nerve cell, it conducts electrical impulses toward the brain
c. It transmits information to different neurons, muscles or glands

Neuronal morphology play important roles in information processing in the nervous system.

The diverse morphology of axons and dendrites provides the basis for synaptic integration, signal transmission, network connectivity, and circuit dynamics.

2 GENERATION AND CONDUCTION OF ACTION POTENTIAL

The difference in the electrical charge across the cell membrane of cells in the body is called **membrane potential**. It arises due to changes in the conduction of ions across the cell membrane following alterations in ion channels. It depends on the trans-membrane ion concentration and ion permeability.

There are three types of membrane potential: resting membrane potential, receptor potential and action potential. Resting membrane potential is the membrane potential at rest when the cell is unexcited or inhibited. It develops due to differences in the composition of the ECF and ICF. Local or receptor potential are non-propagated potentials, designated depending on their location, and result from current flow due to localized change in ion channels that alter permeability to one or more ions.

Neuronal membrane has different types of ion channels which are selectively permeable to different ions. At rest, axonal membrane is more permeable to potassium ions than sodium ions. Thus, interior of the axon contains a high concentration of K and negatively charged proteins and low concentration of Na. Conversely, the exterior contains low concentration of K, a high concentration of Na, leading to formation of **concentration gradient.**

The concentration gradients across the resting membrane are maintained by the active transport of ions by the sodium-potassium pump which transports 3 Na+ outwards for 2 K+ into the cell. As a result, the exterior of the axonal membrane possesses a positive charge while its interior has negative charge and therefore is **polarised.** The membrane potential generated across the resting plasma membrane is called the **resting membrane potential.**

Application of adequate stimulus at a site on the polarized membrane, alters the ion channels, membrane at that site becomes freely permeable to Na. This leads to rapid influx of Na to the interior of the axon, neutralizing the RMP of -90mV to positive direction. Thus, there is reversal of polarity at that site, i.e., the exterior of the membrane becomes negatively charged while the interior becomes positively charged. The cell membrane is said to be **depolarized.** Depolarization can be described as **sodium influx.**

Soon after depolarization, the Na channels begin to close and K channels begin to open more than normal. This allows rapid efflux of potassium ions to the exterior of the cell, thus re-establishing the normal RMP to within 70% of its original value. This is called **repolarization** of the membrane.

This temporary change in membrane potential transmitted along the axon from its resting value of about -90mV to its peak and then repolarize to the RMP is called **ACTION POTENTIAL or NERVE IMPULSE.**

The sites ahead of the depolarized membrane region respond to the stimulation provided by the depolarized region close to it. As a result of the sodium ions being expelled from the cell, the previous membrane becomes depolarized again. As a result, there is conduction of impulses

The rise in the stimulus-induced permeability to Na+ is extremely shortlived. It is quickly followed by a rise in permeability to K+. Within a fraction of a second, K+ diffuses outside the membrane and restores the resting potential of the membrane at the site of excitation. The neuron is now ready for another round of stimulation and the sequence is repeated.

1. SENSORY PATHWAYS IN THE NERVOUS SYSTEM

Spinal nerves

Spinal nerves, generally, contain afferent axons from sensory receptors in the periphery, e.g., from the skin, mixed with efferent axons travelling to the muscles or other effector organs. As the spinal nerve approaches the spinal cord, it splits into dorsal and ventral roots. The dorsal root contains only the axons of sensory neurons, whereas the ventral root contains only the axons of motor neurons. Some of the branches will synapse with local

neurons in the dorsal root ganglion, posterior(dorsal) horn, or even the anterior(ventral) horn, at the level of the spinal cord where they enter.

Usually, spinal nerve systems that connect to the brain are contralateral, that is, the right side of the body is connected to the left side of the brain and the left side of the body to the right side of the brain.

Cranial nerves

Cranial nerves convey specific sensory information from the head and neck directly to the brain. For sensations below the neck, the right side of the body is connected to the left side of the brain and the left side of the body to the right side of the brain. Spinal information transmission **is contralateral** whereas, cranial nerve systems are mostly **ipsilateral.** Some cranial nerves that contain only sensory axons include olfactory, optic and vestibulocochlear nerves. Those that contain both sensory and motor axons include the trigeminal, facial, glossopharyngeal, and vagus nerves.

Somatosensory pathways

Somatic senses include touch, proprioception, pain and temperature. Somatosensory pathways carry somatosensory input up the spinal cord to the brain

Specific areas of the CNS coordinate different somatic processes using different sensory inputs and motor outputs of peripheral nerves. Important regions of the CNS that play roles in somatic processes can be divided into: spinal cord brain stem, diencephalon, cerebral cortex and subcortical structures.

Spinal cord brain stem

The sensory pathway that carries peripheral sensations to the brain is called **ascending pathway or ascending tract.** Various sensory modalities each follow specific pathways through the CNS. Tactile and other somatosensory stimuli activate receptors in the skin, muscles, tendons and joints throughout the whole body. Based on the location of receptor neurons, the somatosensory pathways are divided into two separate systems. Somatosensory stimuli from below the neck pass along the sensory pathways of the spinal cord whereas those from head and neck travel through the cranial nerves, specifically, the trigeminal system. The **dorsal column system**, also called **dorsal column-medial lemniscus** and the spinothalamic tract are the two pathways that transmit sensory information to the brain. The sensory pathways in each of these systems are made of three successive neurons.

The dorsal column system starts with the axon of a dorsal root ganglion neuron entering the dorsal root and joining the dorsal column white matter in the spinal cord. As axons of this pathway enter the dorsal column, they are so arranged such that axons from lower levels of the body position themselves medially, while axons from upper levels of the body lie laterally. The dorsal column is divided into two components tracts, the **fasciculus gracilis** that contains axons from the legs and lower body, and the **fasciculus cuneatus** that contains axons from the upper body and arms.

The axons in the dorsal column terminate in the nuclei of the medulla, where each synapses with the second order neuron in their respective pathways. The **nucleus gracilis** is the target of fibers in the fasiculus gracilis, while **the nucleus cuneatus** is the target of fibers in the fasiculus cuneatus. The second order neuron in the system projects from one of the two nuclei and then **decussates** or crosses the midline of the medulla. These axons then continue to ascend the brain stem as a bundle called **medial lemniscus**. These axons terminate in

the thalamus, where each synapses with the third order neuron in their respective pathways. The third order neuron in the system projects its axons to the postcentral gyrus of the cerebral cortex, where somatosensory stimuli are initially processed and the conscious perception of the stimulus occurs.

The spinothalamic tract also starts with neurons in a dorsal root ganglion. These neurons project their axons to the dorsal horn, where they synapse with second order neurons in their respective pathway. Axons from these second order neurons then decussate within the spinal cord and ascend to the brain and enter the thalamus, where each synapses with the third order neuron in its respective pathway. The neurons in the thalamus then extend their axons to the spinothalamic tract, which synapses in the postcentral gyrus of the cerebral cortex.

These two systems are similar in some ways:

a. Both begin with the dorsal root ganglion, as with most general sensory information. The dorsal column system is mainly concerned with touch sensations and proprioception, whereas the spinothalamic tract system is responsible for pain and temperature sensations.
b. The second order neurons in both of these pathways are contralateral, because they project across the midline to the other side of the brain or spinal cord. In the dorsal column system, decussation takes place in the brain stem; in the spinothalamic pathway, it takes place in the spinal cord at the same spinal cord level at which the information entered.
c. The third order neurons in the two pathways are essentially the same.
d. In both systems, the second order neuron synapses in the thalamus, and the thalamic neuron terminates at the somatosensory cortex.

The trigeminal pathway carries somatosensory information from the face, mouth, head and nasal cavity. The sensory pathways of the trigeminal pathway, each involve three successive neurons. At the first order neuron, axons from the trigeminal ganglion enter the brain stem at the level of the pons. These axons then project to one of three locations.

a. The spinal trigeminal nucleus of the medulla receives information similar to that carried by spinothalamic tract, such as pain and temperature sensations.
b. Other axons go to either the chief sensory nucleus in the pons or
c. The mesencephalic nuclei in the midbrain.

These nuclei receive information like that carried by the dorsal column system, such as touch, pressure, vibration, and proprioception.

Axons from the second order neuron decussate and ascend to the thalamus along the trigeminothalamic tract. At the thalamus, each axon synapses with the third order neuron in their respective pathway.

Axons from the third order neuron then extend from the thalamus to the primary somatosensory cortex of the cerebrum.

Diencephalon

The diencephalon lies below the cerebrum and includes the thalamus and hypothalamus. The thalamus is an important relay station for communication between the cerebrum and the rest of the nervous system. The

hypothalamus has somatic function, autonomic function and also communicates with the limbic system which controls emotion and memory functions.

Sensory input to the thalamus comes from most of the special senses and ascending somatosensory tracts. Each sensory system is relayed through a particular nucleus in the thalamus. The thalamus is a very important transfer point for most sensory tracts that reach the cerebral cortex, where conscious sensory perception starts. The only exception to this rule is the olfactory system, whose axons from the olfactory bulb project directly to the cerebral cortex, along with the limbic system and the hypothalamus.

The thalamus has several nuclei that can be categorized into three anatomical groups. The white matter running through the thalamus clearly defines the three major regions of the thalamus, these are: an anterior nucleus, a medial nucleus, and a lateral group of nuclei. The anterior nucleus serves as a relay station between the hypothalamus and the emotion and memory-producing limbic system. The medial nuclei serve as a relay station for information from the limbic system and basal ganglia to the cerebral cortex. The special and somatic senses connect to the lateral nuclei, where their information is relayed to the appropriate sensory cortex of the cerebrum.

Cortical processing

Many of the sensory axons are arranged in the same way as their corresponding receptor cells in the body. This makes for easy identification of the position of a stimulus on the basis of which receptor cells are sending information. The cerebral cortex also maintains this sensory topography in specific areas of the cortex that correspond to the position of the receptor cells. The somatosensory cortex provides a typical example, where the locations of the somatosensory receptors in the body are mapped onto the somatosensory cortex. This mapping is often shown using a **sensory homunculus.**

Homunculus refers to a map of the human body that is laid across a portion of the cerebral cortex. In the somatosensory cortex, the external genitals, feet and lower legs are represented on the media face of the gyrus within the longitudinal fissure. As the gyrus curves out of the fissure and along the surface of the parietal lobe, the body map continues through the thighs, hips, trunk, shoulders, arms, and hands. The head and face are just lateral to the fingers as the fissure approaches the lateral sulcus.

The cortex has specific regions that are responsible for processing specific information: visual cortex, somatosensory cortex, gustatory cortex, etc. In the cerebral cortex, sensory processing begins at the **primary sensory cortex**, then proceeds to an **association area**, and finally, into a **multimodal integration area**. For example, somatosensory information inputs directly into the primary somatosensory cortex in the postcentral gyrus of the parietal lobe where general awareness of sensation (location and type of sensation) begins. In the somatosensory association cortex, details are integrated into a whole.

SENSORY RECEPTORS

Sensory receptors are specialized structures capable of converting stimulus energy to nerve impulse or action potential. They are biological transducers, can detect changes in the environment(internal and external) and provide the central nervous system information from the environment. They are modified dendritic endings of sensory neurons, throughout the body, and monitor most general sensory information.

Despite the characteristic features of each sensory receptor, they can be grouped into two: general/somatic(somatosensory) senses and special senses. The general senses include touch, warmth, cold, pressure, vibration and proprioception while the special senses are for vision, hearing, taste, smell and balance.

Classification of sensory receptors

Sensory receptors can be classified based on: structure, location, adaptation and type of stimulus detected.

1. Structural receptor types
Sensory receptor cells that interpret information about the environment can be either

(a) a neuron with **free nerve ending** (dendrites) embedded in tissue that would receive a sensation, examples are pain and temperature receptors in the dermis of skin.
(b) (b) a neuron that has an **encapsulated ending** in which the dendrites are encapsulated in connective tissue that enhances their sensitivity, examples are lamellated and tactile corpuscles in skin dermis, that respond to pressure and touch or
(c) **Specialized receptor** cell, that has distinct structures that can interpret a specific type of stimulus. Retinal cells that respond to light stimuli are an example of a specialized receptor cell, a **photoreceptor**.

2. **Locational receptor types**
Sensory receptors can be classified based on their location relative to the stimuli.

1. **Exteroceptor** is one located near a stimulus in the external environment, e.g, somatosensory receptors located in the skin, receptors for touch, pressure, pain, temperatureand special sense receptors.
2. **Interoceptor(visceroceptors**) is one that detects stimuli from internal organs and tissues, such as receptors that sense increase in blood pressure in the aorta or carotid sinus, pH, oxygen level, CO, osmolality of body fluids, etc
3. **Proprioceptor** is a receptor located near a moving part of the body, e.g muscle or joint capsule, they monitor degree of stretch.
3.Functional receptor types

This is based on the stimulus detected by the receptor. This is the most commonly used method.

1. Mechanoreceptors- respond to mechanical forces such as compression or stretching of the receptor or of tissues adjacent to the receptor. Examples: meissener's corpuscles, free nerve endings, muscle spindle, Ruffini's endings, vestibular receptors etc.
2. Thermoreceptors- respond to temperature changes.
3. Chemoreceptors- detect chemical stimuli such as taste in the mouth, smell in the nose, oxygen levels in arterial blood, osmolality of body fluids, etc
4. Nociceptors- detect harmful stimuli that can lead to pain, e.g. free nerve endings.
5. Photoreceptors- detect light stimuli, examples are rods and cones located in the eyes.
6. Osmoreceptors respond to solute concentrations of body fluids.

4. Classification by Adaptation

Sensory receptors can be classified based on adaptation capability. Here, we have two types of receptors: fast(rapidly adapting) receptors and tonic(slowly adapting) receptors. Examples of rapidly adapting receptors include Pacinian corpuscles and Meissner's corpuscleswhile Merkel's cells, Ruffini endings, muscle spindle and nociceptors are examples of slowly adapting receptors.

Properties of receptors

Sensory receptors have some common properties.

1. **Transduction**
This is the main function of all sensory receptors, converting stimulus energy into nerve impulses that are then transmitted to certain regions of the brain, including the cerebral cortex. They act as biological transducers.

Transduction is a four-stage process. The stimulus causes:

a. a local change in membrane permeability once it is adequate, which in turn allows
b. The generator current to flow, leading to
c. a local hypopolarization, forming generator potential.
d. Finally, the generator potential leads to the propagated spike in the same or adjacent region of the membrane.
Generator potential can be summed both temporally or spatially, forming action potential or nerve impulse.

2. Adaptation of sensory receptors
Sensory receptors exhibit either whole or partial adaptation to any constant stimulus after a period of time. Adaptation or desensitization is the reduction in the amplitude of generator potential or the frequency of discharge of a sensory fiber due to application of a persistent, constant stimulus.

Receptors that adapt quickly are called **phasic receptors**, **rate receptors or movement receptors** while those that adapt slowly are called **tonic receptors.**

In slowly adapting receptors e.g. muscle spindle and Golgi tendon organ, receptor potentials are prolonged and decay slowly while those in rapidly adapting receptors e.g. hair receptors and parcinian corpuscle, quickly fall below the threshold.

In the eyes, the rods and cones adapt by changing the concentrations of their light-sensitive chemicals.

3. Law of Specific nerves energies: Muller's Law.
Sensory receptors are usually specific or selective in their response, being sensitive primarily to one form of energy. This particular energy or change in energy, forms the adequate stimulus and a receptor transforms or transduces this particular of stimulus into a change in membrane potential. Each type of sensory receptor responds to a specific sensation. For instance, pain receptors give response only to pain sensation. Stimulation of the optic nerve always evokes a visual sensation.

Each type of sensation also depends on upon the region of the brainits fibres terminate. Thus, specificity is due to the synaptic pathway within the brain that is activated by the sensory neurone. This ability of sensory receptors to function as sensory filters and be regularly stimulated by only one type of stimulus (the adequate stimulus) allows the brain to perceive usually the stimulus accurately.

Specificity of response is also called **Muller's doctrine** of specific nerve energies.

However, despite the specificity of nerve energies, some afferent nerve fibres can be excited by more than one modality. For example, skin receptors can respond to pain, touch, temperature sensations.

4. **Fatigue**

Fatique of a sensory receptor occurs when the receptor cannot respond further to a stimulus. A typical example of sensory receptor fatique is found in the auditory system.

5 Response to Increase in Strength of Stimulus- Weber-Frechner Law

During the stimulation of a receptor, to double the response given by the receptor, the strength of stimulus must be increased 100 times. This phenomenon is called **Weber-Frechner law,** which states that intensity of response(sensation) of a receptor is directly proportional to logarithmic increase in the intensity of stimulus.

Weber-Frechner law is derived as follows: $R = k \log S$.

Where

R = Intensity od response (sensation)

K = Constant

S = Intensity of stimulus.

6. Law of Projection.

When any particular site along the sensory pathway, from receptor to the cerebral cortex is stimulated, the sensation caused by the stimulus is always felt (referred) at the location of the receptor, irrespective of the site stimulated. This phenomenon is called the **Law of Projection**. For example, if somesthetic area in the right cerebral cortex, which receives sensation from left hand is stimulated, sensations are felt in left hand and not in the head. Sensation complained by amputated patients in the missing limb(phantom limb) is the best example of law of projection.

Reticular formation

Introduction:
The **reticular formation** is a complex network of nuclei located throughout the brainstem and neurons located in different parts of the human brain including the cerebellum and many other brain regions.Though anatomically not completely defined, it extends from the mesencephalon, through the medulla oblongatainto the cervical spinal cord. For lack of clear boundaries of the its numerous nuclei the reticular formation difficult fully delineate.
Physiologic anatomy of the reticular formation
Phylogenetically, the reticular formation constitutes part of the oldest portions of the human brain. It includes portions of the brainstem extending to the medulla oblangata and into the cervical spinal cord segments. It includes over 100 distinct brain stem nuclei with complex neuronal connections. These nuclei include the red nucleus, the nucleus reticularis tegmntipontis etc. This intricate array of neurons and nuclei enable the reticular formation to serve as a centre for many vital life functions and protective reflexes.

It can be divided into three columns: median raphe nuclei, medial gigantocellular reticular nuclei, and lateral parvocellular reticular nuclei. Serotonin is synthesized in the medial raphe nuclei and plays an important role in mood regulation. The gigantocellular nuclei are involved in motor coordination. The parvocellular nuclei regulate respiratory activities.

Functionally, the reticular formation is composed of two major neuronal systems, these are
Ascending reticular activating system (ARAS): The ascending reticular activating system (ARAS) or simply the *reticular activating system* (RAS). This is a system responsible for regulating wakefulness and sleep-wake transitions. The ARAS is composed of various nuclei in the thalamic nuclei and several dopaminergic, noradrenergic, serotonergic, histaminergic, cholinergic, and glutamatergic neurons.

Descending reticulospinal tracts: The **reticulospinal tracts** descend from the reticular formation in two tracts and unto the motor neurons of the spinal cord and therefore the reticulospinal tracts controls locomotion and posture

Functions of the reticular formation and the reticular activating system
The functions of the reticular formation **and the reticular activating system**includes the following:

1. Motor control
   The reticular formation is involved in somatic motor control. Specifically, the reticulospinal tracts function in the maintenance of muscle tone, posture and balance. The reticular formation also relays impulses to the cerebellum and are important for the integration of visual, auditory and vestibular sensations with motor functions.
2. Cardiovascular and respiratory control
   The vasomotor and cardiac centers are located in the medulla oblangata and are functional components of the reticular formation. Both centres regulate cardiac and cardiovascular functions. The reticular formation is also involved in respiratory control particularly the parvocellular nuclei.
3. Modulation of pain
   All sensations of pain pass through the reticular formation to reach the cerebral cortex. This is part of the arousal functions of the reticular formation. The reticular formation via the descending analgesic pathways acting at the spinal cord can block the transmission of some pain signals to the brain thereby acting to modulate the pain sensation.
4. Wakefulness, arousal, consciousness, and mood regulation
   Reticular projections to the thalamus and the cerebral cortex enable the control of stimulatory impulses to the cerebrumthus playing a critical role in ensuring arousal, alertness and the maintenance of consciousness. Injury to the reticular formation may result in altered states of consciousness. The ascending reticular activating system (ARAS) plays an essential part in the maintenance of the state of consciousness and contributes to wakefulness and arousal.
5. Sleep and sleep-wake cyclesincluding circadian rhythms.
   Conversely, the reticular formation is important for achieving sleep. Sleep results with be a reduction in ascending afferent activity reaching the cortex by suppression of the ARAS. The distinct differences in the brain's electrical activity during periods of wakefulness and sleep is brought about by the ARAS. For instance, low voltage fast burst brain waves are associated with wakefulness and rapid eye movement (REM) sleep while high voltage slow waves occur found during non-REM sleep. Furthermore, physiological change from deep sleep to wakefulness is reversible and is mediated by the ARAS.During sleep, ARAS neurons fire less and conversely fire more during the waking state.

6. Habituation, alertness and attention
   The reticular formation by regulating the volume of sensory impulses reaching the cerebral cortex enables an individual to ignore unnecessary sensory information or impulses from the surrounding environment. This phenomenon is called habituation. The ascending reticular activating system helps modulate the cerebral cortex to achieve habituation particularly during periods requiring high attention. There is increased regional blood flow in the reticular formationand thalamic intralaminar nuclei during periods of alertness and attention.

Clinical significance of the reticular system:

1. Lesions of the reticular system or the ascending reticular activating system (ARAS) causes alterations in consciousness and if severe may lead to coma or death.
2. Studies suggest that some direct relationship between the ascending reticular activating system (ARAS) and physiological pain pathways indicating that the system may be able to modulate pain.

Thalamus
Introduction

The Thalamusarea pair of large ovoid organs that form most of the lateral walls of the third ventricle of the brain. It functions mainly to relay neural impulses from various peripheral receptors to the cerebral cortex. Thethalamus thus plays as essential role in relay of sensory visual, auditory, somatosensory, and gustatory systems to the cerebral cortex. The thalamus also playroles in motor coordination and emotions. In association with the reticular system it also functions inmemory, arousal, and other sensorimotor association functions consciousness, sleep and alertness.

Physiologic anatomy of the thalamus
Anatomically, the thalamus are paired structure of gray matter that lies deep within the brain, adjacent to the third ventriclewith nerve fibers projecting out to the cerebral cortex in all directions. The medial surface of the thalamus constitutes the upper part of the lateral wall of the third ventricle, and is connected to the corresponding surface of the opposite thalamus by a flattened gray band, the interthalamic adhesion. The lateral part of the thalamus is the phylogenetically newest part of the thalamus (neothalamus), and includes the lateral nuclei, the pulvinar and the medial and lateral geniculate nuclei.There are areas of white matter in the thalamus including the stratum zonale that covers the dorsal surface, and the external and internal medullary laminae. The external lamina covers the lateral surface and the internal lamina divides the nuclei into anterior, medial and lateral groups.The thalamus is connected to the spinal cord via the spinothalamic tract and many connections to the hippocampus via the mammillothalamic tract. The spinothalamic tract is a sensory pathway originating in the spinal cord. It transmits information to the thalamus about pain, temperature, itch and crude touch. There are two main parts: the lateral spinothalamic tract, which transmits pain and temperature, and the anterior (or ventral) spinothalamic tract, which transmits crude touch and pressure. The thalamus is also connected to the cerebral cortex via the thalamocortical radiations.

Physiologic functions of the thalamus

The thalamus serves multiple functions. These include the following:

1. A sensory relay stationrelaying visual, olfactory, auditory, sensory and proprioceptive information between subcortical areas and the cerebral cortex.
2. Regulation of arousal, sleep and wakefulness working with the reticular formation.
3. A support for the motor systems by processing sensory impulses necessary for motor control especially at the subcortical level.
4. Memory functions of the thalamus involves recollective and familiarity.

Clinical significance of the thalamus

1. Thalamic pain syndrome results from thalamic injury from a cardiovascular accident. The symptoms include a one-sided burning or aching sensation associated often with mood swings.
2. Alcoholic Korsakoff syndrome results from damage to the mammillary body, the mammillothalamic fasciculus or the thalamus in association with alcoholism causing Vitamin B 1 deficiency.
3. Fatal familial insomnia is a hereditary disease associated with degeneration of the thalamus. Symptoms include inability to sleep (insomnia) which may become fatal.
4. Thalamic damage can result in coma.

Summary

In summary, development of the central nervous system begins from week 2 of gestation. Neural ectoderm gives rise to the neural tube and neural crest, which subsequently give rise to the brain, spinal cord, and peripheral nerves. The neural tube gets separated into an anterior and posterior end. The anterior end forms the primary brain vesicles, prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon (hindbrain), while the posterior end becomes the spinal cord. The primary brain vesicles continue to differentiate, creating secondary brain vesicles. The forebrain separates to form the telencephalon and diencephalon, and the hindbrain splits to form the metencephalon and the myelencephalon (spinal brain).

Neurones are the functional and structural units of the nervous system. There are 3 functional groups: afferent (motor), efferent (sensory and interneurones. Neurones have varied shapes and sizes, though have three common features: cell body, dendrites and axons. Cell body contains nucleus and other organelles, produce proteins. Dendrites are cytoplasmic projections, receive and process information from other cells, contribute to protein synthesis, learning and memory. Axons are single, slender tube-like structures that arise from initial segment (axon hillock), conducts impulses away from cell body to target cells.

There are three types of membrane potential: resting membrane potential, local potential and action potential. Three processes are involved in the generation and conduction of action potential: polarization, depolarization and repolarization. In polarized condition, the nerve fiber is in a resting state, the exterior is positively charged, interior is negatively charged, no net flow of current. In a depolarized state, the opposite is true. Neuronal stimulation leads to transformational change in ion channels, sodium becomes more permeable, interior becomes positively charged, exterior negatively charged. Depolarization is an undersirable state, hence within seconds, K permeability increased, rapid K efflux, restoration of the resting state. Nerve impulse travels along the axon, synapse and neuromuscular junction before reaching its target. The period between depolarization and repolarization is the refractory period.

Sensory receptors are biological transducers, that convert stimulus energy to nerve impulses. They detect changes in the environment(internal or external) and transmit to the CNS about the environment.

Can be classified based on location, structure, stimulus detected and adaptation.

Sensory receptors have certain characteristic features such as transduction and adaptation. They obey the laws of projection, Weber-Frechner law, and Muller's law.

The following regions of the CNS play important role in somatic processes: spinal cord brain stem, diencephalon, cerebral cortex and subcortical structures. Ascending pathway or ascending tracts is the sensory pathway that carries peripheral sensations to the brain.

The Dorsal column system and spinothalamic tract are the two major pathways that bring sensory information to the brain. In each of these systems, the sensory pathways are composed of three successive neurons.

1ST order neuron: cell body in spinal cord or brainstem, synapses with 2nd order neuron

2nd order neuron: cell body in thalamus, project onto 3rd order neurons in thalamus

3rd order neurons: cell body in thalamus, sends signals to somatosemsory cortex.

Each receptor type conveys a distinct sensory modality to integrate into a single perceptual frame eventually. This information is achieved by the conversion of energy into an electrical signal by specialized mechanisms. In this report, we will discuss a basic overview of sensory systems, focusing on sensory receptors.

Sensory receptors are generally highly analytical.

The reticular formation is a complex network of nuclei dispersed throughout the brainstem. Though anatomically not completely defined, it extends from the mesencephalon, through the medulla oblongatainto the cervical spinal cord.The functions of the reticular formation **and the reticular activating system** functions in motor, cardiovascularand respiratory control, pain modulation, Wakefulness, arousal, consciousness, and mood regulation, Sleep and sleep-wake cycles including circadian rhythms Habituation, alertness and attention.

The Thalamus area pair of large ovoid organs that form most of the lateral walls of the third ventricle of the brain. It functions mainly to relay neural impulses from various peripheral receptors to the cerebral cortex. The thalamus serves multiple functions including relay of visual, olfactory, auditory, sensory and proprioceptive information between subcortical areas and the cerebral cortex, regulation of arousal, sleep and wakefulness working with the reticular formation, support for the motor functions and memory particularly recollective memory and familiarity.

EXERCISE

1. Briefly describe the development of the central nervous system
2. State the divisions of the brain
3. What is a neurone?
4. With the aid of a well-labelled diagram, describe a motor neurone
5. State the common parts of a neurone and their functions
6. Mention the main functional classes of neurones and their functions
7. What is membrane potential?
8. State the three types of membrane potential and write short note on any two
9. Outline the sequence of events that lead to generation and conduction of nerve impulse.

10. Describe the dorsal column system
11. Describe the spinothalamic tract system
12. Describe the trigeminal pathway
13. What is a sensory receptor?
14. Classify the sensory receptors
15. Describe the common properties of sensory receptors
16. What is the reticular formation
17. Describe the functions of the reticular system or the ascending reticular activating system (ARAS)
18. How does the reticular system ensure alertness and attention?
19. Describe the physiologic functions of the thalamus
20. What isthe clinical significance of thalamic lesions?

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Chapter 7

PHS 207. PHYSIOLOGY PRACTICAL I

Maisaratu A. Tukur, Ahmed I. Salisu, Adesoji A. Fasanmade, Aliyu Mohammed, Walter C. Nwafia, Victor D. Dapper

OSMOTIC FRAGILITY OF RED BLOOD CELL

Introduction

Osmotic fragility is the ability of the red blood cells to resist haemolysis when exposed to fluid of varying hypotonicity. The osmotic fragility is affected by cell size, surface area to volume ratios, cell membrane integrity and composition. The test is conducted to aid in the diagnosis of disorders linked to red blood cell abnormalities such as hereditary spherocytosis and hypernarremia. Osmotic fragility is decreased in hereditary xerocytosis, thalassemia, iron deficiency anemia, sickle cell anaemia, chronic liver disease and polycythemia vera. Normal blood undergoes partial haemolysis at 0.45% and complete haemolysis at 0.30% of NaCl.

Aim: To assess the presence or absence of spherocytes and evaluate the integrity of the red blood cell membrane exposed to osmotic stress.

Principle: At room temperature, red blood cells volume changes in hypotonic and hypertonic solutions. Cells with low surface area-volume ratio are more osmotically fragile in hypotonic solutions than normal RBC with discoid morphology.

Materials required: Sodium chloride, blood sample in EDTA bottle, 16 test tubes (5ml), Centrifuge, Analytical balance, measuring cylinder, Colorimeter, cuvette, dropper and beaker.

Methodology:

a. Preparation of Stock Concentration of 1% sodium chloride (NaCl)

Weigh 1g of NaCl and make up to 100ml with distilled water to have a stock concentration of 1% NaCl.

b. Preparation of Hypotonic Concentrations from 1% sodium chloride (NaCl)

Assume that you have 10 ml of 1% NaCl and you are required to prepare 5ml of each the following concentrations 0.1-0.9 % of NaCl.

For 5 ml of 0.1% NaCl

$\frac{0.1}{1} \times 5$ = 0.5ml of 1% NaCl + 4.5ml of D/H_2O

Calculation of concentration of NaCl

No of Test Tube	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Vol. of NaCl(ml)	0.5	1	1.5	1.75	2	2.25	2.5	2.75	3	3.25	3.5	3.75	4	4.25	4.5	5
Vol. of DiH_2O(ml)	4.5	4	3.5	3.25	3	2.75	2.5	2.25	2	1.75	1.5	1.25	1	0.75	0.5	00
Conc. of NaCl (%)	0.1	0.2	0.30	0.35	0.40	0.45	0.50	0.55	0.60	0.65	0.70	0.75	0.80	0.85	0.90	1

Procedure

1. Arrange and label the test tubes (1-16) on test tube rack.
2. Transfer 5 ml of the various concentrations of NaCl (0.1-1%) into test tubes 1-16 respectively.
3. Mix the blood thoroughly
4. Use micropipette to aspirate 0.05 ml of blood
5. Dispense the blood into Test-tube No.16 with 1% NaCl
6. Repeat the blood aspiration and dispense into test tubes 1-15 (0.1-0.9%) respectively.
7. Mix thoroughly and allow to stand for 30 minutes as shown in figure 1A or transfer to centrifuge and spin for 5 minutes at 2000g revolutions per minute
8. Record your observation as partial, complete and no haemolysis as in Fig.1B
9. Decant the supernatant into the cuvette
10. Transfer the cuvette into Colorimeter and read the absorbance at 540 nm.
11. Record your results and calculate percentage haemolysis.
12. Plot Osmotic fragility curve

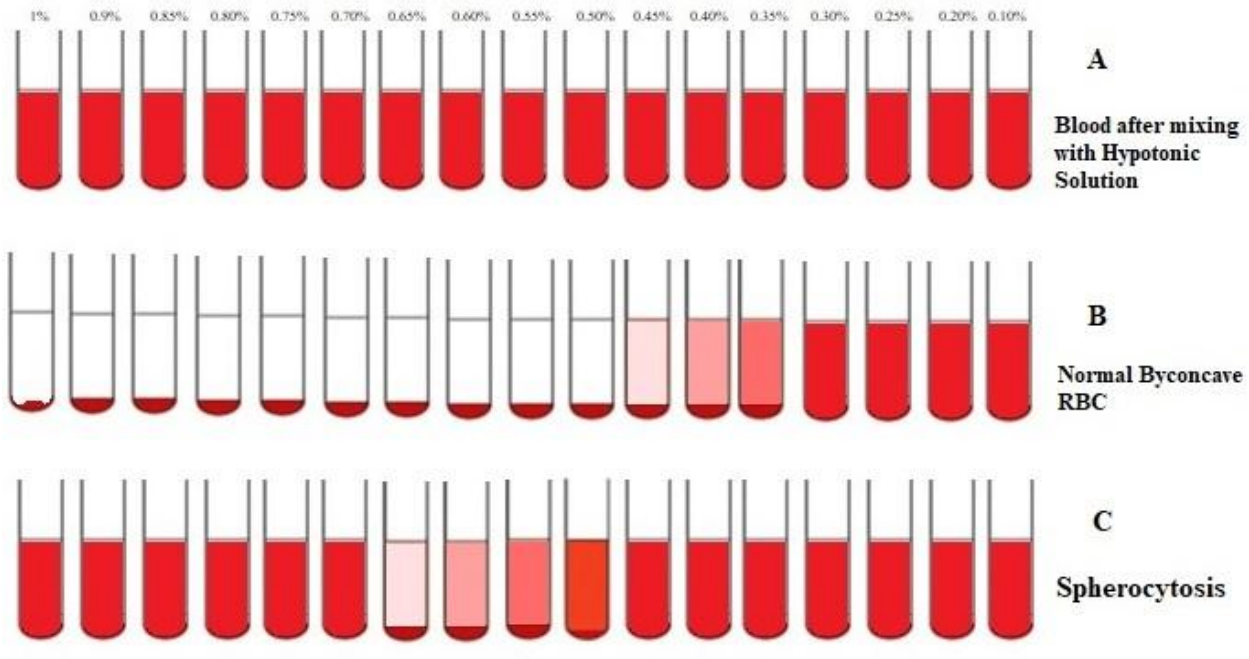

Fig. 7.1 Title??

Alternative Method of Osmotic Fragility Test of Red Blood Cell

1. Use the blood provided
2. Dilute the blood with Hayems' fluid
3. Count the red blood cells in the sample
4. Dilute the blood with 0.45% NaCl and
5. Count the red blood cells in the sample
6. Compare the RBC count in 2 with 4

CLOTTING (COAGULATION) TIME

Material

Stop clock, non- heparinized capillary tube, glass slide, office pin

Capillary blood clotting time

1. From a finger prick, fill in the plain capillary tube to the brim by capillary action

Fig. 7.2 A and B: Title??

2. Note the time the blood start to enter the plain capillary tube
3. Keep the capillary tube between the palms of your hands to maintain the blood near the body temperature
4. At interval of 30 seconds, break and separate about 1 cm of the capillary tube

Fig. 7.3: Title??

5. Look out for thread like fibrin from each broken piece.
6. Repeat the process until fibrin is seen
7. Count the number of broken pieces and divide by two

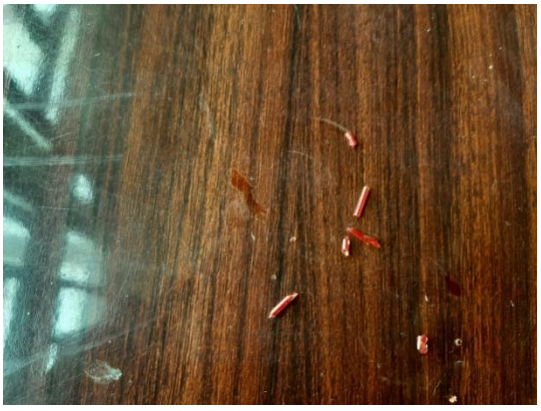

Fig. 7.4: Title??

8. Express result in minutes

Normal clotting time: 3-6 minutes

Drop Method of Capillary blood clotting time

1. From a finger prick, place a drop of blood at the centre of clean, grease free glass slide

Fig. 7.5: Title??

2. Use the cap of an office pin to draw (strike out) blood from the centre to the periphery

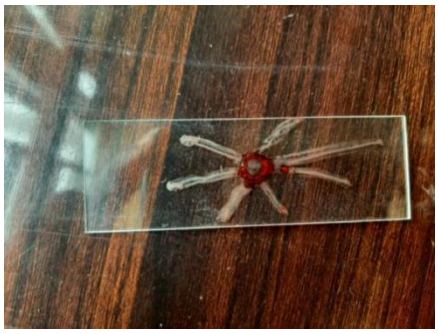

Fig. 7.6: Title??

3. Repeat the process after every 30 seconds until a thread like fibrin is observed
4. Count the number of strokes and divide by two

Normal clotting time: 2-4 minutes

PROTHROMBIN TIME

Materials

Water bath, calcium chloride (0.02M), activated thromboplastin, pipettes, test tubes (2ml), and fresh plasma.

Procedure

1. Place 0.10 ml of activated thromboplastin into a test tube. Add 0.10ml of 0.02 calcium chloride into the tube. Place the tube into water bath and incubate for one minute at 37^{o}C
2. Add 0.10 ml of warm plasma into the mixture in the tube in step 1 above and start timing
3. Gently shake the mixture continuously in the water bath for 10 seconds
4. Quickly remove the tube from the water bath and expose it to bright light. Tilt the tube back and forth until a thread like fibrin appears.
5. Record the time it takes for the fibrin emerge.

The normal time at 37°c is about 4 minutes but it can vary between 3 and 10 minutes.

BLEEDING TIME

It is the time taken for blood to spontaneously cease to flow from a punctured skin unassisted. This is an *invitro* test for platelet function. The time is prolonged in purpura, platelet deficiency and vessel wall defects but normal in Haemophlia.

Materials

Stop clock, sterile disposable lancet, blotting paper, cotton wool, methylated spirit, and sphygmomanometer

Dukes' Method of Bleeding Time

Procedure

Scrub and disinfect the tip of the middle finger or the tip of the ear lobe with cotton wool soaked in methylated spirit

Prick the disinfected portion with lancet start and timing immediately

Fig. 7.7: Title??

Use the blotting paper to absorb blood from the site of puncture after every 30 seconds until when there is no trace of blood spot

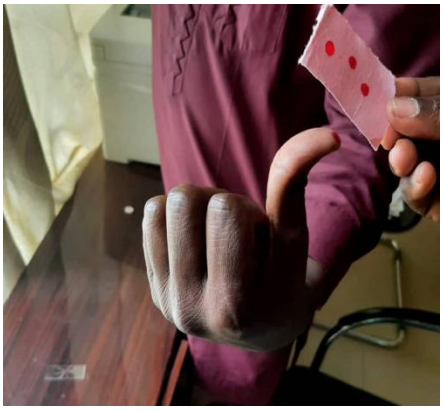

Fig. 7.8: Title??

Count the number of blood blot on the paper and divide by two

Express your result in minutes

Normal bleeding time: 1-5 minutes

It is increased in purpura, in which the coagulation time is normal. It is normal in hemophilia and similar blood coagulation disorders.

Discuss the difference between the bleeding time and the coagulation time. On what factors do they depend?

DETERMINATION OF TOTAL WHITE BLOOD CELLS

Principle: a known quantity of blood is taken and diluted with a given quantity of a dilution fluid. A drop of this is taken and placed on the counting chamber, and under the microscope, the cells are counted.

Materials required: Haemocytometer, Neubauer counting chamber, sterile blood lancet, 70% alcohol, Turk's solution, cover slip, microscope, cotton gauze,

Procedure:

- Take a drop of the given sample of blood (or obtain it from the subject by a prick of the pulp of the finger).
- With a pipette, suck up the blood, up to the 11 mark on the pipette
- Mix the blood in the pipette with the Turk's solution by rotating the pipette for about 3mins, between the palms of your hand. (Turk's sfluid is 2%glacial acetic acid, and 1% gentian violet)
- Put some drops of blood on the graduated region of the counting chamber gently under the cover slip (allow the cover slip and the blood to rest well without air bubbles)
- Turn to the lower power objective (x10) of the microscope.
- Count the cells in the four big squares of the graduated region od the chamber.

Note:

The appropriate dilution ratio is 1:20.

Volume of chamber = 4/10 mm^3

1 mm^3 will contain N x 20/0.4

i.e., N x 50cell/mm^3

DIFFERENTIAL WHITE BLOOD CELLS COUNT

Materials required: microscope, slides, Leishman's stain, oil immersion, filter paper, stop clock, pipette, tally counter, staining rack.

Procedure:

- Clean and dry two slides
- Prick the finger of the subject, and apply it to the edge of the slide
- Quickly place the slide on the slide, holding it between the index finger and the thumb. Place the edge of the second slide at an angle of 45^o on the blood, and carefully spread the blood.

- After spreading the blood, allow the slide to drug. Examine the slide to be sure the cells are in the proper places.
- Stain with Leishman's stain; cover the dry film with the stain, and leave for two minutes, uniformly spread with an equal quantity of distilled water. Allow to stand for about 10 minutes. Pour off the mixture of water and the stain. Then dry the back of the slide with filter paper.
- Examine under low power (x10) microscope, and later under the high magnification for the differential counts. A drop of immersion oil is placed on the dry film, and examined.

Note:

Characteristics of the differential cells:

- Neutrophil: multisegmented nucleus with 3 to 5 lobes, joined with chromatin starnds. Cytoplasmic granules are tiny, many and stain pink, otr a ground glass appearance.
- Eosinophil: bilobed nucleus, large granules, brick red granules.
- Basophils: large dark blue /blackgranules scattered in the cytoplasm obscuring the nucleus
- Lymphocytes: two small or large outline. Central nucleus, dense chromatin and scanty cytoplasm. Sky blue cytoplasm.
- Monocytes: indented nucleus/kidney shaped, eccentric. Nuclear chromatin is a loose fine meshwork. Cytoplasm is vacuolated and has a grey frosted appearance.

DETERMINATION OF BLOOD GROUPS AND DIRECT CROSS MATCHING TEST

- Blood groups refer to the presence or absence of certain antigens on red cell membranes, the so called blood group factors. There are a large number of different blood groups antigens. They are inherited characteristics. The two classifications which are of most important in the transfusion of blood are the ABO and Rhesus system. You are going to determine which blood group of the ABO system you belong to.
- REAGENTS AND APPARATUS REQUIRED
- Anti A, Anti-B, Anti AB and Anti D (are provided for your use)
- Your own blood (by finger prick)
- Tiles or glass slide and glass marking pencil
- Glass rod with tips rounded off
- Microscope

- The blood sample for determination of blood group may be obtained by: -
- Finger prick; A small drop of whole blood or an isotonic saline cell suspension may be used for the test or Venipuncture and then treated with double oxalate.

PROCEDURE:

- DETERMINATION OF ABO GROUPS; (CLASSICAL BLOOD GROUPS)
- Slide or tile techniques used in the labs
- The test tube techniques - used in the blood bank (more blood is needed).
- Slide or tile method: - cells and sera may be examined on slide or tile by mixing a drop of appropriate cell suspension and serum (as the case of the test tube method)
- First, suspension of red cells in a normal saline (0.9%) sodium chloride is prepared.
- Two clean glass slide are taken and they are divided into two (2) equal position
- Test control Test control
- Anti A + saline Anti B + saline
- Red cell Red cell Red cell Red cell
- Suspension Suspension Suspension Suspension
- Note: Anti-A serum refers to serum from a group B person (donor) and this serum contains A agglutinin.
- On slide 1
- On the right hand side, a drop of saline and red cell suspension is placed.
- On the left hand side, a drop of anti A serum and red cell suspension are placed.
- On slide 2
- On the right hand side same as that in slide - I
- On the left hand side, A drop of anti-B serum
- And red cell suspension is placed on each of them.
- The contents are mixed separately using separate stirrers
- After mixing, a cover slip is placed on it and examined under the low power objective of the microscope, confirm agglutination (clumping). (Never coagulation).

ON EXAMINATION: If clumping or agglutination occurs with anti A and not with anti-B, the group is A if there is clumping with anti B but not with Anti A then, the group is B. In case of AB group there will be clumping in both, but when there is NO clumping in both then the group is O.

DETERMINATION OF PACKED CELL VOLUME OR HAEMATOCRIT

Definition and aim: The Packed cell volume or Haematocrit is the percentage of the volume of blood occupied by cells, particularly red blood cells. This experiment aims to determine the PCV amongst a cohort of healthy subjects.

Introduction: Blood is composed of two parts: a fluid portion called plasma and a cellular portion occupied by formed elements called cells. The cells are mainly red blood cells. Uncoagulated can easily be separated into a straw-colored fluid and clear portion called plasma and red-colored lower portion composed of red blood cells. These two portions are separated by a sometime unclear portion called the buffy coat occupied by the white blood cells. This process occurs normally if blood is left undisturbed under the influence of gravity, but can be quickened by the mechanical centrifugation of a sample of whole blood. The ratio of the red cells to plasma is the packed cell volume or haematocrit and is expressed as a percentage or fraction of whole blood. The Haematocrit is useful as a simple, routine and field screening test for anaemia. It is also a rough estimate for haemoglobin concentration and can be used for calculation of the various corpuscular indices.

Apparatus and Materials: Human subjects, heparinized capillary tubes, lancets, plasticine, Hawksley micro-haematocrit reader, micro-centrifuge, cotton wool and 70% rubbing alcohol.

Methods: The method used here is the microhematocrit method. Blood can be obtained by pricking the pulp of the finger with a lancet or by collecting directly from a specimen collected into an anticoagulant sample bottle. If collected from the pulp of the finger avoid squeezing the finger to encourage blood flow. Place one end of the heparinized capillary tube into the sample bottle or on the blood on the finger pulp. Blood will rapidly move up the tube by capillary attraction. Allow three- quarters of the tube to be filled and seal the other end of the tube with plasticine or a Bunsen flame if available. Place the tube in a groove of the centrifuge with the sealed end outwards. Tightly screw the cover plate and close the lid. You can then centrifuge at 3,000 rpm for about 5 minutes. Allow the centrifuge to stop completely before opening the lid.

Remove the capillary tube and place it in the groove of the Hawksley micro-haematocrit reader ensuring that the lowest blood level is level with the lower line of the Hawksley micro-haematocrit reader. Also adjust the instrument so that the upper level of plasma is level with the slanting line at the top. Then adjust the moveable knob so that the line running from it coincides with junction between the red cell mass and the plasma. Determine the haematocrit value from the scale. Obtain a minimum of 2 samples should be taken per subject. Record your results and ensure you properly document for each subject.

Packed cell volume or haematocrit result are typically indicated as a fraction or as a percentage. Typical values for males are: 0.42 to 0.52 (42% to 52%) and 0.37 to 0.47 (37% to 47%) for females. Children have lower values of 0.36 to 0.40 (36% to 40%) with little or no gender variations.

Discussions and clinical significance: Discuss your results. What are the common causes of anaemia in your environment? What are the physiological effects of anaemia? What is the possible cause of gender variations in

packed cell volume or haematocrit values amongst adults? Why are these gender differences not seen amongst children? What is the clinical utility of the micro-haematocrit method for determination of packed cell volume or haematocrit?

ESTIMATION OF HAEMOGLOBIN CONCENTRATION USING THE SAHLI'S AND CYANMETHEMOGLOBIN METHODS

Definition and aim: Hemoglobin is the major component of red blood cells; it gives red blood cells their characteristic red colour and serves to transport for oxygen and carbon dioxide in the blood. Hemoglobin concentration (Hb) is defined as amount of haemoglobin in grams per deciliter of blood and is expressed as g/dL. The present experiment aims to estimate the haemoglobin content of blood collected from a cohort of healthy subjects.

Introduction: There are several methods for Haemoglobinometry (measurement of haemoglobin concentration). Common methods are the visual and the Spectrophotometric methods. Visual methods include methods of Sahli, Dare, Haden, Wintrobe, and Tallqvist. Spectrophotometric methods are mainly the Oxyhemoglobin and the cyanmethemoglobin methods. There is also a Gasometric method. Haemoglobin concentration can also be determined by automated hemoglobinometry. Other available methods are the Alkaline-hematin method, the sspecific gravity method and the Lovibond comparator method. In this experiment, Haemoglobin concentration will be estimated using the Sahli's method also called as acid hematin method and the cyanmethemoglobin methods would also be described.

Sahli's hemoglobinometry: In this experiment, Haemoglobin concentration will be estimated using the Sahli's method also called as acid hematin method. It is visual method for the estimation of hemoglobin and is thus not subject to precision and accuracy. It is however easily available and recommended for field studies.

When red blood cells are haemolysed, the haemoglobin they contain is released. The haemoglobin concentration can be estimated by comparing the colour density of the haemoglobin solution obtained with a known standard. Haemolysis of the red blood cells is obtained by the addition an acid to the blood to form haematin.

Apparatus and Materials: 20mm³ pipette, freshly prepared 0.1m HCl, filter paper, dilution tube, distilled water, glass rod, Sahli's hemoglobinometer, lancet, and 70% rubbing alcohol.

Methods: A known volume of blood is converted to acid haematin using 0.1m HCl. Obtain a large drop of blood from the pulp of the finger by piercing with a lancet. Making sure the 20mm³ mark. Wipe the outside of the pipette clean in the filter paper, then gently blow the blood into the acid in the dilution tube. Suck up and down two or three times to mix thoroughly and allow all the red cells to haemolyse. Allow standing for exactly 5 minutes. Then add distilled water drop-wise, stirring with the glass rod each time. Compare the colour of the haemolysed blood against that of the standard in bright diffuse day light with a sheet of white paper as background. Continue the dilution until the colour is slightly darker than and slightly lightly than the standard. Note the reading of the meniscus level in both cases and take the average (X%). Since 100% in the Sahli scale represents a haemoglobin concentration of 14g/L00ml of blood, convert from average reading (X%) to g/100ml by simple proportion. Compare your results with that of other students and with textbook values.

The advantages of the Sahli's method are that it is easy to perform and convenient to perform, not time consuming as the entire procedure can be performed within 15 minutes, the Reagents and apparatus are cheap, easily available and are less harmful. Useful for field studies during mass mass surveys and requires no electricity. The disadvantages is that its inaccurate as it does not measure all available hemoglobins it estimates only oxyhemoglobin and reduced hemoglobins. Since HbF is not converted to acid hematin, Sahli's method is not suitable in infants up to 3 months.

The cyanmethemoglobin method: This is also called the haemoglobincyanide method. It is the internationally recommended method for the determination of haemoglobin concentration as it is a most accurate method of choice for determination of haemoglobin concentration. It measures all forms of haemoglobin except sulfhemoglobin which is normally not present in the blood and is thus very accurate.

Apparatus and Materials: Capillary or venous blood. Obtained venous blood should be mixed immediately preferably with EDTA. Haemoglobin standard and Drabkin's reagent containing: 200 mg Potassium ferricyanide, 50mg Potassium cyanide, 140 mg Potassium dihydrogen phosphate, 1ml of a non-ionic detergent and distilled or deionized water up to 1 liter

Methods: Blood is diluted 1:201 in a solution containing potassium ferricyanide ($C_6N_6FeK_3$) and potassium cyanide (KCN). Potassium ferricyanide oxidizes hemoglobin in the sample to methemoglobin. The methemoglobin further reacts with potassium cyanide to form a stable-colored cyanmethemoglobin (hemiglobincyanide- HiCN) complex. The intensity of the colored complex is measured at 540 nm which is directly proportional to the amount of hemoglobin present in the specimen.

Label three clean and dry test tubes as follows: Blank (B), Standard (S), and Test (T). Pipette 5ml of Drabkin's Reagent into each of the test tubes: Blank (B), Standard (S), and Test (T). Pipette 20 µl of Hemoglobin standard into the Standard (S) test tube and another 20 µl of the sample into Test (T) test tube. Mix well each individual test tube and allow to stand at room temperature (25°C) for 5 minutes. Measure the absorbance of the standard and test sample at 540 nm (green filter) against blank in a colorimeter. There would be no obvious color changes for up to several hours. Calculate the concentration of hemoglobin in the blood specimen using the following

$$\text{Conc. of Hemoglobin in the specimen (g/dl)} = \frac{\text{Absorbance of Test}}{\text{Absorbance of Standard}} \text{ X Conc. of Standard}$$

formula:

A calibration graph can also be quickly used to check the hemoglobin concentration corresponding to the obtained absorbance.

Discussions and clinical significance: Typical values of haemoglobin concentration for males range from 13(or 14) to 18 grams per deciliter (dL) and for females range from 12 to 16 grams per dL. Values in children range from 11 to 13 grams per dL. Heamoglobin concentration can easily help to determine the severity of anaemia or polycythemia. What is the importance of haemoglobin to humans? What are the possible causes of a high and low haemoglobin concentration? State the relationship between packed cell volume (PCV) and haemoglobin concentration.

MANUAL DETERMINATION OF RED BLOOD CELL (ERYTHROCYTE) COUNT

Definition and aim: The red blood cell also called the erythrocytes are the most numerous of the formed elements of the blood. Other formed elements are the white blood cells and the platelets. This experiment aims to manually determine the total number of red blood corpuscles per cubic mm of blood.

Introduction: This method attempts to manually count the total number of red blood cells in a known small volume of accurately diluted blood. To determine the total number of red blood cells in only one mm^3 of blood will take several months of laborious counting. This method therefore utilizes a small volume of blood. However, greater care is needed with this smaller volume to ensure adequate representation of blood volume and ensure accuracy. The red blood cells are counted in a counting chamber. Since the dimensions of the counting chambers are known and the quantity of diluents is known, the number of red blood cells in one $mm^3$of blood can easily be calculated.

The count depends on how you state the values. Typically: Men: 4.5 to 6.2 million cells per micro liter (µL): Women: 4.2 to 5.4 million cells per µL: Children: 4.6 to 4.8 million cells per µL.

Apparatus and materials: Red cell pipette, lancet, Hayem's diluting fluid (consisting of 0.05 of $MgCl_2$, 2.5g of Na_2SO_4, and 0.5g of NaCl in 100ml water), optical microscope, cover slips, filter paper, 70% rubbing alcohol, counting chamber (improved Naubauer haemocytometer).

Methods: Draw well-mixed capillary or venous blood exactly to the 0.5 mark on the pipette using gentle suction on the mouthpiece. This blood column must be free of any bubbles. If capillary blood is used, wipe off the first drop of blood as it swells up on the finger. Touch the tip of the pipette to the second drop. Do not touch the pipette to the skin, and avoid squeezing the finger to obtain blood. Wipe the excess blood from the outside of the pipette to avoid transfer of cells to the diluting fluid. Suck the diluting fluid up to the 101 marks, at the same time rotating the pipette between the thumb and forefinger to mix the specimen and diluents. Hold the pipette upright to prevent air bubbles from entering the bulb. Place a finger over the tip of the pipette and remove the rubber suction tubing. Mix the contents of the pipette for about 10 seconds by holding the pipette horizontally, between the thumb and the forefinger of one hand, and rotating in a figure-of-eight fashion. Mechanical mixer may be used if available. Place a clean haemocytometer cover glass on the counting chamber. Moistening the shoulders on which the cover glass rests aids in keeping a thin cover glass in place. Mix the specimen in the pipette for about 2 minutes to ensure even distribution of cells. Expel the unmixed and relatively cell-free fluid from the capillary portion of the pipette-usually 2 to 3 drops. Place the forefinger over the top (short end) of the pipette, hold the pipette at 45-degree angle and touch the pipette tip to the junction of cover slip and the counting chamber. Allow the mixture to flow under the cover glass until the chamber is completely charged. Similarly, fill

the opposite chamber of the haemocytometer. If overflowing to the moat or air bubbles occur, clean and dry the chamber, remix the contents of the pipette, and refill both chambers. Allow the cells to settle for about 3 minutes. Under low power magnification, focus on the ruled section of the counting chamber and locate the area for counting the red cells. Observe for even distribution of cells. Switch to high power magnification and locate the square in the upper left-hand corner. Count all the cells within his square and those touching the center line of the upper and right-hand triple lines. The red cells, which touch the left hand and bottom, centerlines are not counted. In the same manner, count the red cells in the remaining four squares, as illustrated. A variation of more than 25 cells between any of the five areas counted indicates uneven distribution. Should this occur, repeat the procedures starting from mixing. Count the second chamber in the same manner.

Calculation: The volume of 80 small squares V 0 1/400 x 80 x 1/100mm³ x 01/50mm³. The dilution of 0.5 was used 0 1/200. Let N cells by the total number counted in 80 squares. Then, red cells per mm³ 0 N x volume factor x dilution factor = N x 50 x 20 = N x 10,000 cells/mm³. Therefore, count the cells in 80 small squares (5 large squares), and multiply by 10,000 to get the red cell count per mm³ blood. It is important to remember that pipettes are cared for. A chipped or dirty pipette introduces errors in cell counting. After use, it should be rinsed through several times with tap water, and then distilled water using a vacuum pump suction apparatus. Then alcohol, ether and suction should be drawn through by the same mechanism. The clean and dry bead in the bulb of the pipette should move freely and not stick. It is best to replace the pipette in the haemocytometer case after use.

Discussions and clinical significance: Discuss the possible errors of the method used above. What factors could affect your results in relation to the normal and to that of other subjects. What is the clinical significance of a red blood cell count? Are there any racial, ethnic, geographical or other factors that could affect the red blood cell count?

DETERMINATION OF THE VARIOUS CORPUSCULAR INDICES: MEAN CORPUSCULAR VOLUME (MCV), MEAN CORPUSCULAR HAEMOGLOBIN (MCH), MEAN CORPUSCULAR HAEMOGLOBIN CONCENTRATION (MCHC)

Definition and aims: The corpuscular indices are basically three indices used to assess the size and quantity of haemoglobin in each red blood cell. They are haematological indices of immense clinical importance. The aim of this experiment is to determine the values of MCV, MCH, and MCHC.

Introduction:

Mean corpuscular volume (MCV): The mean corpuscular volume is the average volume of red cells. It is the product of the division of the haematocrit in percentage by the total red cell count in (RBC). The mean corpuscular volume is usually expressed in volume units fentoliters (fL). The normal range is 76-94 fL. A reduced mean corpuscular indicates that the red blood cells are smaller than normal. The commonest cause of a reduced MCV in our environment is iron deficiency. Various forms of chronic disease can cause a reduction in MCV. Many people with HIV have a high MCV caused by HIV medication.

Mean corpuscular volume (MCV) = $\frac{PCV/L}{RBC/L}$

Mean corpuscular haemoglobin (MCH): This refers to the average haemoglobulin content of the typical red blood cell. It is usually calculated from the haemoglobin concentration and red cell count. It is expressed in the mass

unit; picograms (pg, 10^{-12} gram). Typically, range is 26-32 picograms. The MCH, something of a minor leaguer among the indices in that it adds little information independent of MCV.

Mean corpuscular haemoglobin (MCH) = $\frac{Hb(g/dl)}{RBC}$

Mean corpuscular haemoglobin concentration (MCHC):

The MCHC is the average concentration of haemoglobin in a given volume of packed red cells. It is the product of the division of the haemoglobin concentration in g/dL by the haematocrit in percentage. Typical range 32 to 36 grams per deciliter (g/dl). Cells with normal, high and low MCHC are referred to as normochromic, hyperchromic and hypochromic respectively. These terms have importance in anaemia classification.

Mean corpuscular haemoglobin concentration (MCHC) = $\frac{Hb(g/l)}{PCV}$

Apparatus and materials: Refer to the apparatus for the determination of Haemoglobin concentration, haematocrit and red blood cell count.

Methods: Refer to the methods for the determination of Haemoglobin concentration, haematocrit and red blood cell count. Use the various formulas stated above for the calculation of the various corpuscular indices.

Discussions and clinical significance: Corpuscular indices provide valuable information about the haemoglobin content and size of red blood cells. Abnormal values indicate the presence of anaemia and suggest the possible type of anaemia. For instance, a reduced MCV is suggestive of microcytic anemia due to low iron levels, lead poisoning, or thalassemia. A normal MCV with features of anemia is typical of normocytic anemia and may result from sudden blood loss, chronic diseases, kidney failure, or aplastic anemia. An above normal MCV is suggestive of macrocytic anemia and is typically seen in low folate or B12 levels, or following chemotherapy. A reduced MCH is seen in hypochromic anemia and suggestive of low iron levels. A normal MCH seen in normochromic anemia suggests sudden blood loss, chronic diseases, kidney failure, aplastic anemia, or man-made heart valves. An increased MCH is seen in hyperchromic anemia and suggests low folate or B12 levels, or chemotherapy.

General Notes on Cell Counting: The principle of cell counting in biological fluids like blood, or of parasites in specimen, is based on enumerating the cells in a diluted specimen in a calibrated, shallow glass chamber followed by computing the number of cells per cubic mm using volume and dilution factors. For example, if N cells are counted in 0.1mm³ and the dilution is l/100, then the cell per mm³ = N x 10 x 100. Blood cell counts are used during diagnosis, treatment, and follow-up to determine the health of a patient. Blood counts thus cannot by themselves determine whether a person has disease (for instance lymphoma) but there are values that can determine if whether everything is fine or if more tests are needed. During treatment blood counts are very important to determine if that treatment is depleting healthy blood cells in addition to cancerous cells.

Cell Counting Chambers: These are of several types. In general, they are ruled in large squares, which are further ruled in smaller squares with definite markings to make the large squares distinguishable, e.g., bright double or triple lines. The specifications of each type are clearly marked on the chamber (area and depth of square).

Haemocytometer: This is a cell counting chamber type, which is used to count blood cells. It is a double-chambered instrument with each chamber having a central area ruled in squares. The large square is 1mm x 1mm. This 1sq.mm area is further subdivided into 16 squares each of which is further sub-divided into 16 squares each of which is further subdivided into 16 smaller squares. The depth of the chamber is 0.1mm. Thus, the area of the smallest or elementary square is 1/400 sq.mm; the area of the large square is 1 sq.mm. The corresponding volumes are 1/400 and 1 cubic mm, respectively.

Dilution Pipettes: The pipette consists of a narrow-graduated stem and, a bulbar portion containing a small bead, and a further graduation on the stem superior to the bulb.

The Red Cell Pipette: This has a red bead in its bulb and graduations up to 1 on the stem below the bulb and 101 above the bulb. In one type (THOMA), there are only two marks on its lower stem, namely; 0.5 and 1. If blood is drawn to the 0.5 mark and fluid drawn to the 101 marks, this gives a dilution of 100. This assumes that the fluid in the lower stem does not take part in diluting the blood.

The White Cell Pipette: This has a white bead in its bulb and is generally smaller than that of the red cell. The graduation on the lower stem is 0.5 and 1, and on the upper stem, 101. The lower stem may have graduations from 0.1 to 1. Blood drawn to the 0.5 or 1 mark and diluting fluid to the 10 mark gives cell dilution of 10 and 20 respectively.

MANUAL DETERMINATION OF THE RETICULOCYTE COUNT

Introduction and aim: Reticulocytes are immediate the precursors of red blood cells. They are essentially immature forms of erythrocytes and have considerable quantities of ribosomal and mitochondrial RNA in their cytoplasm. An insignificant small number of reticulocytes remain in the peripheral blood 24-48 hours following the maturation of erythrocytes. Reticulocyte count is a viable the test for the assessment bone marrow function and evaluation adequacy of erythropoietic activities. It is also useful to classify and monitor treatment for anemias. The reticulocytes are usually expressed as a percentage of mature red cells. The present experiment aims to manually count the number of reticulocytes in specific volume of blood.

Apparatus and materials: Venous or capillary blood in EDTA specimen bottle. Either of New Methylene Blue: 1gm New methylene blue, 0.6gm Sodium citrate, 0,7 gm Sodium chloride made up to 100ml with distilled water = 100 ml or Brilliant Cresyl Blue: 1.0gm Brilliant cresyl blue, 0.6gm Sodium citrate, 0.7 gm Sodium chloride made up to 100ml distilled water.

Methods: The reticulocyte count is based on the property of ribosomal RNA to react with isotonic solution of methylene blue or brilliant cresyl blue. Obtained blood is mixed with any of this stain and incubated. The ribosomal RNA in the reticulocyte gets precipitated as a dark blue reticulum. When a blood smear is made and examined under microscope and a relative count is made against erythrocyte count and expressed as the percentage of the population of erythrocytes. Place 40 cubic mm (2 Sahli pipettes full) of brilliant cresyl blue on a clean glass slide. Add equal amount of capillary (or well mixed venous) blood. Mix well with an applicator stick and allow standing for minutes. To prevent drying, the slide should be placed on a damp towel and covered with a petri dish. Touch a clean glass slide to the mixture, prepare a thin smear, allow drying and countering stain with

modified Wright's stain. After the slide has dried, focus the smear under low magnification and locate the thinner portion of the smear. Cut a 5mm hole in a circular piece of paper and place the disc in the ocular of the microscope to reduce the size of the field. Switch to oil immersion magnification and count 200 red cells, including reticulocytes in each of 5 different areas on the smear (a total of 1000 cells).

Procedure: Take 2-3 drops of dye solution in a test tube. Add 2-4 drops of well-mixed blood sample and mix. Stopper the tube and incubate at 37^0C for 10-15 minutes. After incubation, mix well and make a thin smear of stained blood. When dry, examine the films without fixing or counterstain. Count 1000 RBCs and note the number of reticulocytes among them. A dark-blue reticulum or network will present in reticulocytes.

Record the number of reticulocytes observed as indicated below:

1. Percentage reticulocyte is the percentage of red blood cell that is reticulocyte:

$$Percentage\ reticulocyte = \frac{Number\ of\ reticulocyte\ counted}{Number\ of\ RBC\ counted} \text{x} \frac{100}{1}$$

2. Absolute Reticulocyte Count (ARC) is the is the actual number of reticulocytes in 1 L of whole blood

$$\textbf{Absolute Reticulocyte Count} = \frac{\text{Reticulocyte (\%) x RBC Count } (10^{12}\text{/L})}{100}$$

3. Corrected Reticulocyte Count (CRC) is useful in circumstances of a low hematocrit where the percentage of reticulocytes may be falsely elevated because of the blood contains relatively fewer red blood cells. A correction factor is used with the average hematocrit considered to be 45%.

$$\textbf{Corrected Reticulocyte Count} = \frac{\text{Reticulocyte (\%) x Patient's Hematocrit}}{45}$$

Discussions and clinical significance: Normal values for reticulocyte count in adults is 0.2 to 2 and between 2-6% amongst infants with Childrens up to 5 years having values of between 0.2 to 5.0%. The number of reticulocytes in the peripheral blood is a fair indicator of erythropoietic activity. An increase in erythropoietic activity results premature release of reticulocytes into the circulation. Reticulocytosis occurs in hemolytic anemias, sickle cell diseases, exposure to toxins, following hemorrhage and treatment of anemias. A physiologic increase in occurs during pregnancy and typically amongst infants. Reticulocytopenia typically occurs iron deficiency anemia, aplastic anemia, during radiation therapy, pernicious anemia and tumors of the bone marrow.

PLATELET COUNT

The principle of platelet count is the same as the principle of the RBC count. Although platelet count can be carried out with finger or ear prick blood, the count is lower than those carried out on venous blood. The count is also less constant because certain amount of platelets is loss at the site of the skin puncture.

Apparatus:

Haemocytometer, RBC pipette, sterile lancet and a diluting fluid

Diluting fluid: Rees and Ecker solution is the most commonly used fluid.

The composition of this fluid is as follows

Sodium citrate - 3.8g

Brilliant crestyl blue -0.05g

Formaldehyde neutral (40%) 0.2ml

Distilled water is added to make the volume to 100ml.

In the absence of the Rees and Ecker solution however, ammonium oxalate solution may be used.

PROCEDURE

Draw either venous blood or blood from finger puncture in to the RBC pipette up to mark 1. Clean the tube of the pipette and draw the diluting fluid up to the 101 mark, this gives a dilution factor of 100. Mix the content of pipette by rolling on the palm and then charge the chamber with the mixture.

Observation

With the Rees and Ecker solution, you will see both RBC and platelets in the same field. Platelets are smaller, coloured and $1/7^{th}$ the size of the RBC. They may be seen singly or in groups.

With the ammonium oxalate solution however, no red cell will be visible. Only platelet will be observed. (Can you give an explanation for this?)

Calculation: the procedure for counting platelet is the same as that for RBC. Let the number of cells counted in 80 small squares = n.

Depth of chamber =1/10 mm

Area of one small 1/400 mm = 1/400 mm

Area of 80 small square 1/400 X 80/1

Volume = 1/400 X so/1 X 1/10 = 1/so mms

Dilution factor =1 O0

Number of platelet present in $1mm^3$ = n x 100 x 50 permm^3 = n x 5000/mm^3

DISCUSSION:

What is the clinical significance of performing platelet count?

What factors affects platelets count?

AUTOMATED BLOOD COUNTING TECHNIQUES

Aim: To perform complete blood count with 5 part differentials

Principle: A fully automated multichannel instrument usually measure a panel of between 8-46 variables relating to red cells, white cells and platelets. Some variables have no equivalent in manual techniques. Various technologies are used by different manufactures. They include the Coulter electric impedance, low-frequency electromagnetic current and Laser light scattering to determine and compute all the blood parameters within 2-3 minutes. The Coulter principle of electric impedance for red blood cells is that blood is diluted, aspirated through a very narrow aperture that has electrodes placed on either sides. When direct electric current is pass through the electrodes, the diluted blood cells that passes through the narrow orifice are poor conductors of electricity, will interrupt a current flow. The impedance variation generated by the passage of non-conductive cells through a small, calibrated aperture is used to determine the count (number of particles) and size (volume) of the particles passing through the aperture within a given time period. Final RBC/Plt dilution and the WBC/BASO dilution are analyzed. Flow cytometry / fluorescence is used to measure neutrophils, eosinophils, basophils, lymphocytes and monocytes

Materials: Beckman Coulter GEN-S, LH series, DxH, diluent supplied by manufacturer, facilities for venipuncture/

Procedure:

Before commencement of blood analysis,

i. ensure that the printer has enough paper and switched on,

ii. waste container level is checked

iii. Turn on the instrument and run a Startup routine during power UP. It rinse the machine followed by background count without blood.

iv. At the end of a successful cycle, the machine will record and print result

v. Review the startup results

Blood collection

1. Collect 100µl of venous blood into a microcontainer with K_3EDTA anticoagulant. Mix thoroughly before use.
2. Enter sample identification number manually or set auto numbering
3. Put the blood sample in the probe chamber and press the aspirate switch. The LEDs flash during sample aspiration.
4. When the red LED remains illuminated, remove the tube from the probe.

5. The machine is ready for next analysis when green LED light is shown
6. Results of the sample analysis will appear on the screen and print according to instrument setup
7. Shut down the machine in accordance with manufacturers' guide.

REFERENCE

A Manual of Basic Practical Physiology 2018. Department of Human Physiology, Faculty of Basic Medical Sciences, College of Medical Sciences, University of Maiduguri, Nigeria

Chapter 8

PHS 208: PHYSIOLOGY PRACTICAL II

Maisaratu A. Tukur , Fortune S. Amah-Tariah, Alhassan Abdulwahab, Adesoji A. Fasanmade, Eze K. Nwangwa, Aliyu Mohammed, Walter C. Nwafia, Victor D. Dapper

Learning Outcomes

At the end of this course, students should be able to:

1. demonstrate cardiac cycle and effects of drugs on cardiac muscle of toad;

2. illustrate various methods of measuring arterial blood pressure and determining effect of

posture and exercise on arterial blood pressure, recording and analysis of 12 lead

electrocardiogram;

3. conduct an appropriate cardiac examination;

4. perform spirometry and vitalography;

5. perform urinalysis and urine microscopy; and

6. conduct microscopic examination of saliva.

Introduction

The frog heart has 3 chambers, two auricles and one ventricle. The cardiac muscle (pacemakers) intrinsically initiate its own rhythmic contractions through gap junctions due to "leaky" calcium and sodium ions channels leading to a slow depolarization, then action potential, and muscle contraction without requiring extrinsic stimulation. Cardiac output and rate of contractions (30-50/min) are extrinsically regulated by the sympathetic and parasympathetic-autonomic nervous systems that release variety of neurotransmitters.

Aim: To record and observe normal cardiac cycle and determine the effects of excess ions and drugs in frog *in situ*.

The objectives of the cardiac experiments in frog are to observe and record

i. atrial and ventricular systole and diastole

ii. cardiac phenomena of refractory period, all or non-law, tetanus, ventricular extrasystole, and the compensatory pause in the frog heart.

iii. the effects of atrioventricular block induced by 1st and 2nd Stannius ligature

iv. the effects of excess ions (Na+, K+ and Ca^{2+}) on cardiac cycle

v. the effects of drugs (adrenaline, acetylcholine, atropine, and pilocarpine on the frequency and amplitude of cardiac muscle contraction in the frog.

vi. the effects of vagal stimulation on the frog cardiac cycle.

vii. the effects of temperature on cardiac muscle contractility, rate and amplitude.

Materials Required

Equipment: PowerLab, Bridge Pod + Force Transducer, Stimulator Bar, BioAmp, Mounting stand with micropositioner, Thermocouple Pod and thermocouple, Kymograph, Suture thread, Straight pins, Barb-less hook, Dissection tools, Eyedropper

Chemical and Reagents: Ringer solution at various temperature (Cold- 5^0C, Room-27^{o}C and warm-40^{o}C), Calcium-free Ringer, Potassium-free Ringer, Ringer solution with: Adrenaline (1%) Acetylcholine (0.1 mg/mL), Pilocarpine (2.5% solution), Atropine sulfate (5% solution), Caffeine, Cadmium, Chloride, KCl,

Composition of Ringer solution/ 100ml

Sodium chloride = 0.6 g

Calcium chloride = 0.01 g

Potassium chloride = 0.0075 g

Sodium bicarbonate = 0.01 g

$NaHCO_3$ =0.01 g (NaHCO3 must be completely dissolved before $CaCl_2$ is added)

Na2HPO4 0.001 g

Glucose=1.0g

Distilled water to 100 ml

Methodology

Pithing Procedure:

The brain and the spinal cord are destroyed to abolish reflexes and pain sensation in the frog.

1. Use the left hand to grasp the frog and flex the head with your index finger on the nose and the second finger beneath its jaw.
2. Use the right hand to feel and locate the position of atlanto-occipital joint, a little depression, midline, and soft spot at the end of the skull.
3. Forcefully insert the pithing needle (probe) in the joint and into the spinal canal

4. Push the probe anteriorly into the brain and rotate several times to destroy the brain
5. Push the probe posteriorly into the spinal cord and rotate several times to destroy the spinal cord
6. Test for corneal and withdrawal reflexes to confirm abolition of sensory perception

Figure 8.1a Dissection of heart of a Toad

Dissection to Expose Frogs' Heart

i. Pin the frog through the wrists and ankles on the dissecting board with the ventral side facing you (upward)

Figure 8.1b Dissection of heart of a Toad

Figure 8.1c Dissection of heart of a Toad

ii. Use the Scalpel or scissors to make midline incision from xiphisternum to the jaw. Extend the lower end of this cut laterally (two flaps) and remove both pieces of skin to expose the anterior chest wall.

Figure 8.1d Dissection of heart of a Toad

iii. Cut through the pectoral girdles and remove the chest wall in one piece to expose the heart in the pericardial sac.

iv. Grasp the pericardium with forceps and carefully cut it away to further expose the beating heart.

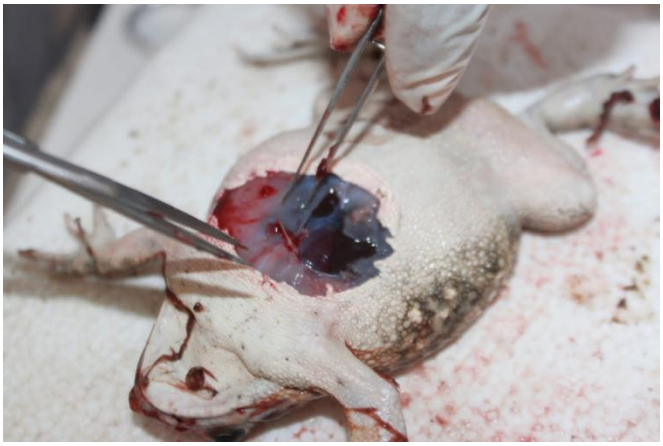

Figure 8.2 Application of Ringers solution

v. Keep the heart moist by applying Ringer's solution regularly

vi. Clip the apex of the ventricle with heart clip tied with cotton thread

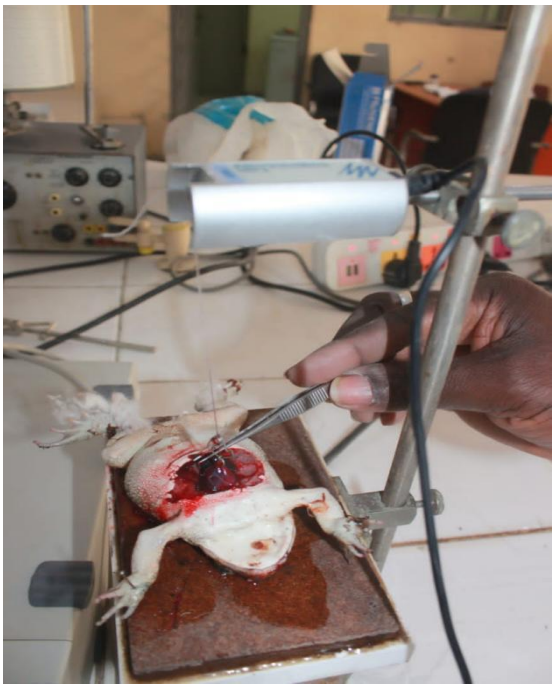

Figure 8.3 Heart mounted on a starling heart lever

vii. Attach the thread to the Starling heart lever placed on the vertical rod stand directly above the heart

viii. Adjust the position of the lever to gently lift the heart so that its movements are satisfactory.

ix. The spring of the lever will pull downward during systole and backward during diastole.

x. Place the lever tangential to the revolving drum on the Kymograph so that the writing point lightly touches the chart paper on the drum

Figure 8.4 Heart Mounted on a Kymograph

xi. Start the Kymograph at the speed of 2.5 mm/sec.

xii. Record the normal cardiogram for 30 seconds on the paper

xiii. Calculate the amplitude and the heart rate.

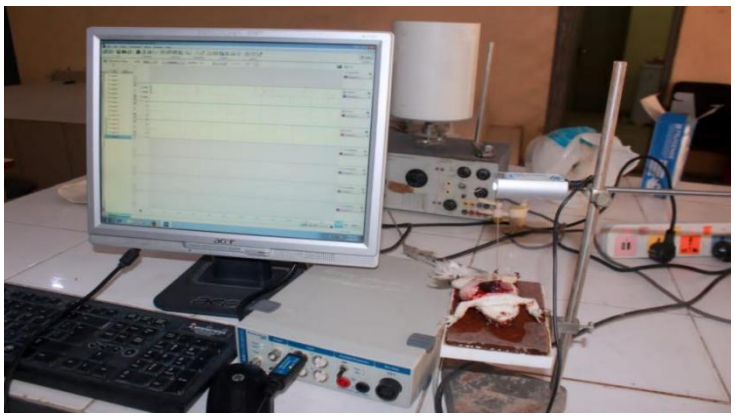

Figure 8-5 Recording of Cardiogram

Effects of Varying Temperatures on Heart Rate

Use dropper and dispense Ringer at 25^{o}C, 5^{o}C and 40^{o}C to the heart respectively,

a. Use arrow to mark each point of temperature change

b. Calculate heart rate for each temperature

Effects of Drugs and Excess ions on Cardiac Cycle in Frog

1. Use the double pithed frog and get a control record of the normal heartbeat.
2. Bathe the heart with 2.0% solution of calcium chloride (CaCl2).
3. Indicate the point of addition of Ca^{2+}. Observe its effects for 30 seconds and stop the recording.
4. Use Ringer solution at room temperature to thoroughly rinse the heart until the heartbeat returns to normal.
5. Consider this new rhythm as the next control.
6. Repeat the procedures in 2-5 to test the effects of

(i) Digitoxin (0.2 g/ 100 mL);

(ii) Pilocarpine (2.5 g/100 mL);

(iii) Atropine (5.0 g/100 mL);

(iv) Potassium chloride (2.0 g/100 mL);

(v) Sodium chloride (2.0g/100ml)

(vi) Adrenaline (0.01 g/100 mL);

(vii) Caffeine (0.2 g/dL); and

(viii) Nicotine (1.0 g/2L; or 6.16 ml liquid/dL).

(ix) Record your results in the table below

Condition	Rate (beats/min)	Amplitude (mm above Baseline)	Atrial and Ventricular Peaks	Remark on Drug Effects
Normal				
Calcium (Ca2+)				

Digitalis				
Pilocarpine				
Atropine				
Potassium (K+)				
Epinephrine				
Caffeine				
Nicotine				

Extrasystole and Compensatory Pause

This experiment will demonstrate the excitability, contractility, autorhythmicity and conductivity of the heart muscle. A stimulation of any part of the heart will lead to contraction of the remaining part.

Electric stimulus that falls during systole does not change heart activity but if the stimulus is within diastole, the heart contracts instantaneously. This extra contraction called extrasystole, or premature beat, is followed by a pause called the “compensatory pause”.

Procedure

1. On a pith frog, record normal cardiogram as explained above
2. Place the stimulating electrode on the contracting ventricle
3. Send single electric stimulus to the ventricle during early systole and diastole. Subsequently, send another stimulus during the middle phase, and in the late phases ventricular activities.

Stannius Ligatures (1st, 2nd and 3rd Degree Heart Block)

Spontaneous and independent rhythm occurs in atria and ventricle with sinoatrial node (sinus Venuses in frog) as the dominant pacemaker. Subsidiary pacemakers are conductors of impulses but act as actual pacemakers in abnormal conditions

Procedure

On a double pith frog, slot in thread between sinus venosus and the auricle and ligate (1st stannous ligature)

Place a thread and ligate between atrium and ventricle i.e. Auriculo-ventricular groove (2nd Stannius ligature)

Measurement of Arterial Blood Pressure

Principle

The method is based on applying sufficient pressure to compress the brachial artery so that arterial pulsations could no longer be transmitted through the artery. The artery is occluded by wrapping an inflatable bladder, which is encased in a non-distensible cuff, around an extremity, and inflating the bladder until the pressure in the cuff exceed that in artery. When the artery is occluded, transmitted pulse wave can no longer be palpated or heard distal to the point of occlusion. As the pressure in the bladder is reduced by opening a valve on the inflation bulb, pulsatile blood flow reappears through the partially compressed artery either producing repetitive KOROTKOV sounds (using a stethoscope, auscultatory method) or the radial pulse can just be felt (palpatory method) generated by the pulsatile flow. Normal systolic and diastolic blood pressure in a young adult is about 120/80 mm Hg respectively. The difference between the two pressures is called the pulse pressure. Blood pressure varied with age, gender, altitude, disease, stress, fear, excitement, exercise etc. A normal range for systolic pressure is usually considered to be 100-140 mmHg and for diastolic pressure below 90 mmHg.

How to Take Blood Pressure Measurement Using the Sphygmomanometer

1. Position the patients arm so the antecubital fold (inside elbow area) is level with the heart. Support the patients arm with your arm or a bed side table.
2. Center the bladder of the cuff over the brachial artery approximately 2 cm above antecubital fold. The arrow should line up with the artery. Proper cuff size is essential to obtain and accurate reading. Be sure the index line falls between the size marks when you apply the cuff. Position the patients arm so it is slightly flexed at the elbow.
3. Palpate the radial pulse and inflate the cuff until the pulse disappears. This a rough estimate of the systolic pressure.
4. Place the stethoscope diaphragm over the brachial artery and the earpieces in your ears. Inflate the cuff to 30 mmHg above the estimated systolic pressure and hold it there by tightening the knurled knob.
5. Release the cuff pressure slowly by turning the knurled knob just until you hear the hiss of air being released (no greater than 5 mmHg per second).

6. The level at which you consistently hear the heartbeat through the stethoscope is the systolic pressure. The needle on the gauge should also start a pulsing movement at this point. Record this value as the systolic pressure.

7. Continue to release the cuff pressure until the sounds muffle and disappear. The point at which you no longer hear sounds and the needle on the gauge stops its pulsing movement is the diastolic pressure. Record the value from the gauge.

8. Record the blood pressure as systolic over diastolic (120/70 for example).

Procedure

1. In each experiment, take three resting (basal) readings of pulse rate and systolic and diastolic blood pressure.

2. Allow the subject to perfume the appropriate change of posture exercise, etc. and try to obtain at least one reading of pulse rate and blood pressure during the maneuver. Obtain a reading of each immediately after the changes of position or exercise, and further reading at 30 seconds intervals thereafter until constant readings are again obtained.

3. The experiment will normally be carried out with groups of at least 5 students per group so that:

a. act as subject throughout the experiment

b. takes blood pressure

c. takes pulse rate

d. acts as timer

e. acts as recorder

NB: it is essential that each member of the group continue with his own allocated job throughout the experiment so that meaning and comparative results may be obtained for the set condition.

If time allows REPEAT, the experiment after reshuffling the members of team.

<u>Factors to be studied</u>

A. The influence of Posture

Determine the influence on pulse rate and blood pressure of the following bodily position.

i. lying at rest

ii. sitting upright

iii. standing

iv. Strap the subject firmly to the tilt-table and study his response in the head-down position.

v. Repeat (four) with the subject in the foot down position.

vi. Repeat (four) several times increasing the rate at which the table is tilted

B. The Effect or Exercise

i. Determine the effect of exercise on blood pressure and pulse rate. The exercise consists of stepping up onto the down from the foot high stool provided 30 times /minute.

ii. Repeat a more severe form of exercise e.g. exercise with a load of approximately half your body weight on your back.

C. The Effect of Temperature

Determine the effect of pulse rate and blood pressure of sudden immersion of both feet in ice cooled water 5°c

Water warmed of 45°c

Effects of Exercise on Arterial Blood Pressure by Alhassan Abdulwahab

Overview

By definition, the arterial blood pressure (ABP) is the force exerted on the wall of an artery by the column of circulating blood over a given area.

The ABP is usually expressed using different terms which include:

1. Systolic BP (SBP): gotten at the ventricular ejection phase of the ventricular systole. It's about 100-139 mmHg in normal adults.
2. Diastolic BP (DBP): gotten at the isovolumetric phase. It's about 60-89 mmHg in normal adults.
3. Pulse pressure (Pp): This is the difference between the SBP and DBP. It's the cause of arterial pulsation. It is about 40 mmHg.
4. Mean ABP: it is the average pressure in the arteries. The normal range is 70-100 mmHg. It is expressed as:
5. DBP + 1/3 x Pp OR $\frac{\mathrm{SBP}+2\mathrm{DBP}}{3}$

The ABP usually oscillates between a maximum (systolic) and a minimum (diastolic) level and conventionally reported as SBP/DBP i.e. approximately 120/80 mmHg. ABP can be measured at different sites on the body such as the arm (brachial artery), thigh (femoral artery), etc.

Objectives

The objectives of this section are to:

1. Know the changes in arterial blood pressure during exercise.
2. Know the changes in arterial blood pressure after exercise.

Effect of Exercise on ABP

Exercise is any physical activity done intentionally following an existing protocol to achieve some goals and must be individualized according to the frequency, intensity, time and type (FITT) principle. It can be classified as mild, moderate or severe; aerobic or anaerobic; dynamic or resistance; acute or prolong; and isometric or isotonic. An isometric exercise is an exercise that keeps the muscle tensed without any movement at the joint such as planks while an isotonic exercise involves movements at the joints such as push-ups.

Systolic blood pressure increases linearly with increases in exercise intensity. As a greater quantity of blood gets pumped from the heart the pressure rises in the blood vessels that transport the blood with each heart beat. In a healthy person with a 'normal' systolic pressure of 120 mmHg, vigorous aerobic fitness training can increase systolic pressure to 180 mmHg and take10-20 minutes to return to resting levels.

The higher the intensity of exercise, the greater the rise in heart rate (HR) will be, and consequently the larger the increase in systolic blood pressure. Low intensity aerobic fitness training tends to have the lowest increases in systolic pressure, and is therefore the safest training for new exercisers or those with cardiovascular risk factors.

Systolic blood pressure normally rises with exercise as cardiac output (CO) increases during exercise in responses to the increased demand of oxygen from working muscles. However, some individuals present with abnormally exaggerated rise in systolic BP during exercise. This phenomenon is known as a hypertensive response to exercise (HRE).

During exercise, the temperature of the human body increases. When this happens, the body undergoes negative feedback by dilating the arteries in the body. Vasodilation happens to increase the blood supply to around the tissues and also to take away heat from the body. Therefore, during exercise, cardiac output increases whereas peripheral vascular resistance decreases due to vasodilation.

Arterial Blood Pressure Changes after Exercise

Closely after exercise cessation, there is a rapid decline in HR attributable to vagal reactivation. Progressive removal of metabolites during exercise recovery decreases metaboreflex activation, restoring baroreflex activity. Also, it induces enlarged vagal activity and decreased sympathetic activity, leading to a progressive decrease in HR. For the first 2 to 3 hours after exercise, systolic and diastolic blood pressure drops below pre-exercise resting level, a phenomenon referred to as post-exercise hypotension. Post-exercise, there is an increase in resting SV to improved O_2 delivery to the skeletal muscles but the HR decreases leading to decrease BP to subnormal level for a while due to the persistent vasodilation. However, the BP returns to pre-exercise level later.

Procedure

4. In each experiment, take five resting (basal) readings of pulse rate and systolic and diastolic blood pressure.
5. Allow the subject to perfume the appropriate exercise, and try to obtain at least one reading of pulse rate and blood pressure during the maneuver. Obtain a reading of each immediately after the exercise, and further reading at 1 min intervals thereafter until constant readings are again obtained.
6. The experiment will normally be carried out with groups of at least 5 students per group so that:

i. act as subject throughout the experiment

ii. takes blood pressure

iii. takes pulse rate

iv. acts as timer

v. acts as recorder

Table: Effect of exercise on ABP

	AT REST					AFTER EXERCISE				
	1st min	2nd min	3rd min	4th min	5th min	1st min	2nd min	3rd min	4th min	5th min
SBP (mmHg)										
DBP (mmHg)										

NB: it is essential that each member of the group continue with his own allocated job throughout the experiment so that meaning and comparative results may be obtained for the set condition.

If time allows REPEAT, the experiment after reshuffling the members of team.

D. The Effect or Exercise

iii. Determine the effect of exercise on blood pressure and pulse rate. The exercise consists of stepping up onto the down from the foot high stool provided 30 times /minute.

iv. Repeat a more severe form of exercise e.g. exercise with a load of approximately half your body weight on your back.

Classification of Hypertension

Category		Systolic Blood Pressure	Diastolic Blood Pressure
i.	Optimal	Less than 120mmHg	Less than 80mmHg
ii.	Normal	Less than 130mmHg	Less than 85mmHg
iii.	High Normal	130-139mmHg	85-89mmHg
iv.	Grade I Hypertension (Mild)	140-159mmHg	90-99mmHg
v.	Grade II Hypertension (Moderate)	160-179mmHg	100-109mmHg
vi.	Grade III Hypertension (Severe)	Equal to or greater than 180mmHg	Equal to or greater than 110mmHg
vii.	Isolated Systolic Hypertension (ISH)	Equal to or greater than 140mmHg	Less than 90mmHg
viii.	Sub Group; Borderline	140-149mmHg	Less than 90mmHg

Exercise

1. Explain the effect of exercise on systolic and diastolic blood pressure.
2. Explain the response of blood pressure to exercise recovery.

Effects of Posture on Arterial Blood Pressure

Overview

Posture is the orientation of the body or part(s) of the body in space or in relation to other body parts when in a static position. Body's posture (sitting, standing or supine) can significantly affect the BP value in both normotensive and hypertensive (least in supine); and the arm used for the measurement also matters a lot as it is less in the left arm compared to the right in any particular position.

Standing for a long time without moving causes accumulation of blood in the calf veins and interstitial spaces as the hydrostatic pressure increases.

Changes in blood pressure due to posture

When body position is changed from a supine or sitting position to standing, pooling of blood in lower extremities occur due to gravitational effects. It reduces venous return and stroke volume with a fall in systolic blood pressure,

and including diastolic blood pressure, a condition known as orthostatic hypotension, also called postural hypotension. It may result in several symptoms, such as headache, blurred vision, and dizziness.

A change from a supine or sitting position to standing shifts one's center of gravity. However, short term regulatory mechanism and long term regulatory mechanism plays a role to maintain balance. The short term regulatory mechanism is also called baroreflex. As arterial pressure decreases, the baroreceptors become unloaded initiating parasympathetic withdrawal and activation of the sympathetic nervous system (long term regulation) via baroreflex-mediated autonomic regulation. The withdrawal of parasympathetic action rapidly increases heart rate (HR), within 1 to 2 cardiac cycles. The sympathetic activation, however, yields a slower response, within 6 to 8 cardiac cycles, causing vascular resistance, vascular tone, and cardiac contractility to increase and further increase HR.

In the long term regulation, the rapid adjustment of the body to maintain blood pressure stimulates modulations of the autonomic nervous system (ANS). There is an increase in the sympathetic nervous system (SNS) activity and a simultaneous decrease in the vagal nerve, or parasympathetic nervous system (PNS), activity. Thus, the predominance of the ANS is shifted from the PNS to the SNS in a change from the supine position to the standing position.

During supine head-up tilt (HUT), a reduction in stroke volume (SV) is associated with a drop in pleural fluid content, cardiac volume, central blood pressure, and hemodynamic changes.

Procedure

1. In each experiment, take three resting (basal) readings of pulse rate and systolic and diastolic blood pressure.
2. Allow the subject to perfume the appropriate change of posture and try to obtain at least one reading of pulse rate and blood pressure during the maneuver. The experiment will normally be carried out with groups of at least 5 students per group so that:

i. act as subject throughout the experiment

ii. takes blood pressure

iii. takes pulse rate

iv. acts as timer

v. acts as recorder

NB: it is essential that each member of the group continue with his own allocated job throughout the experiment so that meaning and comparative results may be obtained for the set condition.

If time allows REPEAT, the experiment after reshuffling the members of team.

Factors to be studied

E. The influence of Posture

Determine the influence on pulse rate and blood pressure of the following bodily position.

vii. lying at rest (supine)

viii. sitting upright

ix. standing

x. compare the value obtained for the different postures

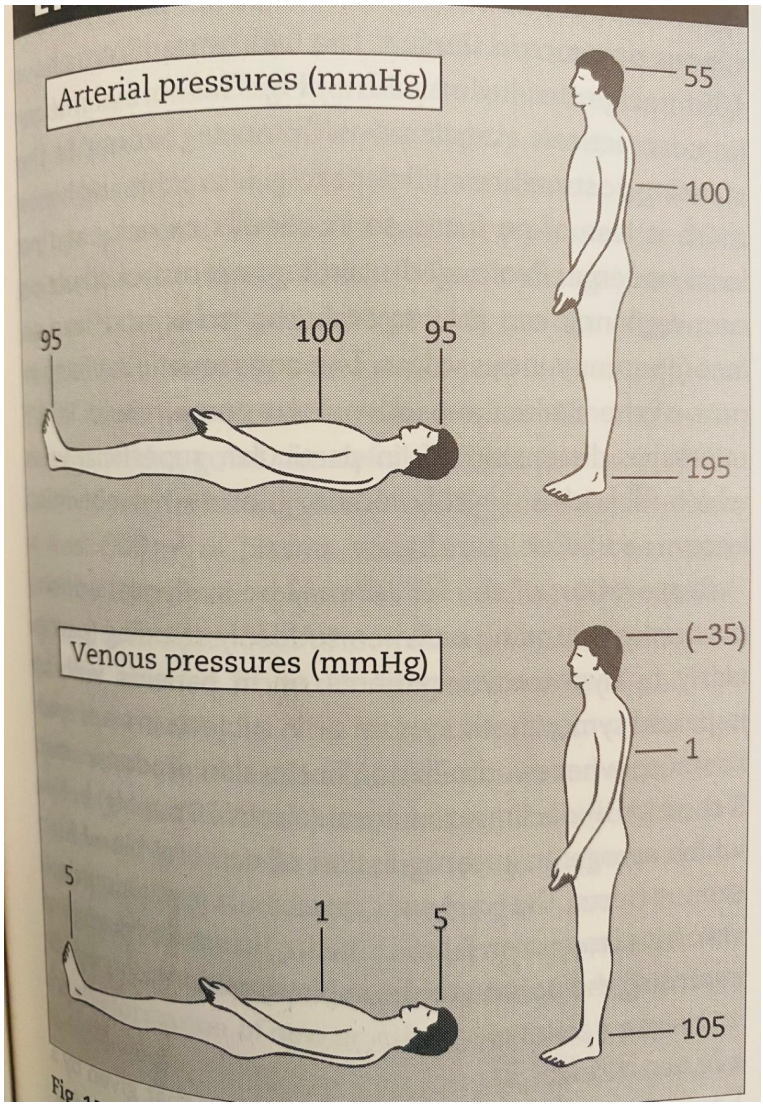

Figure 8.6: Effect of posture (gravity) on ABP

Table: Effect of posture on ABP

	MALE			FEMALE		
	Supine	Sitting	Standing	Supine	Sitting	Standing
SBP (mmHg)						
DBP (mmHg)						

Exercise

1. Briefly describe the compensatory mechanism of the cardiovascular system to prolong standing position.
2. How does the ABP changes with posture (seated and supine) after a prolonged sitting?

Human Electrocardiography

Overview

This is the recording from the body surface of the electrical changes that occur within the heart during the cardiac cycle. This proves very useful in the analysis of abnormal rhythms, detection of hypertrophy of the walls of the atria and ventricles, detection of changes in electrical activities due to pericardial diseases, changes in electrical activities due to electrolyte imbalances, detection of origin of cardiac depolarization and heart rates. The interpretation of the result of Electrocardiogram should not be done in isolation but in combination with the clinical picture.

Objectives

The learning objectives of this chapter are:

i. understand the clinical uses of Electrocardiogram

ii. explain the conventions of Electrocardiogram

iii. describe the positioning of the lead system

iv. identify the waves and intervals and what is responsible for it.

v. To be able to do an Electrocardiogram in human

vi. Interpret the Electrocardiogram findings

Definition

(i) Electrocardiography: is the science of recording and interpreting of electrical activity of the heart i.e. electrocardiograms.

(ii) Electrocardiogram: (ECG, E,K,G.) is a graphic record, made by an electrocardiograph of the electrical forces that produce contraction of the heart. It is normally recorded in mV versus time in milliseconds. A typical normal record shows P, Q, R, S, T and U waves.

(iii) Electrocardiograph: is an instrument that receives electrical impulses as they vary during the cardiac cycle and transforms them into a graphic record. It is an instrument, for recording electrocardiograms. Spread of depolarization and repolarization through a muscular mass is accompanied by measurable electrical potentials, which may be recorded by electrodes placed on the skin since the body is a conductor.

(iv) Bipolar or Standard Limb Leads: Conventional lead I, II and III record the potential difference between right arm – left arm, right arm - left leg and left arm left leg respectively. The right leg usually acts toward the ground (earthing) to reduce the AC interference from external potential fields.

(v) Unipolar Leads: aVR, aVL, aVF and V1 - V6. V1 and V2 Record the potential arm and positions right and left of the sternum respectively at the 4th intercostal space. V3 is between V2 and V4. V4 is at the apex. V5 is left horizontal line from V4 and at the anterior axiliary line. V6 is left of V5 at mid-axiliary line (Note that V4 - V6) are all on the 5th intercostal space.

Apparatus

ECG machine, leads (bipolar and standard limb leads) with electrodes and electrode gel.

Procedure

Leads are attached to the subject's arms and legs. A precordial or chest lead is provided for recording on the chest wall. A selector switch on the ECG machine permits several combinations of the leads to be connected to the amplifier and thus the electrocardiogram recorded. The electrodes are smeared with electrode gel to increase the conductivity between the skin and the electrodes.

A. Recording the ECG

1. Apply the electrodes to the subject.
2. Make short records of leads I, II, III, aVR, aVL, and aVF.
3. Record the chest leads in positions 1-6.
4. Keep a record of your tracings.

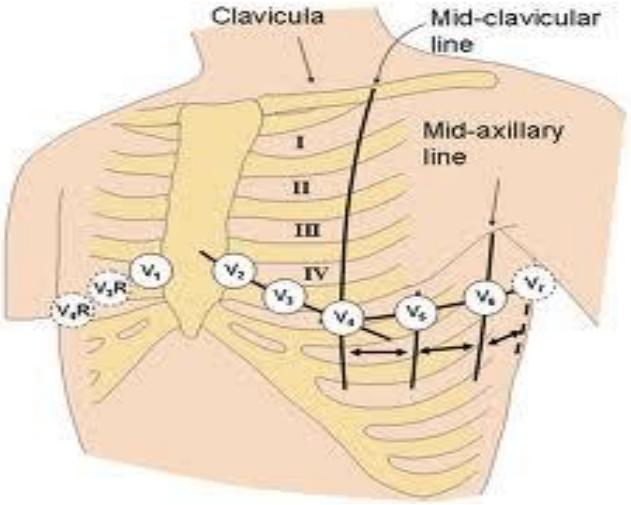

Figure 8.7: Sites of Chest leads

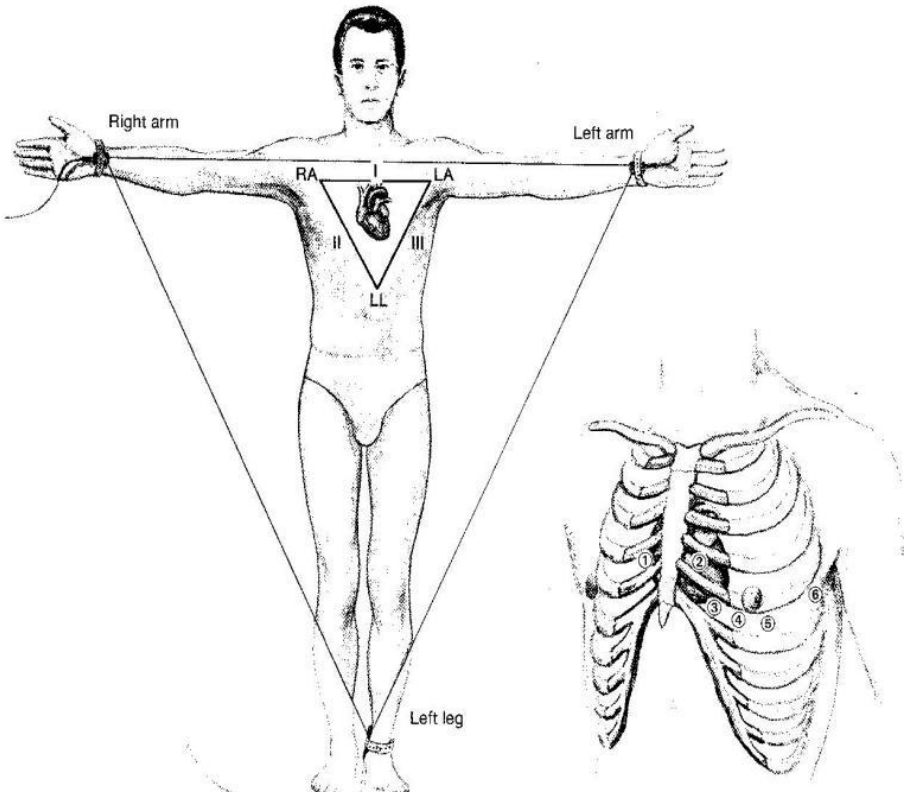

Figure 8.8: Standard Leads

Unipolar Chest (Precordial) Leads

They are six in number, namely V1- V6

V1- fourth intercoastal space, right sternal border

V2- fourth intercoastal space, left sternal border

V3- midway between V2 and V4

V4- fifth intercoastal space, left mid-clavicular line

V5-fifth intercoastal space, left anterior axillary line

V6- fifth intercoastal space, left mid-axillary line

B. Examination of the ECG

1. Identify the principal wave - form on the ECG
2. Calculate the heart rate
3. Calculate the amplitude of P, R and T waves
4. Determine the PR interval
5. Examine the QRS complex and determine its duration
6. Determine the ST interval

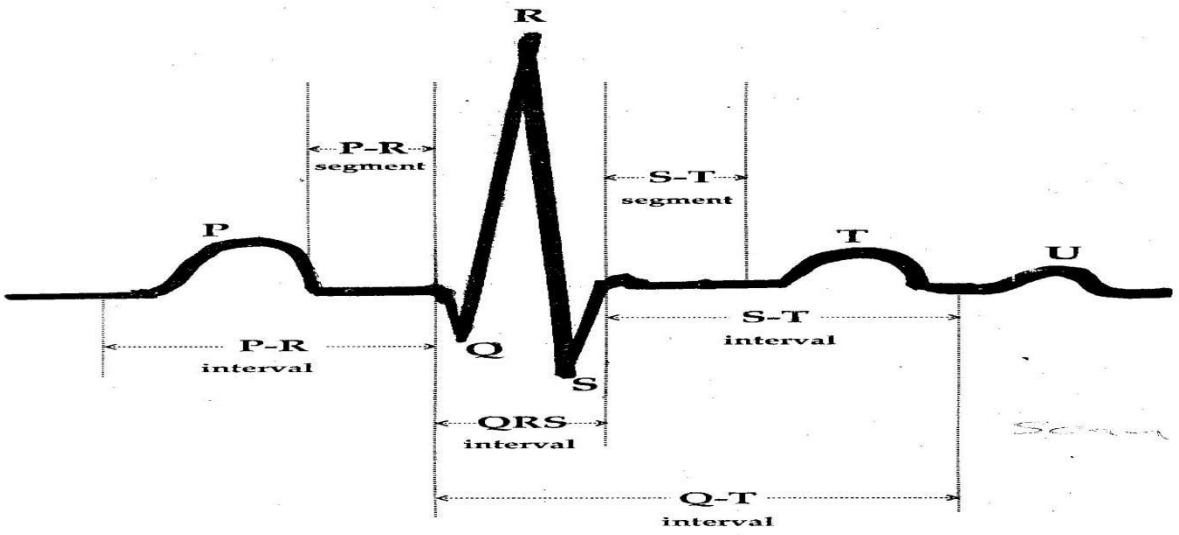

Figure 8.9: . *Electrocardiogram*

C. Analysis of the Electrocardiogram

1. Examine the calibration record to see whether a deflection of exactly 1cm has been produced by 1 mV calibraton signal.

. Make sure that the paper speed has been the standard one (25mm per second). At this speed, each millimeter on the horizontal axis of the record equals 0.04 sec.

3. Measurement of cardiac cycle duration: Measure the length between two successive R waves in mm and multiply it by 0.04 to find the duration of one cardiac cycle in seconds.

E.g. If R - R interval = 18mm cardiac cycle duration = 18 x 0.04 = 0.72 sec.

4. Examination for rhythmicity: The first step is to examine the record by eye and note whether there are some irregularities in the cardiac rhythm. The second step is to apply measurement for more correct examination. Use the procedure described in 3 above to measure 5 successive R - R intervals. If there are R - R intervals which seem to be excessively long or short, measure them also. Write down the findings.

5. Determination of heart rate: You can use one of the following methods:

(a) Calculate the HR of several cardiac cycles as measured in items 3 above.

Then the heart rate HR, is:

$$HR = \frac{1}{\text{Mean R - R interval}} \times 60 \text{ (beat/min.)}$$

Example mean R - R = 0.75 sec.

HR = $\frac{1 \times 60}{0.75}$ = 1.33x60 = 79.8 (or80) beats/min

HR can also be be calculated by $\frac{1500}{\text{No of small squares within R-R Interval}}$

Or $\frac{300}{\text{No of big squares within R-R interval}}$

NB: The multiplication by 60 is applied because the R - R interval is given in seconds, and the HR is given per minute.

(b) Count the number of cardiac cycles per 10 seconds. Let this number be Y, then

10 sec. = Y cardiac cycles

60 sec. (1 min.) = $\frac{Y}{10} \times 60$ = Y.6 cardiac cycles

e.g. 11 cycles in 10 sec.

HR = 11 x 6 = 66 beats/min.

NB: If the heart activity is irregular, the calculation of HR should be based on more cardiac cycles, or on a longer record. The instructions under points 5a and 5b should be considered as examples of the principles and not as rules to be followed strictly concerning the number of cycles or interval within which the cycles are counted.

(6) Measurement of P - R interval: The P - R (from the beginning of the P wave to the beginning of QRS complex) should be measured to see if it is normal, longer than normal or irregular. Increase in P - R interval results from abnormal activity of the conduction system, usually, a delayed transmission through AV node and bundle of His.

(7) Measurement of QRS duration: This is measured from the beginning to the end of QRS complex. Changes in QRS duration occur in bundle branch block, after infarction and during extra systolic beats.

(8) Measurement of Q-T interval: This is measured from the beginning of QRS to the end of T wave. The Q-T interval is altered by abnormal concentration of ions. Since this is related to HR and age, tables must be consulted from normal limits.

(9) Measurement of Voltage of the ECG waves: Select a part of the ECG record without drift (without changes in level of the record). A line between two successive P - R segments. This is the isoelectric line. Deflections above this line are positive and deflections below it are negative. Measure the voltages of P, Q, R, S. and T waves in leads I, II, and III. See whether S - T segment is at the isoelectric line.

Mean Electrical Axis

The mean electrical axis is the average of all the instantaneous mean electrical vectors occurring sequentially during depolarization of the ventricles. The figure below depicts the sequence of depolarization within the ventricles. The septum and free left and right ventricular walls are shown. In this model, each of the four vectors is depicted as originating from the top of the interventricular septum just below the AV node. The electrode placement represents lead II. During ventricular activation, impulses are first conducted down the left and right bundle branches on either side of the septum. This causes the septum to depolarize from left-to-right as depicted by vector 1. This vector is heading away from the positive electrode (to the right of a line perpendicular to the lead axis) and therefore will record a small negative deflection (Q wave of the QRS). About 20 milliseconds later, the mean electrical vector points downward toward the apex (vector 2), and is heading toward the positive electrode. This will produce a very tall positive deflection (R wave of the QRS). After another 20 milliseconds later, the mean vector is pointing toward the left arm and anterior chest as the free wall of the ventricle depolarizes from the endocardial to the epicardial surface (vector 3). This vector will record a small positive voltage in lead II. Finally, the last regions to depolarize will result in vector 4, which will cause a slight negative deflection (S wave) of the QRS.

The shape of the QRS complex is different for each of the leads because each of the leads will "see" the sequence of depolarization vectors from a different perspective. For example, if aVR were used in the above illustration, the QRS complex would have a net negative deflection. That would occur because vectors 2-4 would all be moving away from the positive electrode on the right arm.

In the above illustration, the mean electrical axis will be the sum of all of the mean electrical vectors. The mean electrical axis is depicted by the red arrow in the figure above. In this example, the mean electrical axis is approximately +30º. The mean electrical axis for the heart normally lies between 0 and +90º. Less than 0º is termed a left axis deviation and greater than +90º is termed a right axis deviation. Axis deviations can occur because of the physical position of the heart within the chest (e.g., left axis deviation in severe obesity), or it can occur because of changes in the sequence of ventricular activation (e.g., conduction defects), or because of ventricular regions being incapable of being activated (e.g., infarcted tissue).

The mean electrical axis corresponds to the axis that is perpendicular to the lead axis that has the smallest net QRS amplitude (net amplitude = positive minus negative deflection voltages of QRS complex). In the figure, lead III would have the smallest net amplitude (the ECG would be biphasic with equal positive and negative deflections). The mean electrical axis, therefore, is perpendicular to lead III, which is 120º minus 90º, or approximately +30º in this example. Leads I and II will have equally positive QRS deflections. Lead aVR would have the greatest negative deflection.

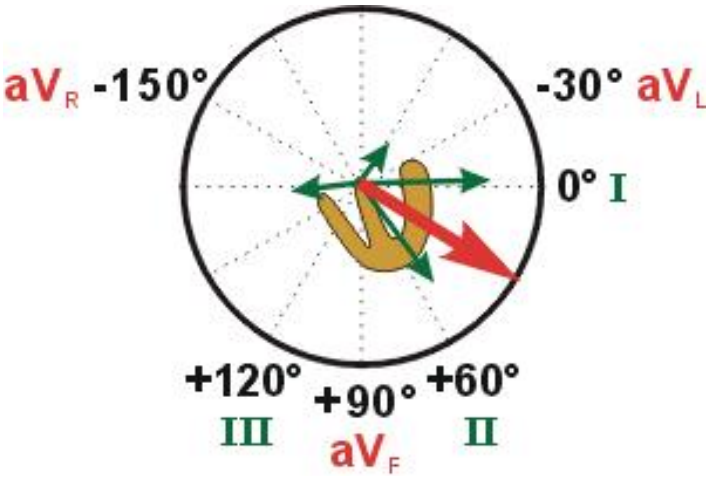

Figure 8.10: Mean Electrical Axis

Determination of Mean Electrical Axis of the Heart

The mean electrical axis is the average of all the instantaneous mean electrical vectors occurring sequentially during depolarization of the ventricles. The mean electrical axis of the heart is calculated according to the method described by Einthoven.

Determine the areas of the positive wave i.e. those above the isoelectric line, as well as of the negative waves for the QRS complex. Subtract negative from positive and obtain the net area in mm. Determine the net areas of QRS in at least 2 leads, preferably I and II. Construct an inverted equilateral triangle with the sides representing Leads I - III. Draw the perpendicular bisectors from the three sides to meet at the centre of the triangle.

Note the positive pole of each side. Project the areas calculated for Leads I and II in mm. on the appropriate side, from the mid-point. Draw perpendiculars at those values from the two sides. The two will intersect at a point. Draw a line from the centre of the triangle to this point of intersection. The angle formed between this line and the horizontal line axis of the heart in degrees.

Exercise:

1. What are the normal values for the PR interval, QRS duration and ST intervals?

2. What do prolongations of the PR interval and QRS duration denote respectively?

3. How can you explain differences in the appearance of the QRS complex from V_1 to V_6 in terms of the mean electrical axis of the heart?

4. What is the normal range for the mean electrical axis of the heart?

5. What do right and left axis deviations indicate?

Examination of The Heart

(a) Inspection

Inspect the front of the subject's chest and look for the apex beat of the heart. This is a pulsation occurring in the fifth intercostal space about the mid-clavicular line. It is most easily seen in a thin person. Incline the subject at 45° and notice if there is filling of the jugular veins. Determine the vertical height of the vein from the sternal angle.

(b) Palpation

This is done with the subject lying down. Place your warm palm over the region of the heart and note the point where cardiac pulsation thrusts maximally against a palpating finger. Determine its location. This is the Apex beat.

(c) Percussion

With the subject supine, place the left palm flat on the chest and tap firmly on the 2nd phalanx of left middle finger with the tip of the right middle finger. Note the character and pitch of the sound produced. Carry out the procedure over the anterior-chest wall, working from the sides towards the midline and note the change in pitch as the finger passes from the resonant lung area to the area of cardiac dullness. The anatomical outline of the heart corresponds to this "area of relative cardiac dullness". Map out this area on the chest

(d) Auscultation

Using the stethoscope, listen to the following areas:

Mitral Area Corresponding to the apex beat

Tricuspid area: Lying just left of the lower end of the sternum

Aortic area: Right of the sternum at the second intercostal space

Pulmonary area: Left of the sternum at the second intercostal space

Note that these positions are where the sounds are best heard and not projections to the surface of the anatomical sites of the valves. The first heart sound is heard as (LUB) while the second is clear short and high in pitch (DUB). The second is followed by a pause.

Summary

Electrocardiogram provides a very important information about the electrical activities of the heart and if properly conducted and interpreted, provides. A good knowledge of the cause of the waves and the normal range of values for the respective intervals and waves provides a reliable information for the diagnosis of cardiac abnormalities.

Exercise:

1. Where is the apex beat located?
2. What are the causes of first and second heart sounds?
3. What type of murmurs are heard best between the first and the second heart sounds?

Spirometry Measurement of Lung Volumes and Vitalography

Overview

The lungs are hidden and protected in the thorax, and this can make assessment and diagnosis of respiratory disorders a bit cumbersome. Lung diseases account for up to 30% of deaths in most countries and a large number of clinic consultations and time away from work. Some of the symptoms of respiratory disorder include: cough, sputum, blood in the sputum (haemoptysis), breathlessness (dyspnoea) and pain in the chest.

Threfore, the role of the respiratory apparatus (the lungs, pleural covering,chest wall and muscles) can be assessed to determine the true state of the respiratory system.

Spirometry is a test used to help diagnose and monitor some lung conditions by measuring how much air that is exhaled in one forced breath. This is done using using a medical device called a spirometer, which is a machine attached via a cable to a mouthpiece. It is the commonest type of pulmonary function assessment. It measures the amount of air an individual can inhale or exhale in the lungs and the ease at which one can force air out of the lungs.

Objectives

The learning objectives are:

1. Identify the symptoms of pulmonary disorders

2. State the usufulness of lung function assessments

3. Identify and set up the equipment used for lung function function test

4. Define the lung volumes and capacities

5. Perform spirometry on a human

Narrative

Measurement of Lung Volumes and Capacities Using a Spirometer

Spirometer measures the rate at which the lung changes volume during forced breathing maneuvers. Spirometry begins with a full inhalation followed by a forced expiration that rapidly empties the lungs. Expiration is continued for as long as possible or until a plateau in exhaled volume is reached. The volumes and capacities usually assessed are Tidal volume (TV), Inspiratory Reserve volume (IRV), Expiratory Reserve Volume (ERV) Forced Expiratory Volume (FEV), Vital Capacity (VC), Timed Vital Capacity (TVC), Inspiratory Capacity (IC), Maximum Voluntary Ventilation (MVV) or Maximum Breathing Capacity (MBC), Ventilation Rate (VR).

This effort is recorded and graphed.

Spirogram of Lung Volume Changes

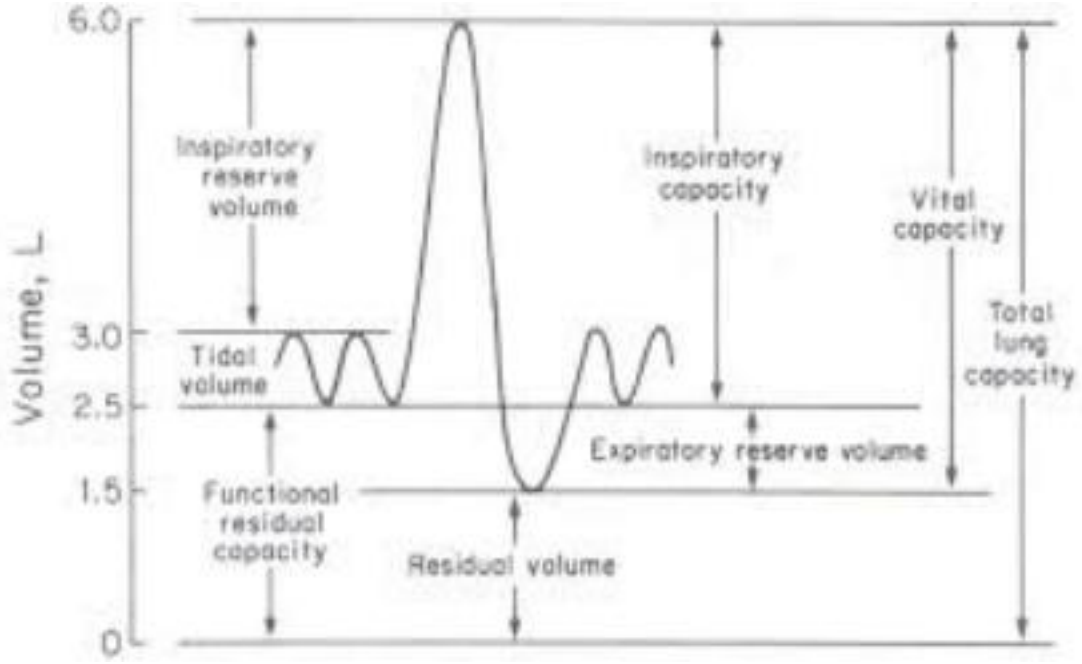

Figure 8.11: Spirogram of Lung Volumes and Capacities

Usefulness of Lung Function Assessment

Spirometric test are performed on a large scale with different objectives in mind e.g.

i. Additional information to help established a clinical diagnosis in a patient.

ii. Assess the prognosis in a patient.

iii. Assess whether disease is present at an early stage, i.e. prior to overt clinical diseases.

iv. Assist in quantifying the severity of air way diseases.

v. Assess the effect of therapy such as corticosteroids, bronchodilators etc.

Lung volume measurement can be done in two ways:

✧ The most accurate way is called body plethysmography. The individual sit in a clear airtight box that looks like a phone booth. The subject will be requested to breathe in and out of a mouthpiece. Changes in pressure inside the box help determine the lung volume.

✧ Lung volume can also be measured when one breathe nitrogen or helium gas through a tube for a certain period of time. The concentration of the gas in a chamber attached to the tube is measured to estimate the lung volume.

Procedure for Spirometry

The steps to be taken vary with the equipment in use and may comprise:

The equipment need to be prepared for the test. Turn the equipment on and allow it to be stable, check for leaks, Fresh hoses, checking recording equipment, performing calibrations. Make available other accessories like fresh mouth piece, nose clip, pieces of gauge etc.

i. Sterilize the mouthpiece with alcohol and apply it in the mouth, between the lips and gums.

ii. Apply nose clips and ensure that there is no leakage.

iii. Let the pointer touch the middle of the drum, which will be moving at a constant slow speed. Take normal inspiration and expiration and record the curves.

iv. This normal curve represents tidal volume, TV

v. Ask subject to take deepest possible inspiration after taking normal inspiration and record the downward and upward movements of the pointer. The length of this record will correspond to the IRV.

vi. Now take the normal respiration, and then take a forceful expiration after a normal expiration. The length of this vertical line correspond to the ERV.

vii. Record normal respiration, and then take a deepest inspiration after normal expiration to record the IC.

viii. In the same vein, take a maximum inspiration, and expire forcibly and completely into the Spirometer. This straight line will give the VC.

ix. Repeat the recording of the VC, but on a moving drum and measure how much volume of air has come out in the first second (FEV_1); how much in the next second (FEV_2) and how much in the third second (FEV_3).

x. Record normal inspiration and expiration for 15 seconds. Multiply the figure obtained by 4 to get maximum voluntary ventilation (MVV) per minute.

xi. Calculate the rate of ventilation by counting the respiratory curves in one minute on the moving drum.

xii. What are the effects of hyperventilation and hypo-ventilation on alveolar gas tension?

The patient

Measure the subject standing height and weight, and confirm if there are any contraindication to performing the test? (Example: recent severe coronary problems, abdominal or thoracic surgery, fractured ribs, lung embolus, severe trauma). Is there any contra-indication to administering bronchodilators? Which drugs are being used at the present, when were they last taken? Is the patient naive to the test or experienced? These are some of the important details needed from the patient before the commencement of the test.

Explain the procedure carefully, demonstrate the maneuvers and get the patients consent and cooperation. Advice against eating a heavy meal before the test and no smoking for 4 to 6 hours before the test.

Let naive patients perform at least two test maneuvers and explain to them how this can be improved.

See to it that the patient's trunk and neck remain erect during the maneuver.

Instruction for an expiratory maneuver

The Patient may be seated or standing See to it that the patient is comfortable, have the patient losing or remove all restricting clotting.

Apply the nose clip with a tissue, hand a tissue out to the Patient for use when removing the mouth piece.

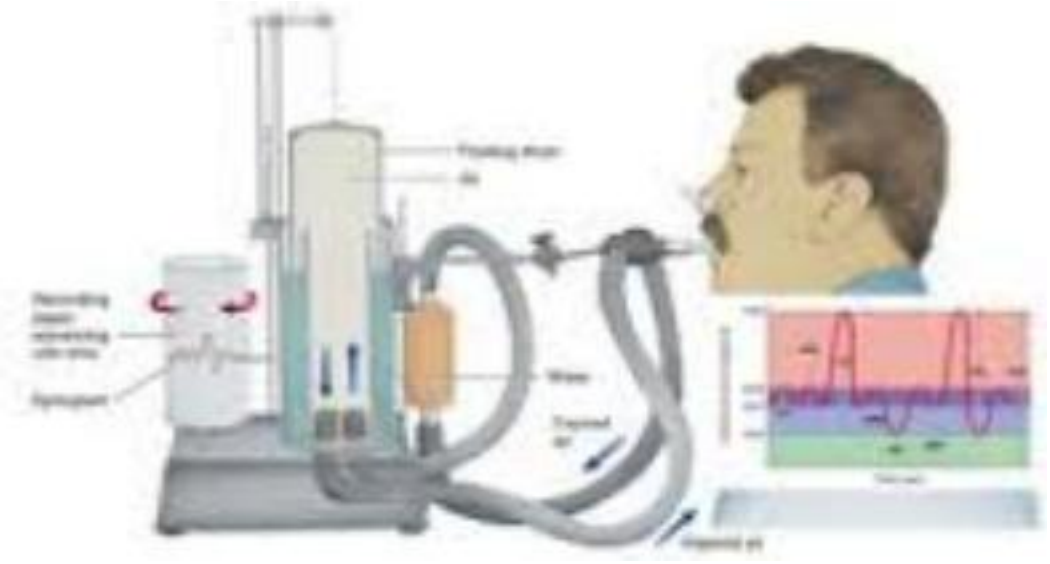

Figure 8.12: Demonstration of Spirometry ~~in Human~~

Ask the patient to gently press against the nose clip to test for leaks

- Hand the measuring device to the patient.
- Ask the patient to place the mouth piece in the mouth, chin slightly elevated, the neck stretched, and
- Allow the patient to get accustomed to breathing in to the apparatus.
- When the patient reached the end of a normal expiration, quickly tell him or her to take a slow deep breath as deep as you can.... Deep ....deep.
- Do not make the patient pause at the level of total lung capacity but say now blow as hard 'as fast as you can

And while the patient blows, out encourage blowing longer by saying blow…. Blow…. keep it coming a little longer… get it all out.

Diagram, showing respiratory excursions during normal breathing, maximal inspiration and expiration.

Discussion: Tabulate your results as follows:

Ventilation Test	Rec	Standing	Exercise
TV			
IRV			
ERV			
IC			
VC			
FEV			
MVV			

Discuss your results.

Normal Result Finding

Normal values vary based on the age, height, race, and sex. Normal results are expressed as a percentage. A value is usually considered abnormal if it is approximately less than 80% of the predicted value.

The measurements that are usually reported after pulmonary function tests include:

- ✧ Diffusion capacity to carbon monoxide (DLCO)
- ✧ Expiratory reserve volume (ERV)
- ✧ Forced vital capacity (FVC)
- ✧ Forced expiratory volume in 1 second (FEV1)
- ✧ Forced expiratory flow 25% to 75% (FEF25-75)
- ✧ Functional residual capacity (FRC)
- ✧ Maximum voluntary ventilation (MVV)
- ✧ Residual volume (RV)
- ✧ Peak expiratory flow (PEF)
- ✧ Slow vital capacity (SVC)

- ✧ Total lung capacity (TLC)

Vitalography

This provides accurate and effective monitoring of lung function for respiratory conditions such as chronic obstructive pulmonary diseases (COPD), cystic fibrosis, emphysema etc.

The key measurements are:

- ✧ Forced vital capacity (FVC). This is the largest amount of air that an individual can forcefully exhale after maximum inspiration. A lower than normal FVC value indicates restricted breathing.
- ✧ Forced expiratory volume (FEV). This is the volume of air one can forcefully exhale from your lungs in one second. This value helps to assess the severity of a respiratory problems. Lower FEV_1 value indicate a more significant obstruction of the airway.

Summary

There are many types of spirometer available which records similar information. There may detect diffuse airflow obstruction,obstructive and restrictive patterns. The popular instrument for the assessment of air flow obstruction id the peak flow meter. There ia a type that is cheap and can be used at homes- the mini peak flow meter

Exercise

1. What is Spirometry

2. What are the parameters that can be assessed using a spirometer

3. Draw a labelled diagram showing a typical spirogram

4. List the lung volumes and capacities

5. Highlight the procedure for spirometry to be done in a human

Urinalysis and Urine Microscopy

Overview

Definition and aims:

Urinalysis is the physical examination of the urine for physical or chemical properties including the presences of urine solutes, cells, casts, crystals, organisms, or even particulate matter. A urinalysis should include the physical (urine macroscopic) examination of the urine, chemical evaluation using urinary strips and a further microscopic (urine microscopy) examination of urine.

Urinalysis is a cheap, common, and easily administered test on urine and can be performed as a first line examination on any prospective patient. It can thus be easily performed on apparently healthy subjects in the physiology laboratory. It is also non-invasive as minimal contact is involved with any subject for urinalysis. Preliminary results obtained from a simple urinalysis or urine microscopy may warrant further detailed chemical, bacteriologic or indeed immunological studies.

These experiment aims at successfully conducting a simple urinalysis and urine microscopy for a cohort of healthy subjects.

Introduction

Urine is an ultrafiltrate of blood, formed at the nephron. The nephron being the basis functional unit of the kidney. The renal artery supplies each kidney with blood which ultimately enters the renal glomerulus a loop of capillaries surrounded by the Bowmans capsule. Normally the glomerulus does not allow cells or proteins to pass through, allowing mostly fluids; in other words, disallowing most formed elements of blood and high molecular weight proteins in blood. The filtrate formed by the kidney goes through the renal tubules where it undergoes modifications via both secretion and reabsorption of solutes or solvents. From the renal tubules the fluid goes to the proximal convoluted tubule, distal convoluted tubules, the loop of Henle, and then to the collecting ducts. The collecting ducts drain to the ureters and into the bladder. Urine exits the body, through the urethra. Via urine formation, the urinary system contributes the maintenance of homeostasis. The final chemical composition and physical properties of urine are therefore critical indicators of the optimal functioning of the bodies physiological processes.

Apparatus and materials

Human subjects, sterile universal sample bottles, bucket centrifuge, binocular microscope, microscope slides, available reagent-impregnated test strips, latex gloves, urinometer, dilute acetic acid, cover slips.

Methods

Allow the subject to visit the convenience and freely provide urine in the universal sample bottle. The sample obtained should be best examined immediately after presentation. At least 10mls of urine should be voided.

Urine macroscopy: This involves the physical examination (inspection) of the urine. Place the urine under a natural light source and observe the following: colour, clarity, consistency (turbidity) and crystals. Normal urine colour is usually described as clear to pale yellow and indicates the presence of normal urochrome pigments. A lighter coloured urine is typically seen with dilute urine. Brown urine suggest the presence of bile pigments or faeces in the urine; while a reddish urine suggests the presence of haemoglobin pigment, myoglobin or drug therapy with rifampicin or laxatives with phenolphthalein. A milky white urine suggests presence of pus indicating a urinary tract infection. Green urine suggests the presence of bilirubinuria.

Smell: Urine is usually odourless but may acquire a strong smell if the urine is concentrated due to subject dehydration. Urine may have a sweet smell in subjects with ketone bodies in the urine (diabetic subjects in ketoacidosis) and a foul smell in subjects with urinary tract infections.

Urinalysis:

This can be loosely defined as the use of urine test strips or ‘dipsticks’ for the rapid and convenient determination of numerous urine parameters and chemical composition. The test strips are previously impregnated with various chemicals that have been standardized for rapid and convenient determination.

Procedure: Wear your gloves and rapidly dip a test strip into the urine sample voided ensure that the urine reaches all necessary portions of the strip. Withdraw the strip and compare colour changes on the strip with that on the test strip standard. It is usually provided on the test strip container.

The presence or absence of the following parameters can usually be determined in the urine with the urinalysis strip: blood, white blood cell, nitrites, protein, pH, glucose, ketone bodies, bilirubin, urobilinogen, and specific gravity.

Blood or haemoglobin are usually absent in normal urine samples. Elevated white blood cells in urine are usually suggestive of urinary tract infection or inflammation. The presence of nitrites is also suggestive of urinary tract infection, although nitrites are not sensitive, and a negative result does not exclude urinary tract infection. Trace amount of protein in urine is normal higher levels however is suggestive of kidney diseases; most proteinuria is usually caused by albuminuria. Glycosuria indicates glucose in urine. Glucose is usually absent in the urine with a normal glucose concentration. Trace amounts can be detected with occasional high blood glucose as glucose in a urinary threshold substance. However, glucosuria may occur in pregnancy. Ketonuria typically occur in diabetic ketoacidosis. It may also occur with severe fluid losses, during starvation or after strenuous exercise.

Bilirubin is a waste product of haem metabolism. Bilirubinuria actually occur in liver diseases or bile duct obstruction. Bilirubin does not present in normally present in urine. Urobilinogen is a product formed from the actions of the bacteria of the intestinal flora actions on bilirubin. Small fractions may appear in normal urine. The presence of urobilinogen indicates liver disease or haemolytic jaundice. The normal range of urine specific gravity is usually between 1.003 to 1.040 depending on the subject's hydration status and the functional integrity of the loop of Henle and the posterior pituitary gland. Specific gravity of urine is the weight of a given volume of urine divided by the weight of an equal volume of water. It can also be determined using a urinometer. Urinary pH is expression of the hydrogen ion concentration in the urine. An elevated urinary pH in the presence of an elevated white blood cell and bacterial count in the urine is suggestive of urinary tract infection particularly if the urine was freshly obtained. The normal urine pH is between 5 to 9. An acidic urine (low urinary pH) is suggestive of acidosis.

Urine microscopy:

This is the examination of the urine using a microscope. Microscopic examination of the urine is usually revealing and is indicated following some abnormal results obtained with urinalysis. It is usually routinely done in infants. A urinalysis indicating abnormal colour or a positive dipstick for blood, white blood cell, nitrites or protein are indications for microscopy.

Methods

Obtain at least 10ml of urine add 1ml of dilute acetic acid if the urine is alkaline to help dissolve urinary phosphates. Centrifuge urine at 2000 to 3000 rpm for 3 to 5 minutes. Discard the resulting urine supernatant formed and gently mix the sediment with the remaining fluid. Place a drop on a microscopic slide, cover with a cover slip and examine under the microscope under low light conditions. Scan the slide at low power(100X) and high power (400X) and with polarizing light. The presence of the following parameters should be determined: red blood cells, white blood cells, epithelial cells, casts, crystals, bacterial organisms, fungi or parasites during urine microscopy.

Interpretation is as follows: Less than 5 red blood cells is usually normal under the high power magnification of the light microscope; an increased level being defined as haematuria. Microscopic haematuria may occur in

apparently healthy subjects following exercise or due to menstrual contamination amongst reproductive aged females. Common causes of haematuria include urinary tract infections or trauma, drug toxicity or other renal or systemic diseases. White blood cells typically neutrophils with a clear visible nucleus can be identified. Less than 5 white blood cells under high power magnification are normal amongst healthy subjects. An increased number of white blood cells in the urine is called leukocyturia and indicates either infection or inflammation of the urinary tract. Eosinophils may also be found in the urine with high power magnification of the light microscope. Epithelial cells are usually cell discards from the epithelial lining of the renal tubular system; less than 5 epithelial cells is usually normal under the high power magnification of the light microscope. Renal casts are usually visible and can take various different shapes and sizes occasionally incorporating proteins, erythrocytes, leucocytes, bacteria, yeasts and bilirubin pigments into their moiety. Renal crystals are precipitations of compounds in the urine. These crystals are commonly formed by uric acid, calcium oxalate and calcium carbonate. The presence of crystals are suggestive of renal stones. The presence of renal stones in the urine is called crystalluria. Micro-organisms may occasionally be found in the urine. These may include bacterial and yeast cells and *Trichomonas vaginalis* amongst females. Parasitic infections like *Schistosoma haematobium* the causative organism for schistosomiasis can be found in the urine of affected individuals.

Discussions and Clinical Significance

The proper interpretation of the urinalysis results of a subject should include an appraisal of the results of the chemical, physical and microscopic examination of the urine. Not all abnormal urinalysis results signify disease and vice versa. A positive dipstick will therefor require microscopic confirmation for red blood cells, white blood cells, bacteria and other possible contaminants. An elevated protein in urine is suggestive of renal disease only after excluding exercise, fever, stress and infection.

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Chapter 9

PHS 301: GASTROINTESTINAL SYSTEM

Samuel Odu Odeh, Aliyu Mohammed, Walter Chukwuma Nwafia

OVERVIEW

The gastrointestinal physiology otherwise referred to as the alimentary or digestive system deals with the fate of food ingested, and the fate of the individual after taking in the food. There is the conventional component of the GIT namely the oesophagus, stomach, small intestine (duodenum, jejunum and ileum), and the large intestine (colon). Other structures contribute to the efficiency of the GI system functions, and these include the mouth (oral or bccal cavity), the salivary glands (parotid, submandibular and sublingual), the pancreas, liver, and gall bladder. Food ingested is progressively displaced from the oesophagus until it reaches the rectum from where the waste (stool) is excreted through the anus. The GIT is well supplied with blood. Indeed, about 9 litres of water revolves round the GIT per day. Two litres of this amount is via ingestion while the rest 7 litres is a product of cellular metabolism. The GIT is innervated both intrinsically and extrinsically. The intrinsic innervation is by the plexuses of nerves (Meissner's and Aubach"s). The vagus nerve supplies the GIT extrinsically via the sympathetic and parasympathetic divisions. These divisions of the autonomic nerves act in opposition to each other. The parasympathetic is responsible for the motility while the sympathetic acts more to enhance secretions.

In the GIT, with contributions of the juices, enzymes and hormones, food ingested is hydrolytically broken down and absorbed. In each of the segments of the GIT, the enzymes and hormones present are responsible for the digestion and absorption of food substances. The waste products of food digestion are excreted through the anus.

While the GIT is presented as a near perfect system, it may still present some physiological defects. For instance, in conditions of acid functional imbalance, peptic ulcer disease develops. Similarly, there could be disturbances of movement in the GIT resulting in the syndrome of gastro oesophageal reflux disorders.

OBJECTIVE

At the end of this course, the student is expected to:

1. Describe the structure, blood supply and innervation of the GIT
2. Explain the mechanisms underlying the types of movements that occur in the GIT
3. Explain the various secretions that occur in the GIT (salivary, pancreatic, gastric, intestinal, biliary, etc)
4. Describe the processes involved in the digestion and absorption of the major classes of food (carbohydrate, protein, and lipids)
5. Describe some common disorders of the GIT
6. Explain the structure and functions of the liver, and the biliary tree.

PHYSIOLOGIC ANATOMY OF THE GASTROINTESTINAL TRACT

The gastrointestinal tract (GIT) physiology is the study of the normal functions of what is also referred to as the digestive system or alimentary system. The human gastrointestinal tract is a stretch of muscular tube consisting of the oesophagus, stomach, small intestine, large intestine, rectum and anal canal. The ducts of the salivary glands open into the mouth. The small intestine extends from the pyloric sphincter to the ileum. The bile duct and pancreatic duct jointly open in it through ampula of Vater. The small intestine opens into the next part-the large intestine. The opening between them is guarded by iliocolic sphincter. The large intestine opens into the last part-rectum and anal canal. The latter opens outside through the anal orifice.

Gastrointestinal blood circulation

The splanchnic circulation includes blood flow through the gut itself plus blood flow through the spleen, pancreas and liver. The blood carries the absorbed water, electrolytes, nutrients and hormones etc. from the GIT and flows immediately into the liver via the portal vein. In the liver, the blood passes through the liver sinusoids and finally leaves the liver via the hepatic vein. Gastrointestinal blood flow is usually proportional to the level of local activity. For instance, during active absorption of nutrients, blood flow in the villi and adjacent regions of the submucosal is greatly increased. Likewise, blood flow in the muscle layers of the intestinal wall is greater with increased motor activity in the gut.

Absorption, as would be expected is rather insignificant in the mouth and stomach. The presence of numerous tall villi in the small intestines especially the duodenum and the jejunum (valvulae connivances), provide increased surface area over the gut lumen for the absorption, and the movement pattern in villi derived from the local neural influence aids absorption markedly. However, in the mouth and stomach certain highly lipid soluble substances (e.g. drugs, alcohol) are appreciably absorbed. Absorption of any given substances can be achieved either by simple diffusion or by active transport. Simple diffusion as a means of absorption to a large extent depends on the differential concentrations of the substance across the absorption compartments. It does not involve the expenditure of energy and is known as passive transport. Substances that are actively transported usually do not necessarily have to have different concentrations in the different compartments. There is an energy driven mechanism (usually from adenosine triphosphate, ATP) that is responsible for active transport. Active transport also implies some degree of resistance mounted against the absorption procedure. This resistance could result from the concentration of the substance in the recipient compartment, the mechanical barrier of the cell membrane, the molecular size (weight) of the substance or from some other forms of systemic influence (e.g. malabsorption syndromes).

Absorption takes place over the Villi present in the GIT. A villus is made of the epithelial lining cells which are also referred to as enterocytes. Within the villi interstitium, there is the presence of a good network of capillaries and the central lacteal. The ability of substances to traverse these layers is to a great extent also affected by their lipid solubility. This is described for the different classes of food as below.

The gastro-intestinal tract, like other systems of the body is under some form of controls. These include:

Neural control

The GIT is innervated both intrinsically and extrinsically. It has its own nervous system called the enteric (intrinsic) nervous system. The intrinsic nervous system lies entirely in the wall of the gut, beginning in the oesophagus and extending all the way to the anus. The enteric system is composed mainly of two plexuses.

1) The myenteric plexus or Auerbach's plexus, an outer plexus which lies between the circular and the longitudinal muscle layers. Stimulation of this plexus causes the following; increased "tone" of the gut wall, increased intensity of rhythmical contractions, and increased velocity of conduction.
   The myenteric plexus is also useful for inhibiting the pyloric sphincter which controls emptying of the stomach and the sphincter of the ileocaecal valve, which controls emptying of the small intestine into the caecum.

2) The submucosal (Meissner's) plexus, an inner plexus located between the muscularis mucosae and the layer of circular muscle. In contrast to the Myenteric plexus, it is mainly concerned with functions in the inner wall of each minute segment of the intestine to help control local intestinal secretion, absorption, and contraction of the submucosal muscle.

The extrinsic innervation is basically by the cranial and the sacral nerves divisions. The parasympathetic nerves increase the activity of the enteric nervous system. This in turn enhances the activity of gastrointestinal functions. The cranial parasympathetic division of the vagus innervates the oesophagus, stomach, pancreas and first half of the large intestine. It is responsible for most of the motility efforts in the GIT. The neural impulses in the GI also lead to the changes in types and phases of secretion. The sacral parasympathetics from the pelvic nerve innervate the distal half of the large intestine. The sigmoid, rectal and anal regions have an especially rich supply of parasympathetic fibers that function in defaecation reflexes.

The sympathetic nervous system usually inhibits the activities of the GIT causing many effects opposite to those of the parasympathetic system. The sympathetics innervate all portions of the GIT. The sympathetic nerve endings secrete norepinephrine, which exerts its effects in two ways:

1) by a direct action that inhibits smooth muscle,
2) by an inhibitory effect on neurons of the enteric nervous system.

Gastrointestinal reflexes

Three types of reflexes are essential for gastrointestinal control:

1) Reflexes that occur entirely within the nervous system control gastrointestinal secretion, peristalsis, mixing contractions, local inhibitory effects etc.
2) Reflexes from the gut to the sympathetic ganglia and then back to the gut transmit signals from long distances; e.g., signals from the stomach cause evacuation of the colon (gastrocolic reflex), signals from the colon and small intestine inhibit stomach motility and stomach secretion (enterogastric reflex), and reflexes from the colon inhibit emptying of ileal contents into the colon (ileocolic reflex)
3) Reflexes from the gut to the spinal cord or brain stem and then back to the gut include, in particular: (a) reflexes from the stomach and duodenum to the brain stem and back to the stomach via vagus nerve which controls gastric motor and secretory activity; (b) pain reflexes that cause general inhibition of the entire GIT; (c) defaecation reflexes that travel to the spinal cord and back again to produce the powerful colonic, rectal, and abdominal contraction required for defaecation.

Hormonal control

The hormonal control involves the roles of hormones and neurotransmitters. When these agents bind to specific receptors there would be a release of second messengers. This event is accompanied by the release of

intracellular calcium, with the consequent activation of protein kinase. Some of the hormones influencing the GIT include**:-**

i. Gastrin**;** this is a potent hormone, with trophic effects on the gastric mucosa. It greatly influences secretion and motility.

ii. Secretin**;** secretin increases bicarbonate secretion from pancreatic and biliary ducts.

iii. Cholecystokinin**;** it is trophic on the pancreas and increases pancreatic secretions.

iv. Somatostatin**;** it inhibits the release of gastrin, and reduces gastric acid, pepsin and pancreatic secretions. The hormone also decreases the absorption of fat.

v. Neurotensin**;** it mediates inhibitory effects of fat in , the duodenum, and inhibits gastric secretions.

The gastrointestinal hormones are released into the portal circulation and exert physiological action on target cells with specific receptors for the hormones. The effects of the hormones persist even after all nervous connection between the site of release and the site of action has been severed.

REVIEW OF SMOOTH MUSCLE FUNCTIONS

Smooth muscle is present throughout the body, where it serves a variety of functions. For example, in the stomach and intestines, it helps with digestion and nutrient collection. Smooth muscle differs from skeletal muscle in its ability to be contracted and controlled involuntarily. Smooth muscle contains thick and thin filaments that do not arrange into sarcomeres, resulting in a non-striated pattern. Smooth muscle cytoplasm contains large amounts of actin and myosin. Actin and myosin act as the main proteins involved in muscle contraction. The shape of smooth muscle is fusiform, which is round in the center and tapering at each end. Smooth muscle can tense and relax but has greater elastic properties than striated muscle.

The primary function of smooth muscle is contraction. Smooth muscle consists of two types: single-unit and multi-unit. Connexins allow for cell-to-cell communication between groups of single-unit smooth muscle cells. This intercellular communication allows ions and molecules to diffuse between cells giving rise to calcium waves. Multi-unit smooth muscle differs from single-unit in that each smooth-muscle cell receives its own synaptic input, allowing for the multi-unit smooth muscle to have much finer control. The function of smooth muscle can expand on a much larger scale to the organ systems it helps regulate.

Smooth muscle contraction depends on calcium influx. Calcium increases within the smooth muscle cell through two different processes. First, depolarization, hormones, or neurotransmitters cause calcium to enter the cell through L-type channels located in the membrane. Intracellular calcium then stimulates the release of calcium from the sarcoplasmic reticulum by the process referred to as calcium-induced calcium release. Once calcium has entered the cell, it is free to bind calmodulin, which transforms into activated calmodulin. Calmodulin then activates the enzyme myosin light chain kinase which then phosphorylates a regulatory light chain on myosin. Once phosphorylation has occurred, a conformational change takes place in the myosin head; this increases myosin ATPase activity, which promotes interaction between the myosin head and actin. Cross-bridge cycling then occurs, generating tension. Smooth muscle contraction is enhanced even further through the use of connexins. Connexins allow for intercellular communication by allowing calcium and other molecules to flow to

neighboring smooth muscle cells. This action allows for rapid communication between cells and a smooth contraction pattern.

Dephosphorylation of myosin light chains terminates smooth muscle contraction. Unlike skeletal muscle, smooth muscle is phosphorylated during its activation. This creates a potential difficulty in simply reducing calcium levels so that smooth muscles will not produce muscle relaxation. Myosin light chain phosphatase (MLCP), is the one responsible for dephosphorylation of the myosin light chains, ultimately leading to smooth muscle relaxation. Another important clinical aspect of smooth muscle relaxation is the mechanism of nitric oxide. Nitric oxide is formed by the action of nitric oxide synthase in endothelial cells. NO is able to diffuse out of the endothelium into smooth muscle cells. Nitric oxide then induces the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP) by binding to and activating the enzyme guanylyl cyclase. In smooth muscle cells, the increase in cGMP will lead to stimulation of cGMP-dependent protein kinase, which in turn activates MLCP, leading to dephosphorylation of myosin light chains and eventual smooth muscle relaxation.

Smooth muscle action potentials are unique in that membrane potential acts to initiate or modulate contraction. Graded membrane response can become stimulated by multiple factors. These factors include local humoral factors, circulating hormones, or mechanical stimulation like stretching of the cells. Action potentials in smooth muscle cells are slower than skeletal action potentials. Sodium channels may also be present on the smooth muscle membrane and function by increasing the rate of depolarization which will aid in the activation of calcium channels.

Some smooth muscle cells also display the ability to form a spontaneous pacemaker current. This pacemaker current, for example, is maintained in the intestines by the interstitial cells of Cajal. The pacemaker current represents waves of action potential in the membrane potential that occur in several cycles. These slow waves of membrane potential fluctuation are unique in that they are not responsible for the contraction of the intestines, but rather serve to augment the strength of contraction in a particular location in the gut. Calcium influx stimulates Na-Ca exchange, which leads to an influx of sodium; this will effectively increase the rate of the Na-K pump. The slow waves are, therefore, able to allow the smooth muscle to remain tonic without having to maintain continuous action potential firings.

The gastrointestinal tract is mostly dependent on smooth muscle for motility. Any damage to the smooth muscle of the intestines may have a devastating effect on the body. An example of this is gastroparesis. Many conditions can impact gastric motility, including nerve dysfunction, collagen disease, muscular dystrophies, amyloidosis, thyroid disease, diabetes mellitus, Chagas disease, and neuropathies

SECRETIONS OF THE GIT AND THEIR CONTOL

Secretions, generally, is the net movement of water and electrolytes, lipids and proteins into the lumen of the GIT, or into the ducts of digestive glands. Most of secretions are ultra-filtered products of plasma.

Salivary gland secretions

In the human, there are three pairs of salivary glands. These are the parotid, sub-mandibular, and the sublingual. Their product is the human saliva. Saliva is hypotonic to plasma, being secreted at a rate of 1 to 1.5litres/day. That translates to about 1 ml/min., for an actively secreting gland. At rest however, the rate of secretion is

markedly reduced being 0.025ml/min. The constituents of saliva include enzymes (e.g. α-amylase/ptyalin lipase, ribonucleases, and esterases). Saliva also contains glycoproteins, especially mucus (sialic acid, neutral sulphates), and certain blood group substances. Other constituents of the human saliva are electrolytes, immunoglobulins and lysozymes.

The quality of saliva however depends on the stimulus of secretion, and the rate of secretion. For instance, in periods of fasting, the saliva is usually "thick" (i.e. mucoid) while at meals, it is "watery (serous). The salivary glands have great influence from the autonomic nervous system. The sympathetic nervous influence increases blood supply to the glands and also increases the transit time of saliva in the ducts. The overriding influence of the sympathetic innervation therefore, results in the production of serous saliva. The parasympathetic division would promote the production of mucoid human saliva.

The functions of the human saliva are:

i. Lubrication of food substances for the ease of swallowing,

ii. It dissolves materials to facilitate the sense of taste,

iii. It serves as an antiseptic for the mouth and teeth,

iv. It facilitates speech,

v. saliva cools hot food

vi. Saliva serves excretory routes for some substances,

vii. The ptyalin content initiates the digestion of carbohydrates, while lingual Lipase helps the digestion of short chain lipids.

Salivation is controlled via the parasympathetic system from the salivary nuclei in the brain stem. Factors that induce salivation include: taste stimuli, especially sour taste, higher centres appetite anticipation, smells and visual clues. Secretion is also induced in response to signals from the stomach and upper GI tract, particularly irritating stimuli. Salivation can also occur as a prelude to vomiting.

Gastric secretion

Gastric secretions refer to secretions of stomach origin. One of the basic functions of gastric secretions is the production of gastric acid for the maintenance of relative sterility of the gut. The gastric secretions also enhance the processes of the hydrolytic breakdown of food, and the absorption of minerals and vitamins.

The secretions of the stomach include hydrochloric acid (Hcl) pepsinogen, mucus, glycoprotein, intrinsic factor, and electrolytes. The secretions of the stomach include hydrochloric acid (Hel) pepsinogen, mucus, glycoprotein, intrinsic factor, and electrolytes. The gastric secretions are regulated at three planes. Firstly, there is a psychological influence on gastric secretion. This is also referred to as the cephalic phase, and is mediated by some fibres of the vagus nerves following taste, smell, and sight or swallowing of food. This phase is inhibited by depression, grief, fear or drugs. Secondly, local Meissner's and myenteric nerve plexuses act at what is referred to as gastric phase to promote gastric secretions. There is also a vagal reflex contribution to the gastric phase, in addition to the effects of hormones and direct stimulation. The third phase is known as the intestinal

phase. The exact model by which it increases gastric secretion is not yet known. However, the presence of some peptides, gastrin and histamine in the gastric and intestinal mucosa is being implicated. The gastric phase is inhibited by excessive acids in the stomach while the intestinal phase is inhibited by fats and hypertonic saline. The functions of HCl include;

a. Activation of pepsinogen to pepsin.

b. Provides an acid medium for the action of pepsin.

c. Being a strong acid, it can kill many bacteria that have entered stomach along with the food.

d. HCl in the duodenum can stimulate and increase the secretion of bile from liver and the exocrine secretion from pancreas.

Acid is secreted in large quantities when the stomach is distended with food, helping to facilitate the initial breakdown of proteins. Once the stomach has emptied, gastric acid secretion stops, and remains shut off during the inter-digestive period. This shut-off in acid secretion prevents the excessive acid from damaging the mucosa of the stomach and small intestine.

Pancreatic secretions:

The pancreas is a slender, long organ lying below the greater curvature of the stomach. The pancreas has two cell types, the exocrine and the endocrine. Exocrine pancreas secretes the juice while the endocrine pancreas secretes hormones like insulin, glucagon and somatostatin. Pancreatic juice contains enzymes which include trypsin, carboxypeptidases, pancreatic amylase and lipase, among others. The juice also contains immunoglobulins, other proteins (in a concentration of 7mg/ml) and electrolytes. The pancreas secretes juice at a rate of 0.2 to 0.3 ml/min. Trypsin displays an additional property of being able to activate other proteolytic enzymes in the pancreas.

Pancreatic juice contains enzymes which include trypsin, carboxypeptidases, pancreatic amylase and lipase, among others. The juice also contains immunoglobulins, other proteins (in a concentration of 7mg/ml) and electrolytes. The pancreas secretes juice at a rate of 0.2 to 0.3 ml/min. It is actively involved in the synthesis of proteins, and its secretion is isosmotic with plasma. The potassium and sodium ions in the juice are nearly isotonic to plasma irrespective of the blood flow to the organ. However, bicarbonate and chloride ions concentrations vary significantly, depending on the rate of flow of the juice.

The pancreatic secretion is regulated at two levels, neural and hormonal. The neural control corresponds to the cephalic and gastric phases of the gastric secretion. The hormonal phase of regulation involves the role of hormones like secretin and cholecystokinin in stimulating the pancreas to secrete.

Biliary secretion

This refers to the secretion of bile. Bile is secreted by the liver but is concentrated and stored in the gallbladder. The liver has the ability to form 0.5g bile salts daily. The bile salts are converted to bile acids, cholic acid and chemodeoxycholic acid, which conjugate with glycine or taurine. Bile contains cholesterol, water, bile salts and acids, and phospholipids especially lecithin. Bile also contains electrolytes, protein and the yellow pigment,

bilirubin. The liver secretes about 600ml of bile daily. Biliary secretion is controlled principally in the entero-hepatic circulation.

Bile performs several functions in GIT physiology. It has the property of emulsification, decreasing the surface tension of fat particles (i.e. a detergent. action) to ease digestion. It helps in increasing surface area to help enzyme action, and thus aids in their absorption in the small intestine. Bile prevents the reversible reaction between free fatty acids and Glycerol, Monoacyl glyceraldehyde and diacyl glyceraldehyde. It also makes the acidic food coming from the stomach alkaline, so as to enable the action of pancreatic enzymes whose activities are inhibited by acidic chyme.

Intestinal secretions

The secretions in the small and large intestines are derived from some specialised cells in these locations. The Brunner's gland and mucus cells in the small intestine produce mucus. The mucus production usually follows tactile stimulation of the mucosa, vagal stimulation, or release of intestinal hormones. The small intestines also produce digestive juices from the crypts of lieberkuhn. This juice contains enterokinase, amylase, lipase and peptidases. The large intestine secretes mucus from the goblet cells, and following irritation, secretes water and electrolytes.

MOVEMENTS OF THE GASTROINTESTINAL TRACT

Mastication

Mastication (chewing) takes place in the mouth. The structures of relevance here include the teeth, tongue, cheek, jaw bones and muscles. The muscles of mastication include the masseter, medial pterygoid, temporalis (these on one hand); and, the lateral pterygoid and digastric (on the other hand). The teeth crush solid particles and the tongue initiates the process of swallowing (deglutition). The cheeks hold the food particles in place within the buccal cavity. The importance of the cheek becomes more glaring in the condition known as cancrum oris. In this condition, usually in malnourished children, diminished blood flow to the mouth leads to an eventual neurotic breakdown of the cheek. The tissue sloughs off, revealing the teeth from the side, and food escapes chewing through this pathologic orifice.

Movements at the jaw joints are the basic mechanism in the chewing process. Nerve endings in the gum get stimulated when they come in contact with food particles. The impulse from this stimulation passes on to muscles of mastication. In one phase, the simultaneous contraction of the masseter, medial pterygoid and temporalis, lead to an opening at the jaw joint. While this is taking place, there is a spontaneous relaxation of the lateral pterygoid and the digastric muscles. The next phase reverses the contraction and relaxation between the two muscle groups: The continuous, alternate contractions and relaxations these groups of muscles lead to the apposition of the upper and lower sets of teeth and the eventual crushing of the food particles on them. Because of the involvement of the neural pathway in this process, it is also referred to as the chewing reflex.

Mastication could be voluntary though, to as much as the desire to do so is concerned. The rest of the processes are involuntary. In mastication, the aim is to decrease the size of foe particles, creating an increase in surface area for enzymic activity, and to make the process of swallowing more convenient.

Deglutition

Deglutition means swallowing, and is the passage of food from the buccal cavity through the oesophagus to the stomach. There are three phases to swallowing:-

i. The buccal phase:-

The buccal phase is voluntary, and involves the sides, the tip rolls up, and the entire tongue then retracts. The roll-up and retraction effects pass the food substance towards the pharynx. The soft palate is pulled upward

ii. The pharyngeal phase:-

This is an involuntary phase. It involves the regulation of the food particle into the oesophagus. The epiglottis closes and the food is directed into the oesophagus. This phase once commenced cannot be stopped.

iii. Oesophageal phase:-

This refers to transit of food substances through the oesophagus. Normally, an individual would attempt swallowing in a sitting or reclining positions. These postures confer an extra advantage from gravity. Gravity aids the oesophageal transit of food. Another factor that enhances the oesophageal phase of deglutition is the wave of peristalsis. The wave of peristalsis is ordinarily a weak force but the effect of gravity assists the propulsive movement of the food substance, to make it a relatively stronger force. It must be appreciated however, that there are sphincters which could obstruct passage in the oesophagus. One for instance, is the constriction on the oesophagus by the fibres of the diaphragm that surrounds the oesophagus. During respiration, the diaphragmatic movement creates a pull on the oesophagus that may impair food passage. The other sphincter is the gastrooesophageal sphincter that is located at the lower end of the oesophagus and the stomach. The force of deglutition in the oesophageal phase is usually sufficient to surmount the resistance posed by these sphincters.

Emesis (Vomiting)

Emesis is the expulsion of the contents of the stomach through the mouth. It is also called vomiting. Emesis differs from regurgitation in that, for regurgitation, the food would normally not have entered the stomach prior to expulsion. Vomiting as a phenomenon could be employed as important diagnostic tool in GIT studies. Vomiting (emesis) could be a response to some chemical, physical or psychological stimuli. For instance, an ingestion of a large amount of table salt (sodium chloride) could induce vomiting. In pregnant women, the fluid retaining property of some hormones may result in an excessive degree of vomiting. When in excess in pregnancy, this phenomenon is described as hyperemesis gravidarum.

Physical induction of vomiting may be by the insertion of physical objects including the human fingers into the posterior aspects of the mouth. This act stimulates nerve ending that integrate at the emetic centre in the brain. This
method is usually employed in an attempt to expel unwanted agents that have already been swallowed.

The process of vomiting involves the anterior abdominal wall muscles, and the diaphragm. The alternate raising and lowering of the diaphragm introduces some changes in the volume and pressure in both the intra-thoracic

and intra-abdominal cavities, relevant to the act of vomiting. Implying from Boyle's law, pressure changes are inversely related to changes in volume. At the onset of vomiting, there occurs a rise in intra-abdominal pressure with a corresponding decrease in intra-abdominal volume. This is usually sufficient to assist the gastric content to overcome the resistance at the gastro-oesophageal sphincter. While the pressure and volume changes in the intra-abdominal space are taking place, there is also the simultaneous decrease in intra-thoracic pressure and a rise in intra-thoracic volume. When the gastric content enters the thoracic region, the pressure and volume changes are reversed, and the substance forcefully expelled.

The process of emesis affects other systems, such as the respiratory and the cardiovascular systems. The intra-thoracic changes in pressure and volume tend to impair respiration at some stages during the act of vomiting. The dynamics is also accompanied by an increase in cardiac output, tachycardia and other responses consequent upon a transient vasoconstriction.

Gastric motility

The pattern of gastric/stomach motility features rather unique patterns of movement, relative to the other segments of the GIT. It is aimed at achieving the goal of breaking the food particles into smaller sizes and to expose the particles maximally to enzymatic action.

In the stomach, in between phases of entry of food into it, the stomach experiences what could be termed receptive relaxation. This is fundamentally a reflex, originated in the myenteric plexus of nerves. Peristalsis also occurs on the wall of the stomach. There is a very weak wave known 'as the inter-digestive migrating motor complex. A stronger force of movement is seen in segmentation, also referred to as systolic contraction. The movement takes place on the curvatures of the stomach, independent one of the other. The systolic contraction throws the walls of the stomach into various folds that mechanically displace food particles randomly in the gastric lumen. One achievement of this form of movement is the collision of food particles that further mechanically break up the particles into smaller sizes.

In this pattern of movement too, the stomach assumes an unpredictable shape, depending on the stage during which the movement is viewed.

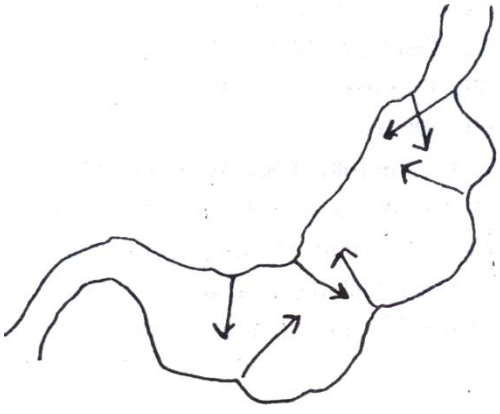

Fig. 9.1: Diagram showing the waves of contraction on the walls of the stomach with the arrows indicating the path of possible displacement and collision of food particles that serve to mechanically further break them down.

It is also to be noted that chyme passing out of the stomach does not move with a sustained velocity. As it were, the chyme moves back and' forth and discharges slowly and gently into the duodenum. Specifically, the passage is described as antral pumping, comprising of propulsion, grinding, retropulsion and another phase of propulsion.

Intestinal motility

Segmentation, which refers to the mechanical displacement of chyme from one segment to another, rather than peristaltic wave which plays a minor role, is the greatest force behind movement in the small intestine. The outer longitudinal muscle and the inner circular muscle layers and the nerve plexuses create allowance for local generation of action potential, or the potentiation of an already generated nerve impulse are responsible for such intestinal motility. The process of segmentation is repeated and chyme moves further on in the GIT.

Two muscle groups play an important role in the movement in small intestine. These are the outer longitudinal muscle and the inner circular muscle layers. The nerve plexuses create allowance for local generation of action potential,
or the potentiation of an already generated nerve impulse. Peristalsis plays a minor role in small intestine motility. Usually, the peristaltic wave observed is the one generated at a proximal segment of the GIT. The indigestive migrating motor complex is also present.

Segmentation is the greatest force behind movement in the small intestine. This refers to the mechanical displacement of chyme from one segment to another. The longitudinal muscle layer contracts, that is, being shortened in length. This is initially accompanied by a relaxation in the circular group. Later on, the circular - muscle also contracts. As the muscle groups again relax returning to their initial fiber lengths, the chyme fails to return to its initial location. Thus, there occurs a dislodgement of the chyme from one segment to another.

Colonic Motility

In the colon, there is a modification of the basic histology. Characteristically, there is a condensation of the longitudinal muscle fibres into three bands known as taenia coli. The circular muscle fibres separate further apart into what is called haustra (Singular: haustrum). The content of the colon is usually of a large volume of fluid.

The histology of the colon makes an allowance for an additional capacity to distend to accommodate the large volume of fluid matter imposed on it.

In the colon, there occurs haustral shuttling or propulsion. This is a pattern of movement similar to segmentation except that in the colon substances are being displaced from one haustrum to another. Haustral propulsion occurs at a velocity of 8cm/hr in the anal direction, with a milder degree of retropulsion at a velocity of 3cm/hr. The differential velocities favour propulsion of substances at a net velocity of 5cm/hr towards the anal canal. When more than one haustrum are involved in evacuating their contents simultaneously, the pattern of motility is termed multi-haustral propulsion. Another pattern similar to multi-haustral propulsion is a case of a disordered evacuation in what is known as mass colonic movement. At periods of quietness in the contraction, the inter-digestive migrating motor complex also takes place.

Defaecation

Defaecation is the evacuation of the contents of the rectum through the anus. For the adult human, the process of defecation is normally a combination of both voluntary and involuntary processes that create enough force to

remove waste material from the digestive system. The rectal ampulla acts as a temporary storage facility for the unneeded material. There are free nerve endings in the rectum that respond to stretch. The first phase in the defaecation process is the integration of the impulses from distended rectum, in the lumbo-sacral plexus of nerves. Efferent nerve fibers go to the rectal wall and to the anal sphincters. There is also the involvement of the peri-anal group of muscles. A sufficient increase in faecal material in the rectum causes the stretch receptors from the nervous system, located in the rectal walls, to trigger the contraction of rectal muscles, the relaxation of the internal anal sphincter, and an initial contraction of the skeletal muscle of the external sphincter. The relaxation of the internal anal sphincter causes a signal to be sent to the brain indicating an urge to defecate.

The rectum now contracts and shortens in peristaltic waves, thus forcing faecal material out of the rectum and down through the anal canal. The internal and external anal sphincters, along with the puborectalis muscle, allow the faeces to be passed out by pulling the anus up and over the exiting faeces in shortening and contracting actions.
If this urge is not acted upon, the material in the rectum is often returned to the colon by reverse peristalsis where more water is absorbed, thus temporarily reducing pressure and stretching within the rectum. The additional faecal material is stored in the colon until the next mass peristaltic movement of the transverse and descending colon. If defecation is delayed for a prolonged period, the faecal matter may harden and autolyze, resulting in constipation.
There is also the psychic component to defaecation especially with regards to place and timing for defaecation. There occurs changes in pressure and volume in both the thoracic and the abdominal cavities. These pressure and volume changes result in contraction of the anterior abdominal wall muscles. Defaecation usually takes place at mid inspiration and particularly if done against closed mouth and nostrils, could interfere with the cardiovascular system. It is not unusual to have a rise in blood pressure, sweating, syncope, and even death occasionally following defaecation.

DIGESTION AND ABSORPTION OF VARIOUS FOOD SUBSTANCES

Digestion is the enzymatic breakdown of food particles to facilitate their assimilation into the bloodstream. Digestion is basically a process of hydrolytic breakdown. There are three major classes of food. They include carbohydrates, proteins and fats.

Digestion of carbohydrates:

The sources of carbohydartes include; sucrose (cane sugar) lactose (milk) and starch (grains). Other sources are glycogen, alcohol dextrin, cellulose and pectin. The enzymes for the digestion of these carbohydrates are readily available except for cellulose which is absent in man. Digestion of carbohydrates starts in the mouth; salivary amylase (ptyalin) breaks starch into disaccharides (e.g. maltose and isomaltose) but has insignificant effect on lactose and sucrose. Ptyalin effects about 30% to 40% of starch digestion from the buccal cavity to when inactivated by the gastric acid. It must be appreciated that the secretion of gastric acid suffers a little delay, and it is this time lag that is utilized by the salivary a-amylase in the stomach. The a-amylase of gastric origin does not contribute significantly to starch digestion in the stomach. This is because of the unfavourable acid environment. A greater digestion of starch is accomplished by the pancreatic a-amylase at the level of the duodenum and intestinal epithelial enzymes (e.g, lactase, sucrase, maltase and isomaltase) which contribute to the hydrolysis of these types of carbohydrates. The end-product of carbohydrate digestion depends on the substrate involved. For instance, maltose, isomaltose, lactose and sucrose would all end up as glucose. However, lactose could also terminate as galactose, and sucrose as fructose.

Digestion of proteins

Proteins abound in diet, being found in meat and vegetable. The digestion of protein is delayed, starting in the stomach rather than in the mouth. Digestion of protein starts in the stomach by the enzyme pepsin which digests all protein types, including collagen. Proteins are hydrolytically broken down into proteoses, peptones, polypeptides, 'and amino acids. In the small intestine, the enzymes present include trypsin, chymotrypsin, carboxypolypeptidases (all of pancreatic origin) and intestinal epithelial enzymes (e.g. aminopolypeptidases and dipeptidases).

Digestion of fats

Fats are widespread in human diet. The fate of fats depends primarily on whether it is of short chain or long chain type. Lingual lipase found in the saliva, initiates the, digestion of short chain fats in the mouth. In the stomach there is the presence of gastric lipase. Gastric lipase ordinarily can digest short chain triglycerides of butter fat origin, but the extent of digestion is insignificant. The pancreas elaborates lipase, and this passes into the gut lumen at the second segment of the duodenum. Another facility at this point is the bile from the gall bladder. Bile emulsifies fat, that is, in a detergent fashion splitting the parent chain, and this is an important step in fat digestion. Indeed, the bile emulsification of fat is the rate limiting step in the digestion of long chain fats. Subsequent to emulsification, fat is digested to fatty acids, glycerol and mono glycerides. These are the end products of fat digestion.

ABSORPTION

When digestion is completed, the end products are presented to the body in a readily available form. These end products are consequently taken from the gut lumen into the bloodstream. This assimilation of the end product of digestion from the lumen to the bloodstream is known as absorption. Absorption of product of digestion is aided by the venous drainage of the GIT through the splanchnic circulation.

Absorption of carbohydrates

Carbohydrates are absorbed as monosaccharide: (glucose, galactose, and fructose). There are three types of active transport system available for the absorption of end products of carbohydrate digestion. Firstly, there is the glucose single- agent selective transport. By this mechanism, the system is specific and indeed selective for the passage of glucose from the gut lumen into the bloodstream. The second mechanism is the fructose single agent selective transport which is unique for fructose. The third system involves a glucose galactose non-specific competitive transport mechanism. In this mechanism, there is a competition by glucose and galactose for the carrier system. The two substances would not be carried at the same time as the carrier system is selective for one at any given passage.

Absorption of proteins

The end products of protein digestion are amino acids, and peptides. The absorption of amino acids/peptides is mostly active, though frequently selective and competitive. Four carrier mechanisms have been described for amino acids. These are separate systems for neutral, basic, and acidic amino acids, and the specific system for proline and hydroxyproline. Amino acids exist in two stereoisomeric forms, the L - and the D-- stereoisomers. Reports have indicated that the absorptive transport of amino acids favours the L - stereoisomers more than the D- stereoisomers.

Absorption of fats

Fats are digested to free fatty acids and monoglycerides. Free fatty acids and rnonoglycerides are lipid soluble, and could be absorbed at the site of production. The body attempts, however, to redistribute, as it were, these end products of fat digestion. To this extent, there is the formation of micelles. Micelle formation is the rate limiting step in lipid absorption. A micelle is formed by bile salts surrounding fat globules. The carboxyl portion (i.e. water soluble portion) of the bile salts project outwards, while the steroid portion (fat soluble portion) projects into the fat globules. This is represented in Fig. 7.

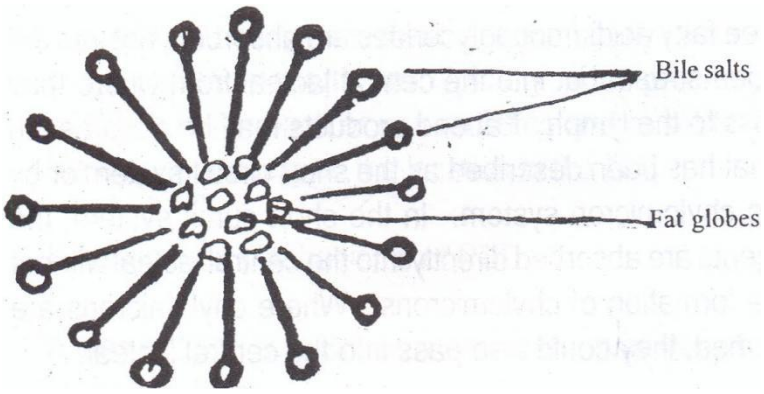

Fig. 9.2: Structure of the micelle.

While embedded in the bile salts, the fat globules are transported to the site of absorption. The micelle gives off the fat globules at the absorption site, and then migrates back into the chyme, to absorb more of free fatty acids and monoglycerides. This process of micelle migration is repeated until the free fatty acids and monoglycerides are nearly completely delivered to the absorption site.

Monoglycerides and free fatty acids pass across the enterocyte lining passively into the interstitium of the villus. Depending on the availability of free fatty acids in the system, they may be reconstituted into triglycerides by the endoplasmic reticulum in the enterocyte. The triglycerides again collect into globules and form chylomicron. A chylomicron comprises of triglycerides, cholesterol and phospholipids coated with proteins.

Free fatty acids/monoglycerides are absorbed, not into the blood stream but into the central lacteal from where they pass to the lymph. Fat end products may be absorbed in what has been described as the short circuit system or by the chylomicron system. In the short circuit system, the agents are absorbed directly into the central lacteal without the formation of chylomicrons. Where chylomicrons are formed, they could also pass into the central lacteal.

LIVER AND ITS FUNCTIONS

The liver is the largest of the abdominal viscera, located in the right upper part of the abdominal cavity. It performs a wide range of metabolic activities necessary for homeostasis, nutrition and immune defence. It is

composed largely of epithelial cells (hepatocytes), which are supplied by the hepatic portal veins and hepatic arteries. The liver is important in the removal and breakdown of toxic materials from the blood. It regulates blood glucose and lipids, and plays a role in the storage of certain vitamins, iron, and other micronutrients. The liver forms part of the mononuclear phagocyte system of the body, and are important in the removal of particulates from the blood stream. In foetal life the liver is an important site of haemopoiesis.

Classification of the liver by internal architecture divides it into lobes. The biliary, hepatic arterial and portal venous supplies of the liver tend to follow the internal architecture. The liver has two venous systems;

i. The portal system conveys venous blood from the majority of the gastrointestinal tract and its associated organs to the liver.

ii. The hepatic venous system drains blood from the liver parenchyma into the inferior vena cava

Kupffer cells are hepatic macrophages derived from circulating blood monocytes. They originate in the bone marrow, and form a major part of the mononuclear phagocyte system involved in defence. Kupffer cells remove aged and damaged red cells from the hepatic circulation. One of the other functions of the liver is to secrete bile. Bile is secreted in two stages by the liver:

i. The initial portion is secreted by the hepatocytes into the canaliculi, and contains large amounts of bile acids, cholesterol, and other organic constituents.

ii. The bile flows in the canaliculi to the interlobular septa, and then empties into terminal bile ducts, finally reaching the hepatic duct and common bile duct.

Bile serves two important functions;

i. plays an important role in fat digestion and absorption

ii. as a means for excretion of waste products from the blood; (e.g., bilirubin, cholesterol).

The bile acids in the bile do the following;

a. help to emulsify the large fat particles into many minute particles, the surface of which can then be acted on by lipase enzymes, and

b. aid in absorption of the digested fat end products through the intestinal mucosal membrane.

DISORDERS OF GIT

PEPTIC ULCER DISEASE

Peptic Ulcer Disease (PUD) is a gastrointestinal disorder conventionally believed to result from excessive gastric acid secretion. The clinical presentations are typically of epigastric pain, radiating to the back or non-radiating, and at set times of the day depending on the location in the GIT. It was in 1910 that Schwerz stated the principle

of ulcer formation, thus; "*no acidic gastric juice, no peptic ulcer*". This statement is now shortened as "*no acid, no ulcer*".

Secreting mucosa is relatively impermeable with the intercellular junctions selectively permitting passage of cations. The metabolic integrity of the mucosa cells also predisposes them to potentially injurious ions. The mucosal surface is relatively negatively charged with respect to the serosa, reflecting the active transport of chloride ions into the lumen by surface epithelial cells. Gastric juice concentration is characteristically a function of the rate of secretion. With a rise of secretion rate, H^+ concentration rises, Na^+ concentration falls, and concentration remains fairly constant. The upper limit of Hcl concentration in man is 150mN. HCI provides optimally low pepsin activity.

Mechanism of Gastric Acid Secretion:

The initial mechanism involved in acid secretion is still relatively unknown. Two theories are advanced to explain the process of acid secretion. In the Redox mechanism theory, the process involves four steps;

a. The generating of high potential energy from the mitochondra of the oxyntic cells.

b. At the secretory membrane, a repeated cycle of conditioned oxidation and reduction separate protons and electrons with the proton being delivered to the secreted fluid and the electron to the respiratory chain.

c. Electrons are delivered from the respiratory process to oxygen.

d. The generation of hydroxyl ion which reacts with carbondioxide, a by product of tissue metabolism. This reaction catalysed by carbonic anhydrase result in the formation of bicarbonate, which is exchanged for chloride.

The ATPase theory suggests a significant importance of ATPase (enzyme) in the membrane of the oxyntic cells. Bicarbonate activates the enzyme. The bicarbonate activated ATPase containing vesicles secrete acid into their fluid, making use of ATP. ATP is usually translocated, hydrolyzed, and its energy used to transport H^+ into the 'gastric juice. At the same time, a HCO_3^- is transferred to the cell cytosol and eventually exchanged for chloride.

Pathophysiological Aspects of Peptic Ulcer;

Gastric acid-pepsin secretion plays a permissive role in chronic gastric ulcers and it is probably a major contributing aggressive factor in duodenal ulcer. HCI hypersecretion plays a primary role only in duodenal ulcers, reflux oesophagitis. Zollinger - Ellison's syndrome and stress haemorhage. In the gastric ulcer, HCI does not play the primary pathogenic role. Rather, disequilibrium, between aggressive exogenous and endogenous substances, and the defense mechanism of the mucosal, barrier seem more fundamental. This is consequent upon the fact that the anti-peptic lesions by gastric juice are inhibited by the body's defense mechanism. Four theories have been, propounded to explain the pathophysiology of peptic ulcer development.

The Disequilibrium Theory: This theory describes the fact that aggressive factors are not the only influence responsible for peptic ulcers, but that; there is a need for a concurrent weakening of the protective mechanisms of the gastric mucosa.

Hyposecretion and Hypersecretion Theory: This theory presents the position that by whatever mechanisms the presence of acid is cardinal to the development of peptic ulcer.

Endogenous Aggressors Theory: Hydrochloric acid, pepsin, bile acids and lysolecithin are endogenous substances capable of provoking mucosal damage. The reflux materials from the duodenum (e.g. bile acids) have greater pathogenetic significance than HCI. The effects of the duodenal reflux material are more pronounced on pyloric insufficiency with or without motility disturbances. Lecithin is acted upon by phospholipase in the stomach, to form the cytotoxic lysolecithin. Cytotoxic lysolecith in, with other duodenal materials in the presence of Hcl and pepsin have a detergent effect on the gastric mucosa. Epithelial and mucus cells are usually damaged by this detergent effect causing the passage of aggressive substances across the mucosal barrier.

Mucosal Barrier Defence Theory: The mucosal barrier defence consists of both intrinsic and extrinsic protective phenomena, The intrinsic protection is offered through the transmembrane and trans junction H^+ back diffusion, and also through the processes of cellular regeneration. The extrinsic protection is offered by mucus secretion, bicarbonate secretion, optimal mucossl blood flow and the maintenance of adequate interstitial fluid environment.

Risk Factors in Peptic Ulcers

Aspirin mediates inflammation and nociception, as well as inhibiting prostaglandin synthesis by inactivating the cyclo-oxygenase (i.e., PG- synthetase), Aspirin also antagonistically displaces kinins from their receptors, inhibits the kinin cleaving enzymes, and inhibits the release of serotonin and histamine from mast cells. Indomethacin has been reported to markedly increase gastric acid secretion by stimulating both basal and provoked acid secretions. Peptic ulcer disease is commonest in the low income group. This results from non availability of the food or the improper combination with respect to balance of diet and more infection with H. Pylori, a bacterium that is also important in PUD causation.

Plantain (*Musa paradisiac*) contains serotonin, nor adrenaline, dopamine and glucose especially when ripe. Noradrenaline and dopamine stimulate the secretion of gastric acid in man. *Cola nitida* (Kola nuts) significantly increases gastric acid secretion. This effect results largely from the presence of nicotine in the substance. Nicotine is also present in cigarettes. Alligator pepper, taken alone inhibits gastric acid secretion and when combined with *Cola nitida*, further decreases secretion. Alcohol generally enhances gastric secretion, but palm-wine has been reported to decrease gastric acid secretion.

There is a higher incidence of peptic ulcer among the males than the females. Progesterone does not increase gastric secretion but may inhibit the action of oestrogen in decreasing acid secretion.

The chronic administration of thyroxine increases basal gastric acid secrefion. The risk of developing peptic ulcer disease increases with age. This probably is neurogenic in origin. Other factors implicated as risk factors are emotional responses and the microorganism, *Helicobacter pylori*. Indeed *H. pylori* is now about the commonest prevailing actiologic agent in PUD.

Management: The best principle of management is to identify the cause and treat, by either withdrawing the harmful habits, application of mucosal coating, use of antihistaminics, proton pump inhibitors and antimicrobials. In extreme case of protraction, bleeding or perforation, a surgical intervention may be considered.

GASTRO - OESOPHAGEAL REFLUX DISEASE

When substances move into the stomach from the oesophagus, it is intended that it should move caudally. However, there may be the backflow (reflux) of substances from the stomach into the oesophagus. Remembering that the stomach is an environment of high acidity, the refluxed substances bring an increased acidity to the oesphageal lumen. In occasional (ie non frequent) re-fluxes, there would be no damage to the oesophageal mucosa. However, with repeated, frequent gastro-oesophageal reflux, the mucosal irritation leads to an increase in blood flow to the area (a stage in the inflammatory process). Following the erythema of the oesophageal mucosa, erosion occurs with progressive epithelial damage. Without an intervention, the erythema progresses to frank **oesophagitis**. The body attempts a healing process, and this is usually by fibrosis. It thus results in the development of **strictures** in the oesphagus or of gastric type epithelium in the oesophagus (**Barrett's oesophagus**).

Aetiology: - Gastro-oesphageal reflux disease usually follows heavy smoking habits, ingestion of large meals, fatty foods and obesity. These are behaviours with chemically and mechanically negative effects on the mucosal surface, in the oesophagus and stomach areas.

Symptoms The symptoms of the disorder can be classified into local and systemic. The influence of the gastric acid on the oesophageal mucosa leads to the feeling of heartburn. This is also frequently accompanied by regurgitation. When the disorder has progressed to a stage in which there are mechanical affectations on the oesophageal mucosa, the individual would experience difficulty in swallowing frequently painful, and a chest pain of non-cardiac origin.

The systemic manifestations of the gastro esophageal reflux disease include cough, pneumonia and .induction of asthmatic attack in predisposed subjects. These symptoms follow aspiration in. cases associated with regurgitation. Dental erosions are not uncommon; and vocal cord polyps have also been described.

Management: An understanding of the pathophysiology predicts the course for management. For example, if the disorder is related to harmful habits, a change of habit is required. Because of the effect of H^+ on the mucosa, stimulating the production of mucus by prostaglandins or surface coating with antacids would relive the discomfort. Antihistamines (H2 antagonists) and proton pump inhibitors would inhibit gastric acid secretion, and provide relief to the subject. Other possible physiologic approaches include the augmentation of .the lower oesophageal sphincter tone to prevent a reflux, or to enhance, gastric, emptying by the use of parasympathomimetics (antagonists of dopamine; cholinergic agonists, agonists of 5' hydroxytryptamine, motilin agonists)

ACHALASIA

This is a disorder characterized with difficulty in swallowing food, and even liquids at times. It results from damage of nerves supplying the oesophagus. Peristalsis is thus impaired as the lower oesophageal sphincter fails to relax appropriately. Three types of achalasia are known: type 1 which is the classic, type 2 in which there occurs some pressure build up and compression within the oesophagus, and type 3 often referred to as spastic achalasia due to the abnormal contractions that take place in the lower end of the oesophagus.

The causes of achalasia are not clear, but herpes virus has been implicated. It has been suggested that it may be an autoimmune disorder. Achalsia can occur at any age but appears most frequent in people between ages 30 to 60 years. Symptoms os this condition include dysphagia, heartburn, impaired appetite, regurgitation, an occasionally chest pain. The management is to relax the muscles involved by myotomy or dilation, to enable easier passage of food into the stomach. Injection of butolinum toxin into the gastro-oesophageal sphincter may be useful. Drugs containing nitrates or calcium channel blockers can help in a temporary relief of the symptoms.

CROHN'S DISEASE

This is an inflammatory bowel disorder characterized by a chronic inflammation of the entire GIT. The disease has the tendency to penetrate into deeper structures. There are no specific known causes yet. However, certain risk factors have been described, including a genetic predisposition, autoimmune reaction, and smoking. Depending on the location in the GIT, Crohn disease may present as ileocolitis, ileitis, jejunoileitis, or as gastroduodenitis.

Symptoms of Crohn's disease include abdominal pain, prolonged diarrhea, fever, and weight loss. There might also be rectal bleeding, anal fissures and even fistulae. CD may be diagnosed by stool microscopy, colonoscopy, endoscopy, X-ray or computed tomography scan. CD disease is managed based on the identified causative agent, or a withdrawal from known risk agent.

ULCERATIVE COLITIS

Ulcerative colitis is an inflammatory bowel disorder which often results in ulcers in the GIT. The exact cause of UC is unknown. However, it is associated with immunodepression. Stress and certain foods have also been implicated as aetiologic factors. It can affect people of any age but appears to be most common between ages 15 and 30 years.

The symptoms of UC include abdominal pain, blood stained stool, frequent stooling, fever, and weight loss. Other not uncommon presentations are joint pain, nausea and vomiting, mouth ulsers and skin ulcers. Stool test for lactoferrin, full blood count, barium enema and an assessment of C- reactive protein, may assist in the diagnosis of UC. UC may be managed by control of attacks, diets, immune boosters, and analgesics.

STOMATITIS

Stomatitis is the inflammation and redness of the oral mucosa. It is usually characterized by intense pain, and difficulty in eating and sleeping. The condition most commonly affects the inner cheek, gums, inner lips and the tongue. A type of stomatitis is Canker ulcer (aphthous ulcer) which is a single pale or yellow ulcer with a red outer ring, or as a cluster of ulcers in the mouth. Another is cold sores (fever blisters), a fluid filled sore on the lips, and burning in nature.. The sores usually form crusts with outer scabs.

The symptoms of Stomatitis may result from biting the tongue, wearing dental braces, chewing tobacco, burns from hot food, mouth infection like gingivitis, or from autoimmune challenges. Some drugs used in cancer treatment, and radiotherapy may also result in stomatitis. The treatment for stomatitis may be withdrwal of causative agents, pain relief, and anitimicrobials.

HEPATITIS:

Hepatitis is a general term used to describe inflammation of the liver. hepatitis may be caused by viruses (viral hepatitis), chemicals, drugs, alcohol (alcoholic hepatitis), certain genetic disorders or by an autoimmune process. Hepatitis can be acute, in which case it comes up rather suddenly and then resolves. It may also be chronic, producing more subtle symptoms over a longer period of time, and progressive liver damage.

Types of Hepatitis There are five viruses that cause the different forms of viral hepatitis. These are. hepatitis A, B, C, D and E. Hepatitis A is transmitted mostly as a water/food-borne illness. It is the easiest to transmit, but is also the least likely to damage the liver, being completely resolved usually within six months. Hepatitis B is transmitted through exposure to contaminated blood, needles, syringes or bodily fluids and from mother to baby. It is a chronic disorder and in some cases may lead to long-term liver damage, cirrhosis, and liver cancer of the liver. Hepatitis C is transmitted only through infected blood or from mother to newborn during childbirth. It too can lead to liver cirrhosis and cancer over time. Hepatitis D is only found in people who are also infected with hepatitis B. Hepatitis E is usually drug induced. Some drugs when taken over a long period of time can become toxic to the liver following their accumulation in the system, and cause hepatitis (drug-induced hepatitis). These include acetaminophen, (paracetamol) and even vitamin A.

Symptoms Symptoms of hepatitis include a feeling of general weakness of the body, right sided abdominal pain, jaundice, and abdominal swelling due to fluid retention (ascites), especially in the terminal stage. On a physical examination, the liver is usually enlarged being palpable below the costal margin. Investigations required to confirm diagnosis of hepatitis include; blood tests for liver enzymes and proteins which are elevated when the liver is damaged or infected, ultrasound scan of the liver and on rare occasions, a biopsy.

Treatment There is no cure for hepatitis once it occurs. To prevent infection, individuals should be vaccinated against hepatitis B and hepatitis A. There are no vaccines yet against hepatitis types C, D and E. Treatment focuses on preventing further damage to the liver, reversing existing damage if possible and symptomatic relief. Most cases of acute hepatitis will resolve over time. In autoimmune hepatitis, immunosuppressant drugs may be used to help attacks on the liver.

THE GUT AS AN ENDOCRINE ORGAN

The GIT in addition to the functions of digestion and absorption also serves as an endocrine organ. This involves the secretion of hormones, especially from the accessory structures of the organ. Four polypeptides with hormonal activity are secreted by the islets of Langerhans in the pancreas. Two of these hormones insulin and glucagon, function in the regulation of the metabolism of carbohydrates, proteins, and fats. The third, somatostatin, plays a role in the regulation of islet cell secretion, and the fourth, pancreatic polypeptide, is concerned primarily with gastrointestinal function. Insulin is anabolic, increasing the storage of glucose, fatty acids, and amino acids. Glucagon is catabolic, mobilizing glucose, fatty acids, and the amino acids from stores into the bloodstream. Some cells in the stomach also secrete ghrelin, which has been described as a peripheral analogue of growth hormone, while some cells of the intestines secrete cholecystokinin and secretin.

Insulin

Insulin is a polypeptide containing two chains of amino acids linked by disulfide bridges. Human insulin is now widely used to avoid antibody formation. Insulin is synthesized in the rough ER of the B-cells. It is synthesized as a preprohormone Insulin excess causes hypoglycemia, while its deficiency, causes diabetes mellitus, a complex metabolic disease.

Plasma contains a number of substances with insulin-like activity in addition to insulin. However, the insulin-like activities are weak compared to that of insulin. The half-life of insulin in the circulation in humans is about 5 minutes. Insulin binds to insulin receptors, while some of it is internalized. It is destroyed by proteases in the endosomes. Insulin causes K^+ to enter cells, and increases the activity of Na^+-K^+ ATPase in cell membranes, so that more K^+ is pumped into cells. When the plasma glucose is high, insulin secretion is normally increased and hepatic glucogenesis is decreased.

Glucagon

Human glucagon, a polypeptide with a MW of 3485, is produced by the α – cells of the pancreatic islets and the upper GIT. All mammalian glucagons appear to have the same structure. Human preproglucagon is found in pancreatic α – cells, in L cells in the lower GIT, and in the brain. It is the product of a single mRNA, but it is processed differently in different tissues. In α – cells, human preproglucagon is processed primarily to glucagon and major proglucagon fragment (MPGF). In L cells, it is processed primarily to glicentin, a polypeptide that consists of glucagon with additional amino acid residues at either end, plus glucagon-like polypeptides 1 and 2 (GLP-1 and GLP-2).

Glucagon is glycogenolytic, gluconeogenic, lipolytic, and ketogenic. It contributes to the hyperglycemia, and glucose output by the liver, and is facilitated by catecholamines, cortisol, and growth hormone. In the liver, it acts via G_s (i.e., serpentine receptors) to activate adenylyl cyclase and increase intracellular cAMP. This leads via protein kinase A to activation of phosphorylase and therefore to increased breakdown of glycogen and an increase in plasma glucose.

Glucagon acts on different glucagon receptors located on the same hepatic cells to activate phospholipase C, and the resulting increase in cytoplasmic Ca^{2+} subsequently stimulates glycogenolysis. It also decreases the concentration of fructose 2,6-diphosphate, and this in turn inhibits the conversion of fructose 6-phosphate to fructose 1,6-diphosphate. Glucagon does not cause glycogenolysis in muscle, but gluconeogenesis from available amino acids in the liver and elevates the metabolic rate. It increases ketone body formation by decreasing malonyl-CoA levels in the liver. Glucagon stimulates the secretion of growth hormone, insulin, and pancreatic somatostatin. In large doses, exogenous glucagon exerts a positively inotropic effect on the heart without producing increased myocardial excitability. This is presumably because of the increase in myocardial cAMP.

Cholecystokinin

Cholecystokinin (CCK) though a hormone, is secreted in response to fats and peptides in the upper small intestines, particularly the duodenum.

Actions of CCK include:

- Secretion of Pancreatic Enzymes

- Contraction of Gallbladder
- Relaxation of the sphincter of Oddi
- increased tension in the pyloric sphincter, inhibiting stomach emptying

Secretin

Secretin is released in response to the presence of acid in the duodenum.

The actions of secretin include:

- Secretion of copious amounts of bicarbonate rich fluid by the biliary and gall bladder ducts
- Secretion of alkaline rich mucous by Brunners glands
- Increased tension in the pyloric sphincter, inhibiting stomach emptying

Somatostatin

Somatostatin 14 (SS 14) and its amino terminal- extended form somatostatin 28 (SS 28) are found in the D cells of pancreatic islets. Both forms inhibit the secretion of insulin, glucagon, and pancreatic polypeptide and may act locally within the pancreatic islets in a paracrine fashion. SS 28 is more active than SS 14 in inhibiting insulin secretion, and it apparently acts via one of its receptors.

Patients with somatostatin-secreting pancreatic tumours develop hyperglycaemia and other manifestations of diabetes that disappear when the tumour is removed. They also develop dyspepsia due to slow gastric emptying and gastric acid secretion.somatostatin can also cause gallstones, precipitated by decreased gallbladder contraction due to inhibition of CCK secretion. The secretion of pancreatic somatostatin is increased by several of the same stimuli that increase insulin secretion, i.e., glucose and amino acids. Somatostatin is released from the pancreas and the gastrointestinal tract into the peripheral blood.

SUMMARY

The gastrointestinal system is responsible for the handling of food substances in the body. When food is ingsted into the mouth, what happens to it is a function of the form in which it is ingested. Solid forms of food are mainly broken down by the process of mastication. Thereafter, by swallowing, it is passed on to the oesophagus and stomach. The wave of peristalsis and the inter-digestive migrating motor complex assist the passage in the oesophagus. From the stomach, the food substances pass to the small intestine. Here, it propelled by specific motility patterns until the waste products get to the rectum and is stored waiting for an appropriate stimulus for daefecation. Enzymes and hormones in the GIT break down the food substances further, and the final products are absorbed (glucose, galactose and fructose for carbohydrate), amino acids and proteoses for protein, and free fatty acid and gylycerides for fats and lipids). The salivary glands, pancreas, liver and gallbladder contribute

substances that help in the digestion and absorption of food in the GIT. Disorders of the gastrointestinal system are not uncommon. Peptic ulcer disease, especially is a common disorder that affects many people.

EXERCISES

Essay questions:

1. Describe the control mechanisms in the GIT
2. Write an essay on the secretion, composition, functions and regulation of saliva
3. Describe the processes involved in the digestion and absorption of a meal of jollof rice and a piece of beef.
4. Explain the mechanisms of emesis and defaecation.
5. Describe any two movement patterns in the GIT
6. Explain the role of the liver in the body's handling of a fatty meal
7. Write an essay on the pathophysiology of peptic ulcer disease.
8. Describe ant three disorders of the GIT that you are familiar with.

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Chapter 10

PHS 303: ENDOCRINOLOGY AND REPRODUCTION

A. A. Fasamande, Maisaratu A. Tukur, W. C. Nwafia, F. S. Amah-Tariah

THE ENDOCRINE SYSTEM

OVERVIEW

The endocrine system is involved in the adjustment and correlation of activities in the body, making them appropriate to changing demands of internal and external environment. It is actively involved in development with regards to physical appearance and behaviour. The communication property of the endocrine system is accomplished by hormones, which serve as blood-borne messengers. Hormones are produced by ductless glands, which are located in several organ systems in the body. Overproduction or underproduction of hormones gives rise to a series of malfunction of the body systems. Some may be life threatening while others may be mild. The reproductive system acts as a coordinated cycle of events aimed at preparing the male and female for the purpose of procreation. This is done chiefly under the influence of the hormonal control system specific for reproduction. The male reproductive system is functions in the production, nourishment of sperm cell viable for fertilising the female ovum. The female reproductive system is generally involved in the production, sustenance and fertilisation of egg cells (oocytes) by the male sperm. It also supports the development of an offspring (gestation) and gives birth to a new individual (parturition). The complications associated with multigravidas and multiparity have given rise to the discovery of different methods of contraceptives, so as to give the females and their families options on birth control and child spacing. The choice of contraceptive method is largely dependent on each individual of family's desire, usually after being informed of both the benefits and adverse effects.On the other hand, the option of assisted reproductive techniques (ART) have given hope to many people who have found it difficult to get pregnant. There also, have been several methods of ART, where the concerned persons make their choices depending on the success rate, aetiologic factor of infertility, as well as the cost of the technique.

OBJECTIVES

1. Compare and contrast the modalities of functioning of Nervous and Endocrine systems
2. Identify spectrum of hormone signaling through the endocrine, paracrine, and autocrine systems.
3. Define the terms hormone, target cell, and receptor.
4. Identify the major classes of hormones and the differences in cellular mechanisms of action of the various types.
5. Understand the secretion and carriage of hormones in the blood to their target cells.
6. Identify the control mechanisms of hormone secretion.
7. Know the secretions and functions of the hypothalamus, pituitary, thyroid, adrenal, Parathyroid, gonadal, and pancreatic islet cells' secretions.
8. Explain effects of hyper- and hypo-secretion of hormones.
9. Describe the physiologic and anatomic relationships between the hypothalamus and the anterior and the posterior pituitary.
10. The anatomic compositions of the organs in the male and female reproductive systems.
11. The functions of the male and female gonadal hormones.

12. The events that occur during the female reproductive cycle, in the ovary and uterus.
13. The hormonal interplay in the regulation of the menstrual cycle.
14. The events in fertilisation and implantation.
15. The hormonal and other physiologic changes in pregnancy.
16. The application of the different contraceptive methods.
17. The application of the different assisted reproductive techniques.

INTRODUCTION AND NEUROENDOCRINE RELATIONSHIP

Endocrine system may act independently or may be integrated with the nervous system. There are common characteristics between the two signaling systems:
Both are capable of secreting signaling molecules, both can generate electrical potentials and be depolarized, the same molecule can be a neurotransmitter and a hormone, mechanism of action of both hormone and neurotransmitters requires interactions with specific receptors in target cells.

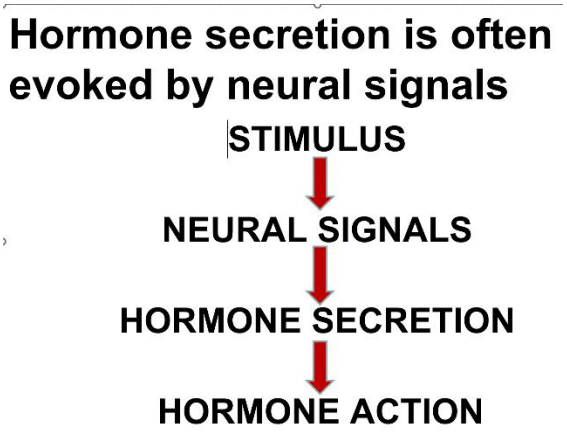


Figure 10.1: Spectrum of hormone signaling

Endocrine function – transmission of a molecular signal from a classic endocrine cell through the blood stream to a distant target cell.
Neurocrine function – transmission of a molecular signal from a neuron down its axon and then into the blood stream to a distant target cell.
Paracrine function – transmission of a molecular signal from one cell type to a neighbouring different cell type by diffusion through intercellular fluid channels or gap junctions.
Autocrine function – transmission of a molecular signal through the intercellular fluid or gap junctions to neighbouring identical cells or back to the cell of origin.

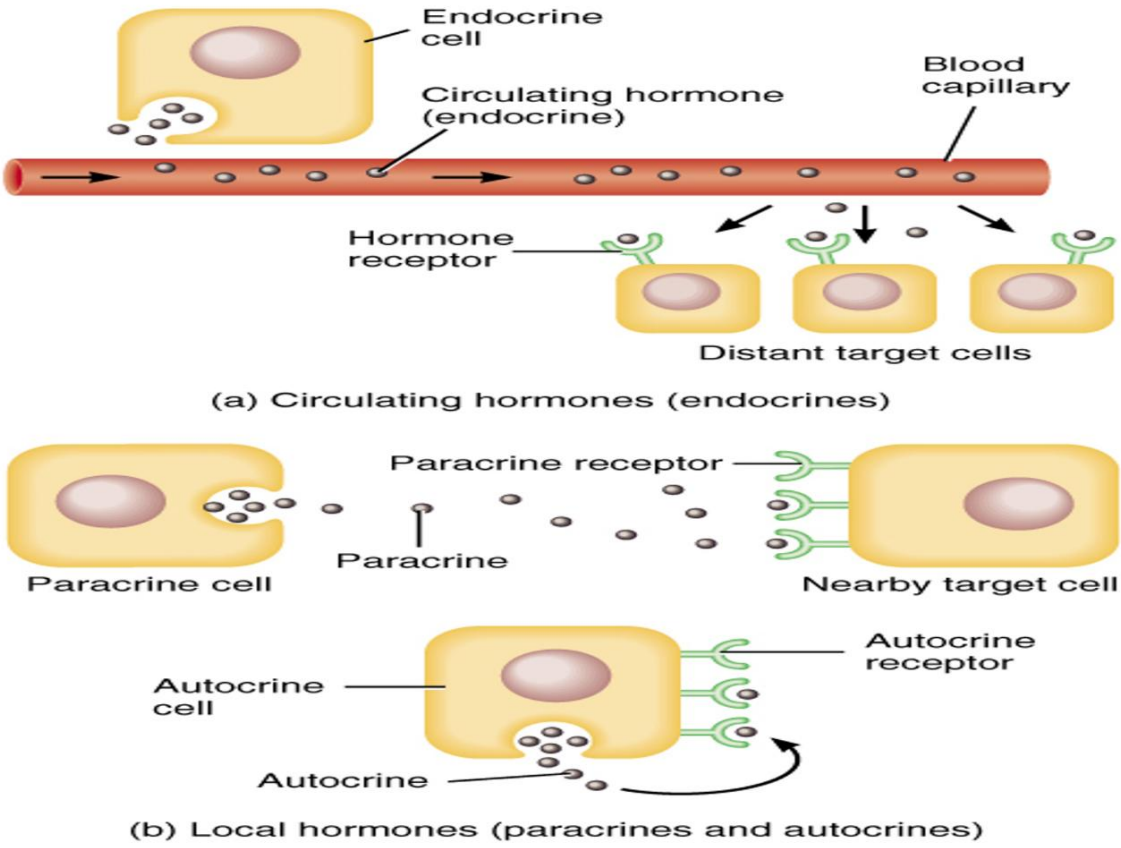


Figure 10.2: Mode of hormone secretion

HORMONES

Hormones are chemical messengers produced by endocrine glands that are secreted directly into the blood that have effects on distant organs e.g. thyroid hormone, insulin, testosterone, oestrogens etc.

Hormones are:

- "Messenger molecules"
- Circulate in the blood
- Act on distant target cells
- Target cells respond to the hormones for which they have receptors in specific manners.
- The effects are dependent on the programmed response of the target cells.
- Hormones are just molecular triggers

CHARACTERISTICS OF HORMONES

- They either increase or decrease the rate of chemical reactions i.e. they do not initiate the reactions in cells de novo.
- They are usually not secreted at precisely uniform rates.

Note: (i). Diurnal cycles e.g. cortisol
(ii). Complicated cycle e.g. sex hormone

- Effects are exerted in bio-catalytic concentrations.

- They are mainly concerned with the different metabolic functions of the body.

There are some non-endocrine cell types known to produce and secrete substances that act on other cells, making them to behave as hormones. These are:

- Renal cells – erythropoietin, vitamin D, rennin
- Cardiac atrial cells – atrial natriuretic hormone
- Endothelial cells – endothelin, nitric oxide
- Lymphocytes, monocytes and macrophages – interleukins, interferons
- Platelets and mesenchymal cells – growth factors, annexins, integrins
- Adipose cells – leptin
- Placental cells – practically all known hormones.

CHEMICAL CLASSIFICATION OF HORMONES

There are four main types:

1. Peptides and proteins. There are the most common
2. Eicosanoids
3. Amines
4. Steroids

They differ on the basis of synthesis, storage, release, transport and cellular mechanism of action.

PROTEINS AND PEPTIDES

Initially synthesized on ribosomes of endocrine cells, as preprohormones, which are cleaved to prohormones by proteolytic enzymes in the granular endoplasmic reticulum of the cell.

The Golgi apparatus of the cell packages the prohormone into secretory vesicles. The prohormone is cleaved to yield the active hormone and other peptide chains found in the prohormone.

When the cell is stimulated to release the contents of the secretory vesicles by exocytosis, the other peptides are co-secreted with the active hormone.

Peptide hormones can be produced in the circulation from a protein precursor, e.g. synthesis of angiotensin II from a plasma protein.

EICOSANOIDS

These include prostaglandins, leukotrienes and thromboxanes. They are derivatives of arachidonic acid and are synthesized by nearly all cells in the body. They are produced by COX in response to cell damage. They are useful as mediators of inflammation (NSAIDS are COX inhibitors). They possess many other activities.

AMINES

They originate from the amino acid, tyrosine. They are not stored in granules but are released into the blood from the cells by simple transfer through the plasma membrane. Thyroid hormones and catecholamines are typical examples of amines.

STEROIDS

These include adrenocortical and reproductive gland hormones and the active metabolites of Vitamin D. Cholesterol is the common precursor and the steroid hormones are not stored in granules but are released into the blood like the amines.
Hormones can also be divided into **polar** and **non-polar**. The polar hormones are water soluble and the non-polar are water insoluble but lipid soluble. Peptides and proteins are water soluble whereas the steroid hormones and amines are water insoluble.

MECHANISM OF HORMONE ACTION-RECEPTORS

- Membrane-bound hormone- receptor complex (amine and peptide hormones).
- Intracellular hormone-receptor complex (steroid hormones and T3, T4).

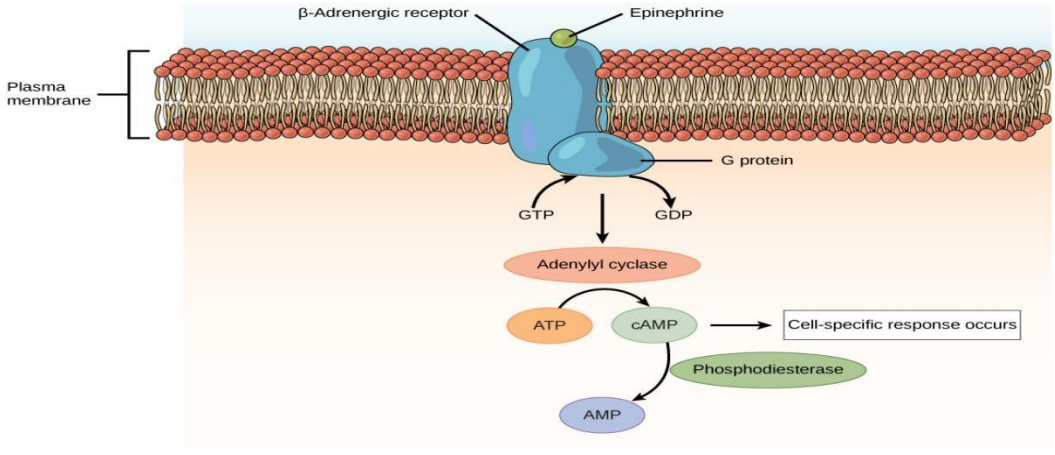


Figure 10.3: Membrane-bound hormone-receptor complex

a. Membrane bound (Protein hormones)

In summary, it takes place in the following sequence:-

i. Combination of hormone with receptor in the cell membrane
ii. Activation of adenyl cyclase in the cell membrane
iii. Adenyl cyclase converts ATP to cyclic 3,5-AMP
iv. Cyclic AMP exerts the hormone effects such as:-
    a. Activation of enzymes
    b. Causes muscle contraction
    c. Causes protein synthesis
    d. Causes secretion
    e. Alters permeability

b. Intracellular hormone receptor complex (Steroid hormones).

The receptors are located within the cell, this is particular to steroid hormones. They thus have to travel through the membrane into the cytoplasm to bind with receptors for the formation of hormone-receptor complex, now leaves the cytoplasm for the nucleus where they bound reversibly with DNA. This binding leads to formation of messenger RNA (mRNA) (actinomycin D blocks this process). mRNA then diffuses back into the cytoplasm where it promotes the translation process in ribosomes to form new proteins that are formed that is responsible for the specific physiological effect of the hormones.

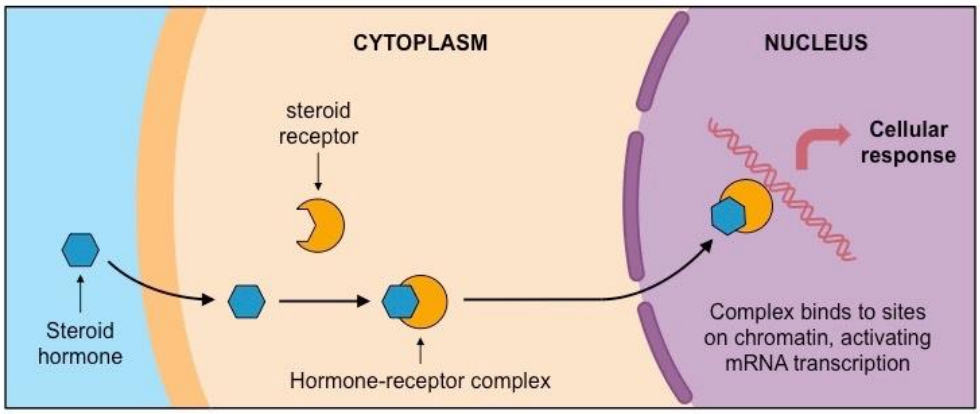


Figure 10.4: Intracellular hormone-receptor complex

NB: Examples of intracellular messengers (second messenger)

i. Cyclic AMP (cAMP)

- Exists at low levels (10^{-3} to 10^{-6} mmol/L) in all cells
- Degraded by phosphodiesterase

ii. Ionic calcium (Ca^{2+})

- Couples to excitation to contraction in skeletal muscles
- Couples to excitation to transmitter release in nerves
- Acts as a secretagogue to secretion in endocrine and exocrine glands
- Its action results from its ability to bind to ca-binding proteins e.g. calmodulin

iii. Cyclic GMP

- Cyclic guanosine monophosphate (cGMP)
- Formation from ATP is catalyzed by guanylate cyclase.

RECEPTORS

Location:

a. Cell membrane, for catecholamines, peptide and protein hormones
b. Cytoplasm; for steroid hormones
c. Nucleus (mainly), for thyroid hormones

CHEMICAL NATURE OF RECEPTORS

- Large protein molecule e.g. plasma membrane receptors may additionally contain carbohydrates and/or phospholipid moieties.
- There are about 20-100,000 receptors per cell.

N.B. receptor capacity is regulated by its hormone concentration:

a. Up regulation- prolonged exposure of the target cell to low concentration of the hormone act to increase the number of receptors. The hormone thus appears to recruit its own receptors. This amplifies the action of the hormone over a period of time e.g. ovarian follicle and local concentration of FSH and LH.

b. Down regulation- sustained high concentration of a hormone acts to decrease the number of receptors at the target site. This serves to moderate the effect of chronic exposure to excess hormones e.g. the reduced number of functional insulin receptors in obesity is due to high levels of plasma insulin.

Hormonal Interactions

Other characteristics of hormonal actions are such that:

1. Two adjacent cell types in a single gland may interact so that hormone A from cell A is modified by cell B to produce hormone B. Production of oestrogens from androgens in the ovaries is a typical example of this.
2. Modification of a precursor molecule of low activity to one of higher activity by successive steps that take place in several different tissues. Activation of a sterol produced in the skin by the liver and kidneys to produce potent vitamin D is an example of this.

Hormone interactions can be

1. Synergistic: Two hormones work together to produce a result.
2. Additive: Each hormone separately produces response, together at same concentrations stimulate even greater effect – Norepinephrine and Epinephrine.
3. Complementary: Each hormone stimulates different step in the process – Follicle Stimulating Hormone and testosterone.

Effects of hormones can be permissive or antagonistic:

Permissive effects: Hormone enhances the responsiveness of a target organ to a second hormone. This Increases the activity of the second hormone. For example, prior exposure of uterus to estrogen induces formation of receptors for progesterone.

Antagonistic effects: Action of one hormone antagonizes the effects of another. E.g. insulin and glucagon.

GENERAL ACTIONS OF HORMONES

The actions of hormones are the following:

- Fetal development,
- Cell growth and cancer development,
- Intermediary metabolism,
- Mineral and water metabolism,
- Cardiovascular function,
- Renal function,
- Skeletal function,
- Reproductive function, and functions of the
- Immunity
- Central nervous system functions.

HORMONE TRANSPORT

Catecholamine and peptide and protein hormones circulate unbound in the plasma with the exceptions of growth hormone, oxytocin and vasopressin.

Steroid and thyroid hormones and Vitamin D circulate bound to plasma proteins. The major plasma binding proteins are:

- Corticosteroid-binding globulin – binds cortisol and progesterone
- Sex hormone-binding globulin – binds testosterone and oestradiol
- Thyroxin binding globulin, Transthyretin (also known as thyroxin binding pre-albumin TBPA) and Albumin – bind T_4 and T_3

- Vitamin D-binding protein – binds vitamin D.

HORMONE DISPOSAL

Hormonal effects or activities are usually terminated via:

- Target cell uptake,
- Metabolic degradation,
- Urinary excretion or
- Biliary excretion.

REGULATION OF HORMONAL ACTIVITY

This can be by Positive feedback or Negative feedback mechanisms.

POSITIVE FEEDBACK

Acts to amplify the initial biological effect of the hormone. Hormone A, which stimulates secretion of hormone B, may in turn be stimulated to greater secretion rates by hormone B, but only through a limited dose-response range. Once sufficient biological momentum for secretion of hormone B is reached, other influences, including negative feedback will reduce the response of hormone A to fit the final biological purpose. An example is effect of oxytocin in parturition.

NEGATIVE FEEDBACK

Acts to limit the excursions in output of each partner in a pair. Hormone A, which stimulates secretion of hormone B, will in turn be inhibited by an excess of hormone B. This is the commonest way of control of hormone action. Hormones of the anterior pituitary act in this way to control the secretion of most of the major endocrine glands in the body.

HORMONE RECEPTOR LOCATION

Receptors are proteins located in the cell

- Steroid hormones – located within the cytosol of target cells
- Thyroid hormones –located in the nucleus of target cells
- Peptide and protein hormones – located in the plasma membrane of target cells
- Catecholamines – located in the plasma membrane of target cells.

ENDOCRINE PATHOLOGIES

May be due to:

1. Hyper-secretion, which can be primary hormone excess or secondary hormone excess
2. Hypo-secretion, which may be primary or secondary. Hypo activity of hormone function can also be due to: abnormal tissue response, abnormal hormone/receptor interaction, and abnormal signal transduction or non-endocrine problems in endocrinopathy.

ANALYSIS OF ENDOCRINE ACTIVITY

1. Ablation (malfunction) of the suspected tissue→ deficiency symptoms e.g. destruction of β-cell of pancreas → diabetes.

2. Replacement (re-implantation) of the ablated tissue corrects or reverses the deficiency symptoms.
3. Injection of crude extracts of the tissue should relief the deficiency symptoms.

PRINCIPLES OF DIAGNOSES OF ENDOCRINOPATHIES

- History and Physical examination
- Laboratory studies
- Blood and urine hormonal assay
- Dynamic testing
- Stimulation and suppression tests
- Radiological and imaging studies
- Biopsy and pathological studies
- Genetic studies and endocrinopathy screening.

THE HYPOTHALAMO-PITUITARY AXIS

Physiologic and anatomic relationship between the hypothalamus and the pituitary gland. We will discuss the roles of the hypothalamus and the pituitary gland in the orchestration of the activities of endocrine glands.

The hypothalamus is a small part of the diencephalon, just below the thalamus. It is made up of several nuclei grouped into four main regions:

- Mammillary: in the posterior hypothalamus. The mammillary bodies serve as relay station for reflexes along with the posterior hypothalamic nucleus.
- Infundibulum connects the hypothalamus with the pituitary gland. The median eminence encircles the infundibulum.
- Supraoptic: lies above the optic chiasma. It contains the supraoptic, paraventricular, anterior hypothalamic and suprachiasmatic nuclei. The posterior pituitary gland is connected with the supraoptic and paraventricular nuclei through the infundibulum.
- Preoptic: contains the lateral and medial preoptic nuclei, which participate in autonomic activities.

The hypothalamus is the major regulator of homeostasis through its hormones as well as the control of other hormonal functions in the body. It is important for autonomic activities as well as regulation of temperature.
The hypothalamus has two major connections to the pituitary, and secretes hormones that control the hormones of the anterior pituitary and hormones that are stored in the posterior pituitary for later release when required.
The **hypothalamo-adenohypophyseal tract** is made up of blood vessels (capillaries) that connect the hypothalamus with the anterior pituitary. Hormones that are transported through this tract are the releasing hormones (growth hormone releasing hormone, gonadotropin releasing hormone, thyrotropin releasing hormone, corticotropin releasing hormone and prolactin releasing hormone) and inhibiting hormones (Growth hormone inhibiting hormone and prolactin inhibiting hormone, also known as dopamine).
The **hypothalamo-nuerohypophyseal tract** is a network of nerves connecting the hypothalamus with the posterior pituitary. Hormones secreted by the supraoptic nucleus (vasopressin – antidiuretic hormone) and paraventricular nucleus (oxytocin) are transported by axonic transport to the posterior pituitary for storage. When required, the posterior pituitary stores release the hormones.
Other functions of the hypothalamus include:

- Maintenance of daily physiologic cycles

- Control of appetite
- Control of sexual behaviour
- Regulation of emotional responses
- Maintenance of body temperature
- Blood pressure maintenance

THE ENDOCRINE GLANDS

Endocrine glands are glands that have no ducts known as “ductless” glands. An endocrine or ductless gland is a collection of secreting cells with a specific function of production, storage and release of a chemical substance called “hormone”. Hormones pass directly into the blood stream and have wide spread effects:
Many of the endocrine glands are under the control of nervous system which is via the hypothalamus and the pituitary gland which is suspended from it.

Classic Endocrine glands

- Pituitary gland – Produces tropic hormones and others
- Thyroid gland – Produces thyroid hormones
- Adrenal glands – Produce adrenal cortical/medullary hormones
- Gonads – Produce male/female sex hormones
- Parathyroid gland – Produces parathyroid hormone
- Pancreatic islet cells – Produce insulin, glucagon and others

CHARACTERISTIC OF ENDOCREINE GLANDS

- Ability to synthesis and or store their secretions
- Highly vascularized.
- Secrete biologically active molecules into the bloodstream to target their sites.
- They lack ducts.

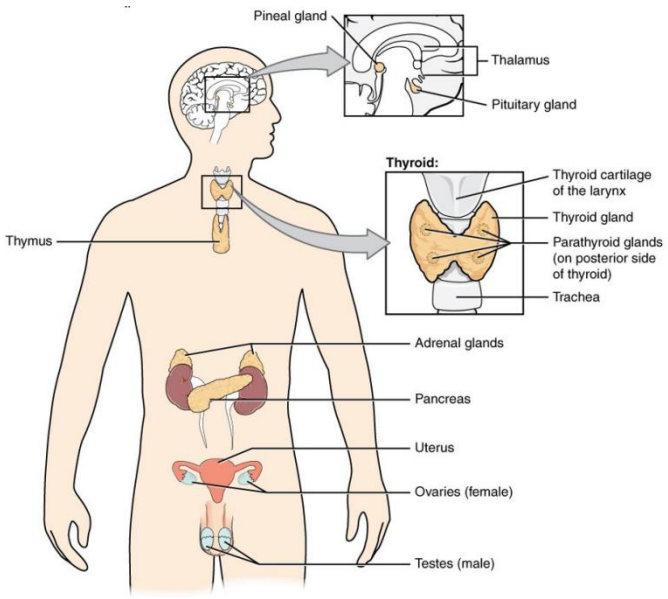


Figure 5: The endocrine glands in the human body

THE HYPOTHALAMUS

This is a part of the CNS and has several neural functions. Apart from the neural function it has endocrine functions which it is capable of doing due to the presence of special cells called nuclei. The hormones of the hypothalamus are either releasing hormones or inhibitory hormones. They are as follows:

1. growth hormone releasing hormone
2. growth hormone inhibitory hormone also called somatostatin
3. Prolactin inhibitory hormone
4. Thyroid stimulating hormone releasing hormone (TSH-RH).
5. Gonadotropin releasing hormone. There are 2 types: Follicular stimulating hormone releasing hormone (FSH-RH) and Luteinizing hormone releasing hormone (LH-RH).
6. Corticotrophins or adrenocortitrophic hormone releasing hormone (ACTH-RH).

All these hormones exert their actions or effects on other endocrine glands.
There are two other hormones produced in the hypothalamus which are not trophic hormones. They are

1. Oxytocin, synthesized in the paraventricular nucleus
2. ADH or vasopressin, synthesized in supraoptic nucleus.

RELASHIOPSHIP BETWEEN HYPOTHALAMUS AND OTHER GLANDS

The hypothalamus is known to exert its effects on virtually all the endocrine glands in the body. Being part of the nervous tissue, it contains nerve cell bodies known as nuclei are found in the hypothalamus. These cells have axons that ramify some parts of the body.

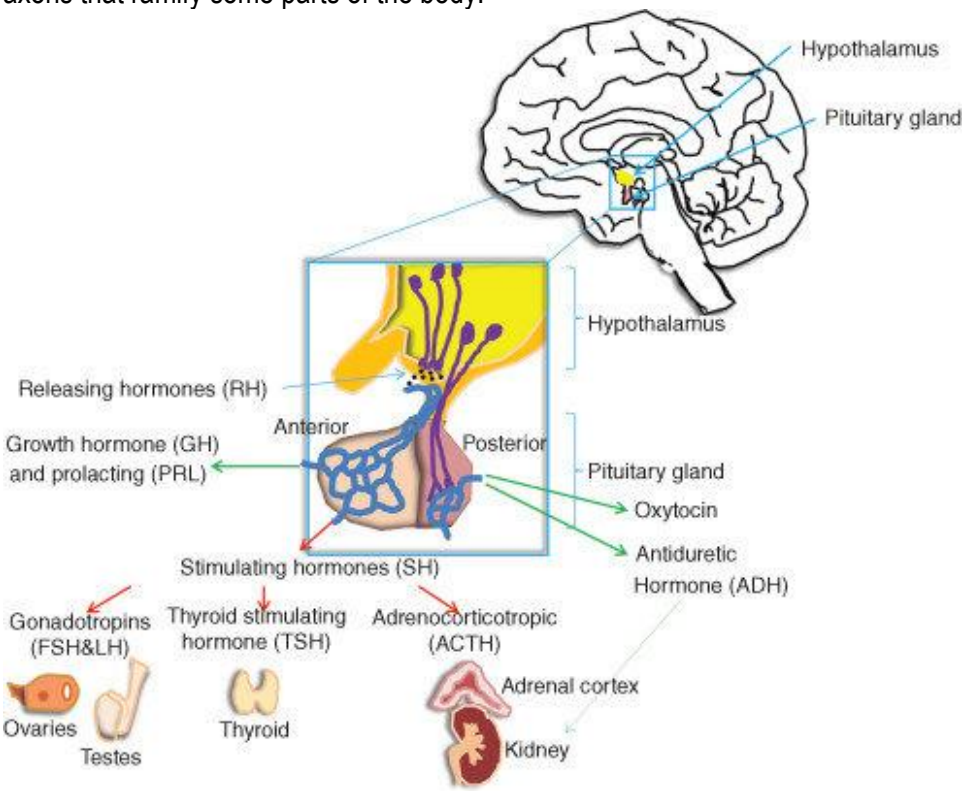


Figure 10.6: Hypothalamopituitary relationship

These cells that make up the nuclei send fibers to the median eminence and the posterior pituitary gland. The tract formed by the fiber is the route which the hypothalamic secretions are carried to the target organs.
The hypothalamus is richly supplied by the circle of Willis. The venous drainage pass through the median eminence where the blood vessel conveying it break up into primary capillary plexus or sinusoids. These sinusoids converge and form some portal vessels through the pituitary gland to supply it. The portal vessels break up again in the anterior pituitary gland to form secondary plexus. Both the primary and secondary capillary plexus form what is called the hypothalamo-hypophysial portal system.
Of all the hypothalamic nuclei, the supra-optic which is a group of cells above the optic chiasma and the paraventricular nuclei are of interest. Fibers passing from the nuclei extend down to the posterior pituitary gland.

THE PITUITARY GLAND

The pituitary gland or hypophysis lies in a pocket (the sella turcica) of the sphenoid bone at the inferior part of the base of the brain and is connected by the pituitary stalk. It can be referred to as the master gland because it is the main place for everything that happens within the endocrine system. It is divided into two sections:
The anterior lobe (adenohypophysis)
The posterior lobe (neurohypophysis)

Anterior Pituitary

The anterior lobe derived from oral ectoderm and is composed of glandular epithelium. Communication between the hypothalamus and the anterior pituitary occurs through hormones (releasing and inhibitory hormones), produced by the hypothalamus and delivered to the anterior pituitary via portal network of capillaries. The releasing and inhibiting hormones are produced by specialized neurons of the hypothalamus called neuro-secretory cells. The hormones are released into a capillary network or primary plexus, and transported through veins, or hypophyseal portal veins, to a secondary plexus that supplies the anterior pituitary. The hormones then diffuse from the secondary plexus into anterior pituitary, where they initiate the production of specific hormones by the anterior pituitary. Many of the hormones produced by the anterior pituitary are trophic hormones which are hormones that stimulate other endocrine glands to secret their hormones.

Anterior Pituitary hormones

1. growth hormone (somatotropin)
2. Prolactin (lacto trophic hormone
3. Thyroid stimulating hormone (TSH) or thyrotropin
4. Follicular stimulating hormone
5. Luteinizing hormone (LH)
6. Adrenocorticotrophic hormone (ACTH) or Corticotropin

GROWTH HORMONE

Growth hormone is a protein hormone that contains 191 amino acid residues with two di-sulfide bridges.

Functions:

1. Growth hormone stimulate the growth of all cells that are capable of growing by (i) activation of amino acid uptake by cells and (ii) causing increased protein synthesis. The increase protein leads to positive nitrogen and phosphorus balance, whilst blood urea falls.
2. Growth hormone is known to stimulate transcription processes in the nucleus. It reduces the breakdown of protein that is why it is referred to as protein sparer.
3. It is known to stimulate the growth of bone length by
    i. Stimulation of cartilaginous component at the epiphysis and

ii. Stimulation of osteoblastic activity. Indirectly, it is known to exact its effects on these tissues by causing the secretion of a substance called SOMATOMEDIN by the liver, kidney and muscle which act on the bones and cartilages to promote their growth.

4. Increases lipolysis. Growth hormone causes lipolysis thereby increasing the level of free fatty acids available for oxidation (energy).
5. Diabetogenic by:
    i. Antagonizing the peripheral action of insulin.
    ii. Stimulating hepatic glycogenolysis.
    iii. Stimulating the release of pancreatic glucagon.
6. It stimulates gastro intestinal calcium absorption and reduces Na^+ and K^+ excretion by an action independent of the adrenal gland. The calcium absorption is very essential since the absorbed calcium is transported to the bone for bone formation

The normal level of growth hormone is 0-3ng/ml. In infants, the blood level of growth hormone is higher about 5ng/ml since the rate of growth is higher than that of an adult.

Control of growth hormone secretion

Secretion from anterior pituitary is inhibited by growth hormone inhibitory hormone (somatomedin), which is a 14 amino acid peptide. Other factors associated with deficiency in energy substrate such as exercise, starving, hypo glycaemia will cause an increase or will stimulate growth hormone secretion. Increase in amino acid will increase its secretion. Stress increases secretion. Increase in fatty acid concentration in the plasma decrease secretion.

DISORDERS OF PRODUCTION OF GROWTH HORMONE

A. Under-production of growth hormone

a. In children

Dwarfism – epiphysis do not proliferate and premature arrest of synthesis of bone matrix.

i. Laron dwarf- short stature but proportioned body

ii. Fromlich's dwarf (syndrome) - due to under production of growth hormone as well as other endocrine trophic hormones. Stunting of growth, obesity, lethargic, indolent and sleepy youngsters.

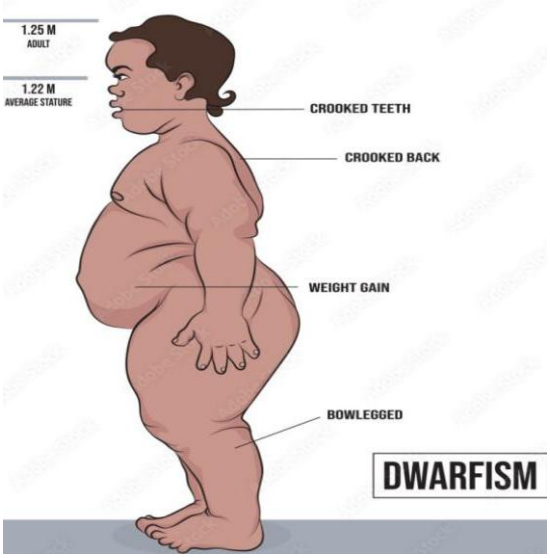


Figure 10.7: Dwarfism

B. Over production of growth hormone:

a. In children

Gigantism

Characteristics of gigantism

- Overgrowth of skeletal tissues, up to 8ft tall
- Splanchomegaly
- hypogonadism (due to decrease gonadototropes caused by over production of cells in somatotropes)

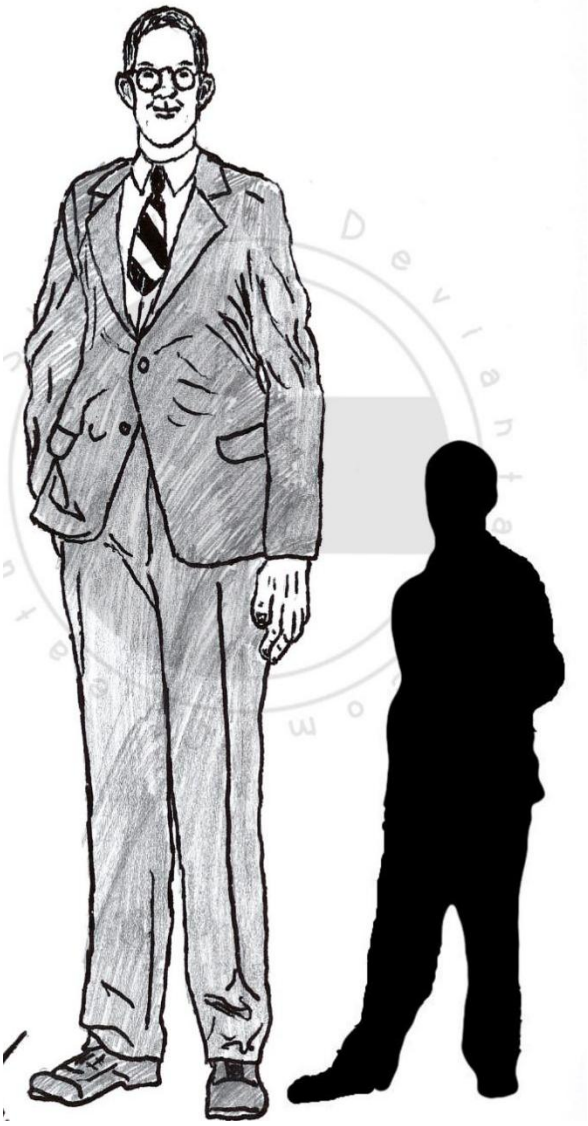


Figure 10.8: Gigantism

a. In adults: **Acromegaly:**

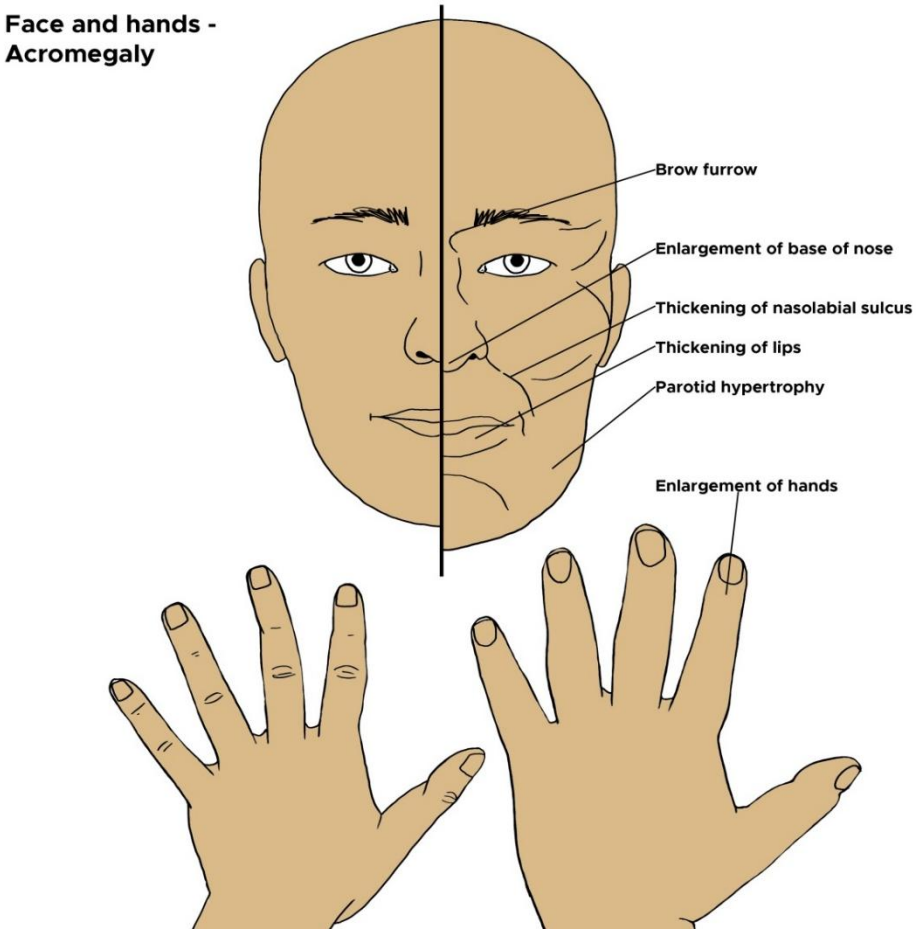


Figure 10.9: Acromegaly

It is usually due to tumours of somatotrophs
Consequences:

1. (a) enlargement of sella turcica
   (b) Headache
   (c) Visual disturbances (bilateral hemianopia)
2. Excessive production of growth hormone leads to:
   i. Enlargement of acral parts (feet and hands), hence the name acromegaly.
   ii. Protrusion of the lower jaw (pragmatism).
   iii. Acromegalic faces-large and widely separated teeth.
   iv. Splanchnomegally- enlargement of viscera i.e. liver, spleen, intestine etc.
   v. Hyperglycaemia-increase glucose in blood.
   vi. Skeletal changes predisposed to osteoarthritis.
   vii. Massive increase in cartilaginous tissue growth e.g. enlargements of ears and nose.

PROLACTIN

- The main role of prolactin is to stimulate and maintain milk production in lactating females.
- It stimulates the growth of mammary gland (the alveoli of the mammary gland specifically).
- It also elicits parental behavior in females.

Prolactin is also found in males, but no known function has been established for it. Prolactin has a half-life of about 20-30 minutes, is known to be inactivated mainly in the liver and kidney. It is secreted rhythmically with a high level early in the morning compared to the other time of the day. Prolactin level is also high during lactation; the stimulus for this is suckling.

Control of prolactin secretion

Prolactin secretion is regulated by the hypothalamus via prolactin inhibitory hormone (PIH). When there is no lactation in humans, PIH secretion is high. The net effect of the hypothalamus is thus to inhibit prolactin secretion. During lactation however, the action of PIH is inhibited via suckling and therefore the mamatropes increase prolactin secretion. Other factors that affect prolactin secretion includes:

1. Sleep increases secretion.
2. Pregnancy increases secretion of prolactin reaching peak at parturition and then declining progressively.
3. Any stressful condition, physical or mental will increase prolactin secretion
4. Some drugs like dopamine and bromocriptine inhibit secretion of prolactin.

THYROID STIMULATING HORMONE (THYROTROPIN (TSH))

Functions

1. Stimulation of secretion of thyroxine (T4) and trio-iodothyronine (T3).
2. It increases the activity of the iodide pump. It increases the rate of iodide trapping.
3. It stimulates the iodination of tyrosine
4. It stimulates the synthesis of thyroglobulin
5. It increases the number and the size of thyroid cells.

FOLLICULAR STIMULATING HORMONE (FSH)

- FSH is a trophic hormone
- It is trophic to the gonads

In the male, it is known to stimulate spermatogenesis.

- in females and it initiates maturation of graffian follicles
- It also stimulates the graffian follicles to produce oestrogen.

LUTEINIZING HORMONE (LH)

- LH is also a trophic hormone
- in the males, it acts on leydic cells to produce testosterone
- In the females, LH stimulates (1) maturation of graffian follicles (2) ovulation (3) production of corpus luteum (4) secretion of progesterone from corpus luteum.

CORTICOTROPIN OR ADRENOCORTITROPHIC HORMONE (ACTH)

- ACTH is a trophic hormone
- It stimulate the adrenal cortex to produce glucocorticoids
- ACTH has some MSH-like properties thus it increases deposition of melanin pigment in the skin.

- ACTH can also mobilize fats from their stores for the production of energy.

POSTERIOR PITUITARY GLAND (NEUROHYPOPHYSIS)

- There are no secretory cells in the posterior pituitary.
- There are no nerve cells but only nerve fibers (Hypothalamo-hypophyseal nerve tracts) whose cells lie in the hypothalamus.

General functions of neurohypophysis

- Regulation of water balance through the kidneys
- Milk ejection from lactating breast.
- Helping child birth and prevention of post-partum haemorrhage
- Transport of seminal fluid in uterine cavity at the end of coitus.

POSTERIOR PITUITARY HORMONES

The posterior pituitary has two hormones oxytocin and antidiuretic hormone (ADH). These hormones are produced in the two nuclei of the hypothalamus, thus

1. Paraventricular nucleus produces oxytocin mainly and ADH to a lesser extent
2. Supra optic nucleus produces ADH mainly and oxytocin to a lesser extent. Although these hormones are often referred to as neurohypophyseal hormones, they are not produced by the neuro-hypophysis but are stored there.

N.B.

a. Both Oxytocin and ADH are transported from the hypothalamus through the hypothalamo-hypophyseal nerve tract to the posterior pituitary gland.

b. The neurohypophyseal hormones are peptides made up of amino acids.

ADH Functions

- It concentrates urine by promoting the facultative reabsorption of water from the distal convoluted tubules. It acts by increasing the permeability of distal and collecting tubules to water by causing either an increase in the number of water permeable "pores" or an increase in the size of such pores, cAMP acts as a second messenger in the process.
- It stimulates the thirst center.
- In large doses (pharmacological action):-
  1. Causes generalized vasoconstriction leading to significant increase in arterial blood pressure (vasopressin effect).
  2. Stimulates peristaltic movement of the gut
  3. Causes contraction of uterine smooth muscle and myoepthelial cells of the breast.

Control of ADH secretion

(a) Changes in plasma osmolality

- Increase osmolarlity--------- increase ADH secretion.
- Decrease osmolarlity-------- decrease ADH secretion.

The effects are mediated through osmoreceptors in the hypothalamus.

(b) Changes in plasma volume

- Increase in plasma volume------- decrease reflex ADH secretion.
- Decrease plasma volume--------- increase reflex ADH secretion.

The effects are mediated through atrial volume receptors.

(c) Afferent impulses from cerebral cortex e.g. emotional stimuli, fear, anger, muscular exercise--------- increase ADH secretion.
(d) Chemicals e.g. nicotine, adrenaline, barbiturates etc. ------- increase ADH secretion.
(e) Alcohol consumption---------- decrease ADH secretion.

OXYTOCIN

1. On the uterus, oxytocin causes powerful contraction (primary function) which has the role to play in:
   (a) Parturition- oxytocin is not essential for birth to occur but it facilitates the process by causing uterine contraction. Oxytocin production at the end of pregnancy is reflexly stimulated by the distended uterus.
   (b) Prevention of post-partum haemorrhage by constricting traumatized uterine blood vessels.
   (c) Facilitating fertilization during coitus as it enhances uterine contraction helps to propel the semen upwards through the fallopian tubes.
   (d) Helping involution of uterus i.e. its return to the normal small pre-pregnancy size. This is helped by suckling.
   (e) Helping females to reach orgasm at end of coitus.

   N.B.: In males, oxytocin probably causes ejection of sperm from seminiferous tubules and epididymis into the vas deferens.
2. Contraction of the myoepithelial cells which lines the ducts of the breast. When there is milk in the alveoli, the contraction of the cells in response to the hormone causes the release of milk from the alveoli. Without oxytocin, only 15-20% of secreted milk can be removed by the suckling baby.

Milk ejection reflex- this is a reflex having receptors at nerve endings on the nipple. When a baby suckle or when the nipple is touched, the nerve endings are stimulated. This sends impulses to the hypothalamus and as a result, the nuclei especially the paraventricular nucleus secrets oxytocin. Signals are also send to neuro hypophysis which causes release of oxytocin. When the hormone gets to the myoepthelial cells, it enhances ejection by contracting the myoepthelial cells surrounding the milk containing alveoli.

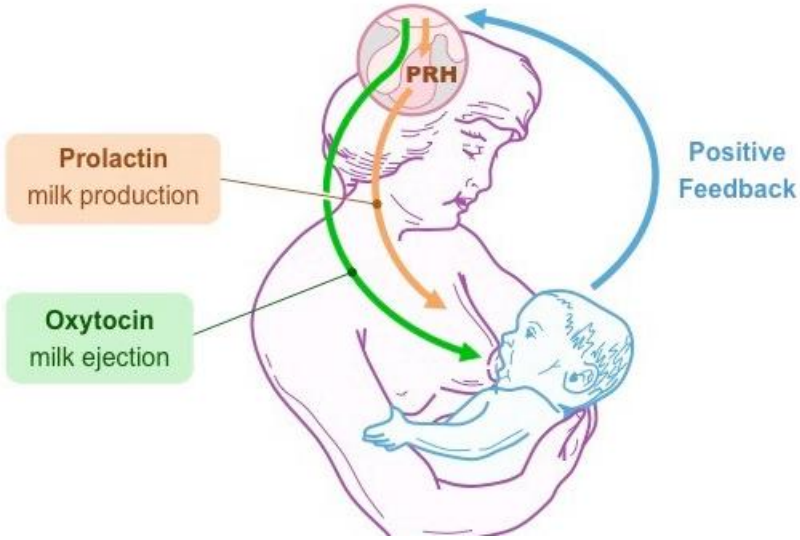


Figure 10.10: The milk ejection (let down) reflex

3. It has been found that oxytocin stimulates or promote fertilization as some workers have observed that there is an increase in oxytocin level during intercourse. This does not apply to all animals. In pharmacologic doses, it has same effect as vasopressin

Control of oxytocin secretion

a. The suckling reflex- stimulation of mechanical receptors in nipples during suckling is the most powerful stimulant of oxytocin secretion (milk ejection reflex).
b. Coital reflex: - oxytocin release during sexual intercourse is postulated to facilitate sperm transport into fallopian tubes by increasing uterine contraction.
c. Labour: - during the second stage of child birth, afferent impulses from birth canal may stimulate increase oxytocin to enhance uterine contraction.
d. Afferent impulses from cerebral cortex through conditioned reflex (vision, hearing, smelling or thinking) may lead to oxytocin secretion.

DISORDERS OF POSTERIOR PITUITARY HORMONES

ADH SECRETION

- Diabetes insipidus- results from hypo secretion of ADH as a result of lesion in hypothalamus, posterior pituitary gland or the tract joining them.

Symptoms of diabetes insipidus

a. Tasteless, colorless urine
b. Polyuria (i.e. 25L/day) i.e. massive volume of urine. The specific gravity of urine is very low (1.000-1.003)
c. Polydipsia (excessive thirst due to polyuria)
d. Loss of vitamins e.g. vitamin B.

- Hyper secretion of oxytocin- this leads to amenorrhea (cessation of menstrual cycle)
- Hypo secretion of oxytocin

a. Perhaps infertility- probably due to loss of contraction of uterus to transport seminal fluid to the fallopian tubes.
b. Inability to breast feed

Hyper secretion of ADH-

- Water retention, hyponatraemia, syndrome of inappropriate water intoxication.

THE THYROID GLAND

The thyroid gland is one of the largest endocrine glands in the body. It is positioned in the anterior neck just below the larynx and has two lobes being connected by a band of tissue called isthmus, with one on each side of the trachea. It weighs about 15-25g (average weight =20g). Histologically, the gland consists of follicles. Each follicle consist of a colloid filled central cavity lined by follicular cells. The follicular cells are essentially cuboidal epithelial cells. Produces two hormones:

a. Thyroid hormone: T4 (thyroxine) and T3 (triodthyronin)
b. Calcitonin involved with calcium and phosphorus metabolism
c. Thyroid is composed of spherical follicles
    a. Follicle cells: produce thyroglobulin, the precursor of thyroid hormone (thyroxin)
    b. Colloid lumen is of thyroglobulin
    c. Parafollicular “C” cells: produce calcitonin

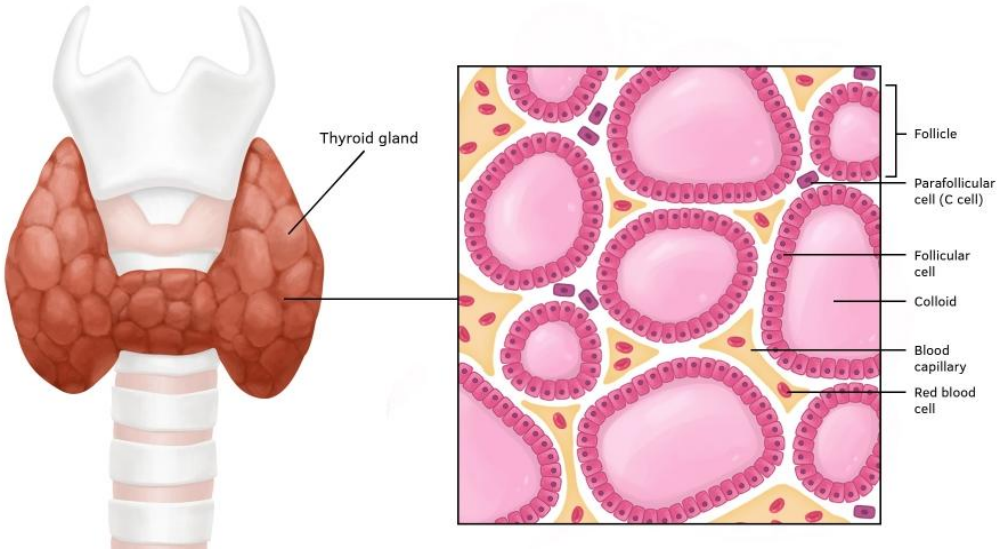


Figure 10.11: The thyroid gland and follicles

The follicular cells have three functions:

a. They collect and transport iodine.
b. They synthesis thyroglobulin and secret same into the colloid.
c. They remove the thyroid hormones from thyroglobulin and secret them into the circulation.

Iodine metabolism

The minimum daily intake of iodine (in form of iodide) is 150µg. the normal plasma level of iodide is 0.3mg/100ml.

Biosynthesis of thyroid hormones

i. Iodide trapping- this is the uptake of iodide from blood by follicular cells. The follicular cells concentrate iodide by means of active pump mechanism to 25-30 times normal plasma level. The activity of this iodide pump is controlled by thyrotropin (TSH) from adenohypophysis.
ii. Oxidation of trapped iodide to elemental iodine: $2I^- - 2I + I_2$
iii. Conjugation of iodine to tyrosine and formation of monoiodotyrosine (MIT) and di diiodotyrosine (DIT) which are biologically inactive.
iv. Condensation of MIT and DIT to form T_3 and T_4.
v. Storage: The hormones (T_3 and T_4) are liberated to the lumen of thyroid follicle conjugated to a protein called thyroglobulin.
vi. Release: The hormones are released when required to the blood through hydrolysis from thyroglobulin molecule by means of proteases enzyme.

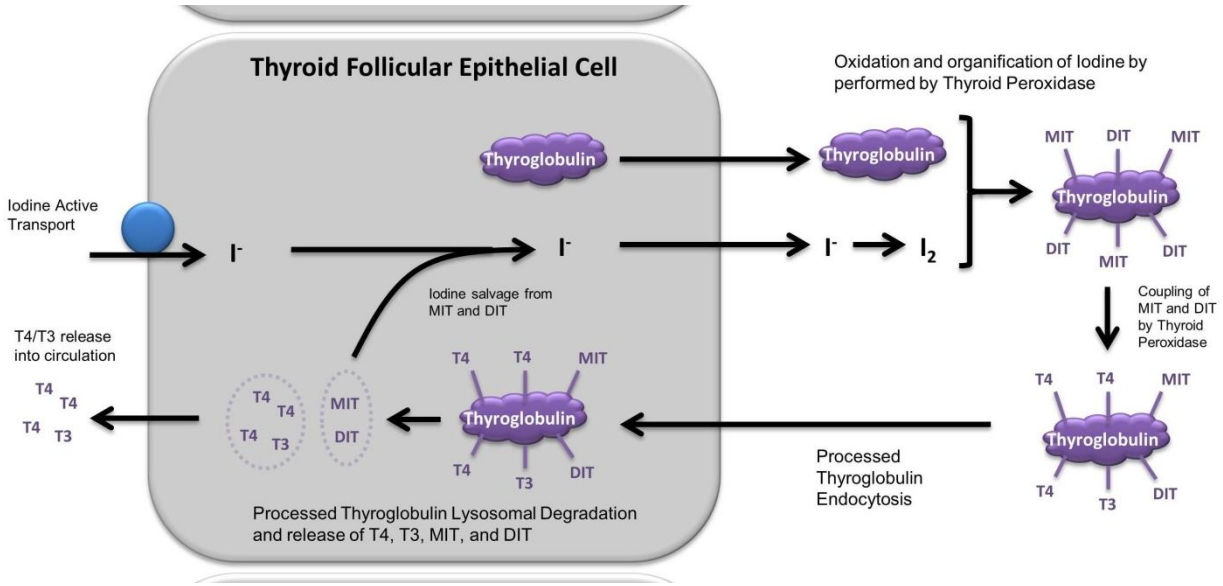


Figure 10.12: Biosynthesis of thyroid hormone

Transport of Thyroid Hormone

- Thyroid hormones are not very soluble in water (but are lipid-soluble).
- Thus, they are found in the circulation firmly and reversible bound to plasma proteins:

a. Thyroid Hormone-Binding Globulin (~70% of hormone)
b. Pre-albumin (transthyretin), (~15%)
c. Albumin (~15%)
d. Less than 1% of thyroid hormone is found free in the circulation.

N.B.: Only free and albumin-bound thyroid hormone is biologically available to tissues.

Plasma levels of T_3 and T_4

T_4 level =8.0µg

T_3 level =0.15µg

The active forms are:

- T_3 is the active form (has 4 times the activity of T_4)
- T_4 serves as reserve, which can be activated by mono-de-iodination to T_3 in peripheral tissues. This conversion takes place mainly in the liver and kidneys. The T3 formed is then released to the blood stream.
- T_3 has a latent period of 6 to 12 hours and maximal effect after 2 to 3 days.

TSH controls both synthesis and release.

Actions of thyroid hormones

1. Calorigenesis: - Basal metabolic rate (BMR) increases; oxygen consumption and heat production are increased (exceptions-brain, testes, anterior pituitary, uterus, and spleen).
2. On the Cardiovascular System:
    - Increase heart rate, increase force of cardiac contractions, increase Cardiac output
    - Augment the action of catecholamine's (increase their affinity for β- receptors
3. On the Respiratory System:

- Increase resting respiratory rate
- Increase minute ventilation
- Increase ventilatory response to hypercapnia and hypoxia

4. On the Renal System:
   - Increase blood flow
   - Increase glomerular filtration rate
5. On Oxygen-Carrying Capacity:
   - Increase RBC mass
   - Increase oxygen dissociation from hemoglobin
6. On organic Metabolism
   i. On carbohydrate metabolism:
      - Increase glucose absorption from the GI tract
      - Increase gluconeogenesis
      - It increases the breakdown of glycogen in the liver (glycogenolysis)
      - Increase blood glucose level and tissue uptake of glucose.
   ii. On fat metabolism:
      - Mobilization of lipids from adipose tissue leading to increased free fatty acids (FFA) in plasma and oxidation of FFA in cells. Plasma cholesterol and phospholipid levels falls.
   iii. On protein metabolism:
      - Increased protein synthesis though excess T_3 leads to protein catabolism.
   iv. On vitamin metabolism:
      - Increased absorption and conversion of carotene to vitamin A.
7. Growth and maturation:
   - Maturation and differentiation of most tissues need T_4. T_4 potentiates the action of growth hormone.
8. On CNS:
   - T_4 is necessary for normal development and functions of cells. Cretins are complete idiots i.e. very mentally retarded.
9. On the Reproductive System
   - Required for normal follicular development and ovulation in the female
   - Required for the normal maintenance of pregnancy
   - Required for normal spermatogenesis in the male

Regulation of Thyroid Hormone Levels

- Thyroid hormone synthesis and secretion is regulated by two main mechanisms:
  - An "autoregulation" mechanism, which reflects the available levels of iodine
  - Regulation by the hypothalamus and anterior pituitary

Autoregulation of Thyroid Hormone Production

- The rate of iodine uptake and incorporation into thyroglobulin is influenced by the amount of iodide available:
  - Low iodide levels increase iodine transport into follicular cells
  - High iodide levels decrease iodine transport into follicular cells

Thus, there is negative feedback regulation of iodide transport by iodide.

Neuroendocrine Regulation of Thyroid Hormones: Role of TSH

- Thyroid-stimulating hormone (TSH) is produced by thyrotroph cells of the anterior pituitary.
- TSH is a glycoprotein hormone composed of two subunits:
  - Alpha subunit (common to LH, FSH, TSH)
  - TSH beta subunit, which gives specificity of receptor binding and biological activity
- TSH acts on follicular cells of the thyroid.
  - increases iodide transport into follicular cells
  - increases production and iodination of thyroglobulin
  - increases endocytosis of colloid from lumen into follicular cells

Negative Feedback Actions of Thyroid Hormones on TSH Synthesis and Release

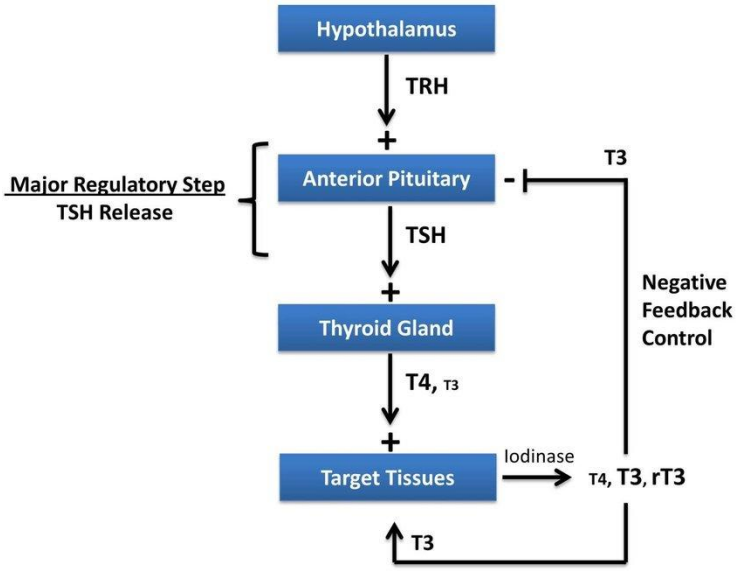


Figure10.13: Negative feedback actions of thyroid hormones

- Diet: a high carbohydrate diet increases T3 levels, resulting in increased metabolic rate (diet-induced thermogenesis).
- Low carbohydrate diets decrease T3 levels, resulting in decreased metabolic rate.
- Cold Stress: increases T3 levels in other animals, but not in humans.
- Other stresses: increased or decreased?
- Any condition that increases body energy requirements (*e.g.*, pregnancy, prolonged cold) stimulates hypothalamus → TRH → TSH (Pit)

DISTURBANCES OF THYROID FUNCTION

UNDERPRODUCTION (hypothyroidism): This may be results from;

i. Thyroid gland defect (e.g. defective thyroglobulin synthesis)
ii. Failure of TSH production
iii. Failure of TRH production
iv. Iodine deficiency

Hypothyroidism in children leads to **cretinism**
Cretinism is a French word describing “one who is human despite deformities”
Symptoms:

i. Decreased BMR
ii. Decrease growth/development leading to dwarfism. Dwarf-mutes are severely mentally retarded individuals because their synapses develop abnormally. Also, myelination of nerve fibers is defective.
iii. The skin is thick, tongue is enlarged and protruding between thick lips with profuse salivation. Sexual organs remain infantile

Figure 10.14: A cretin

Hypothyroidism in adults (myxedema)

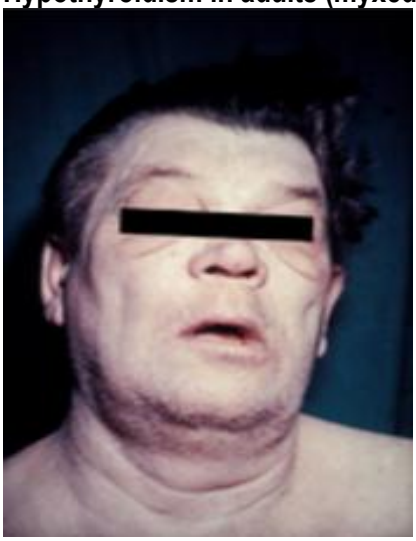


Figure 10.15: Myxoedema

Features of hypothyroidism:

1. ↓BMR
2. ↓Oxygen consumption
3. ↓heat production

On fat metabolism

- ↓fat utilization
- The phospholipid and cholesterol levels in the blood are increased with a tendency to generalized atherosclerosis.

On protein metabolism

- ↑body weight due to protein and water retention.

On CNS.

- Mentation is low and memory is poor i.e. loss of memory and mental sluggishness due to decrease mental activity.
- Slow movements and reflexes are depressed.

On other organs

- ↓respiratory rate
- ↓heart rate, ↓cardiac output, ↑contraction time.
- Anaemia due to depressed bone marrow activity
- Rough and dry skin due to vitamin A deficiency
- Muco-protein and fluids are deposited under the skin (non-pitting edema)
- Face bagginess due to deposition of increased quantity of proteoglycans.
- Gonadal hypo function
- On GIT, loss of appetite, ↓intestinal motility leading to constipation
- Depressed growth of hair and scaliness of skin.
- Husky and slow voice (the basis of the hypothesis that myxedema is one disease that can be diagnosed through the phone).

HYPERTHYROIDISM (thyrotoxicosis or Graves' disease)

Is an autoimmune disease characterized by circulating autoantibodies resulting from either continuous stimulation of the thyroid gland by a substance called long acting thyroid stimulator ((LATS) or over secretion of the hormone by a thyroid tumour.

Symptoms: - Moderate enlargement of the gland (goiter) which causes dyspnea due to pressure on the trachea

1. Body processes are accelerated, increased BMR (100%), heat intolerance, and the skin of the patient is warm, sweating, mild diabetes mellitus, increased protein synthesis and catabolism. This leads to extreme weight loss.
2. Increased excitability of the nervousness system, shown by fine tremors in the out stretched hands, insomnia and irritability.
3. CVS: - Tachycardia, increased cardiac output and systolic blood pressure with a feeling of palpitation. The pulse pressure is increased leading to water hammer (collapsing pulse).
4. GIT- increase motility leading to diarrhea. Increased appetite but body weight decreases due to increase metabolism.
5. Eye: exophthalmos i.e. abnormal protrusion of the eyeballs due to deposition of:
   i. Fat behind the eye and weakness of intraocular muscles

ii. Eyelid retraction
iii. Pupillary dilation due to increase sensitivity to circulating catecholamines.

6. Muscular weakness and extreme fatigue.
7. Inability to sleep

Treatment:

Hypo function is treated by supplying the hormone orally and as early as possible or supplying iodine if deficient.
Hyper function is treated by surgical removal, irradiation or anti-thyroid drugs
N.B. Long- acting- thyroid –stimulator (LATS). This is a protein substance discovered in blood of some hyperthyroid patients and it is considered the real course of the disease.

FACTORS AFFECTING THYROID FUNCTIONS

a. TSH
b. Long- acting- thyroid –stimulator (LATS). This is perhaps the direct cause of Graves' disease (hyperthyroidism).
c. Iodine level
d. Level of thyroxine in blood
e. Anti-thyroid agents- they inhibit thyroid secretion and cause thyroid enlargement (goiter). The three types of goiter are:
   i. Goiter with normal function (simple) as in mild iodine insufficiency e.g. during pregnancy and puberty.
   ii. Goiter with hypothyroid function (colloid) e.g. severe iodine deficiency
   iii. Goiter with hyperthyroid function (toxic) e.g. exophthalmic goiter.

THYROID FUNCTION TESTS

1. Determination of pre-albumin iodine. It is a specific test because it measures the hormonal level in the plasma. It increases in hyper function up to 20µg% and decreases in hypo function to about 0-2µg%.
2. TSH test- this test differentiates various conditions of hypothyroidism, whether primary (lesion in thyroid gland itself) or secondary (lesion in the anterior pituitary gland).
3. Iodine suppression test- it is a therapeutic test for diagnosis of hyperthyroidism. If the symptom improves, this confirm diagnosis. If not the symptom must be of another diseases.

CALCIUM METABOLISM

Daily requirement = 1.5g (adults)
Pregnant females = 1-5g
Lactating mothers = 3g
Sources of calcium- milk, cheese, green vegetables, egg yolk and fish
Absorption of calcium is mainly from the duodenum.

FACTORS AFFECTING ABSORPTION OF CALCIUM

1. PH of intestinal content

-decrease PH → increase absorption
-increase PH → decrease absorption

2. Vitamin D
3. Parathyroid hormone

4. Steatorrhoea – excess quantity of fats are lost in faeces and decrease calcium absorption
5. Phytic acid forms insoluble complex with calcium, this leads to decrease calcium absorption.

FUNCTIONS OF CALCIUM

1. Coagulation of blood (factor iv)
2. They influence membrane permeability to Na and are therefore important in the determination of the degree of neuromuscular excitability.
3. They take part in the release of neurotransmitters; many hormones and exocrine secretions
4. Calcium is a crucial component of the contractile processes in muscle fibers.
5. Formation of bones and teeth.
6. Production of milk.
7. They are involved as co-enzymes and regulation in many intracellular pathways.

Concentration of calcium in blood: 9.0-11.0 mg/dl of blood i.e. 2.3-2.6 mmol/dl of blood.

Plasma calcium exist in three forms:

1. Non-diffusible Ca (bound to plasma proteins)
    - About 47% of total Ca is available in non-diffusible form (37% bound to albumin and 10% bound to globulin).

2. Complex Ca; only 6% of total Ca in blood exist in complex form. They are combined with citrates, bicarbonates and phosphates. They are diffusible but not ionized. They have no physiological activity.
3. Ionized Ca: about 47% of total Ca in blood exists in ionized form. It is diffusible and physiologically active.

REGULATION OF Ca^{++} METABOLISM

Parathyroid gland

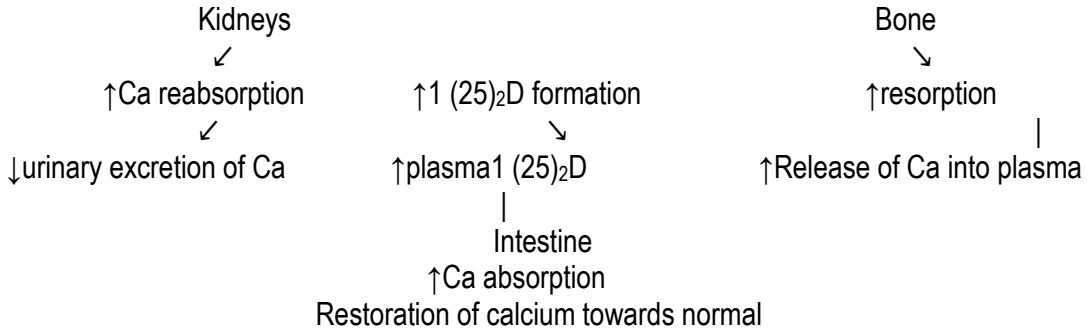
- They are usually four glands, one at each of the superior and inferior poles of the two lobes of the thyroid situated close to the posterior surface.
- Two types of cells are present, chief cells (main) which are secretory and oxyphil cells with unknown function.
- The chief cells secret a protein hormone (parathormone or parathyroid hormone) which is essential for life.

ACTIONS OF PARATHYROID HORMONE

The actions of parathyroid hormone are directed at three main organs chiefly involved in calcium metabolism, bone, kidney and intestinal tract. Calcium ion plays an important role in the regulation of many functions in the body. The plasma Ca levels normally maintained within a very small range at approximately 10mg/100ml of plasma (range between 9-11mg/100ml of plasma).

Actions of parathyroid hormone on bone

↓Plasma Ca
↑Parathyroid hormone secretion
↑ Plasma Parathyroid hormone
|



Key: ↑ = Increases, ↓ = Decreases

1. **On bone**: Removes Ca (increase mobilization of Ca) from bones by stimulating osteoclastic activity leading to increase plasma Ca. Its primary target being the principal calcium store in the body (bone).
2. **On kidneys:** Parathormone acts on tubules:
   - To depress PO4 reabsorption thereby lowering plasma phosphate and promoting bone resorption.
   - To increase Ca reabsorption from glomerular filtrate.
   - To stimulate the production of 1, 25, dihydroxy-cholecalciferol.
3. ON GIT: It increases intestinal absorption of dietary Ca by promoting the formation of vitamin D in the kidney.

CALCITONIN

- Calcitonin is produced by the "C" cells of the thyroid gland.
- Its main function is to lower blood Ca whenever it rises above normal.

Actions of calcitonin

1. On bones: it stimulates bone formation by stimulating osteoblastic activity. It decreases bone destruction by inhibiting osteoclasts.
2. On the kidneys: it decreases Ca and PO4 reabsorption from glomerular filtrate thereby increasing their excretion through the urine.
3. On intestine: calcitonin decreases Ca absorption in the intestine

Control of secretion of calcitonin

By Ca blood level i.e., Increase Ca → increase calcitonin secretion and vice versa.

DISORDERS OF PARATHYROID GLAND FUNCTIONS

a. Hypoparathyroidism- Ca moves into bones togather with PO4; resulting increased bone density (heavier bones).
b. Hypocalcaemia: leading to tetany that is manifested by spasm, particularly of the hands.
c. Reduced Ca causes hypersensitivity of peripheral nerves causing unusual sensation e.g. tingling (parasthesia).

TETANY

It is a state arising from hyper excitability of the peripheral nerves due to a reduction in extracellular ionized calcium level. Spasmodic contraction of the laryngeal and respiratory muscles lead to death due to asphyxia.

Causes of tetany

1. Hypoparathyroidism e.g. due to faulty removal of parathyroid during thyroidectomy.
2. Alkalaemia- decreased ionized Ca. alkalaemia may be caused by:
   i. Hyperventilations leading to CO2 wash.
      ↑PH = PK + log $\frac{(HCO3)}{CO2}$
   ii. Excessive vomiting leading to loss of HCl acid
   iii. Ingestion of large amounts of alkalis in vegetables;
3. Calcium deficiency in diet due to:
   i. Decrease Ca intake in diet
   ii. Decrease absorption from intestine as in vitamin D deficiency; ↑alkalinity of intestinal contents, steatorrhoea, increased dietary oxalates or PO4.
   iii. Relative deficiency in late pregnancy and during lactation.

TYPES OF TETANY

Manifest tetany- this occur when serum calcium drops to less than 7mg%. The manifestation of the disease appears without provocation in the form of attacks of "carpo-pedal" spasm or "Obstetrician's hand". There is flexion of elbow, wrist and metacarpophalangeal joints and extension of interphalangeal joints and the thumb is abducted to the palm of the hand (carpal spasm). The feet are dorsi-flexed and toes are plantar flexed (pedal spasm).

Latent tetany- this occur when the serum Ca decreased but remain about 7mg%. Symptoms usually absent. They appear when the person is exposed to more decrease in serum Ca e.g. during pregnancy, lactation and hypoventilation.

DIAGNOSIS OF HYPOCALCAEMIA

a. Blood analysis for concentration of ionized Ca
b. Provocative tests which makes latent tetany manifestation:-

i. Trousseau's test: - sphygmomanometer cuff is wrapped around the arm and inflated for 3 minutes. This leads to carpal spasm (due to ischaemia and hypocalcaemia)
ii. Chvostek's test: - tapping of the facial nerve in front of the ear leads to twitches of facial muscle especially of the upper lip (due to hyper excitability of nerves plus mechanical stimulation).
iii. Erb's test:-Galvanic current is applied to motor nerves of the upper limb. This leads to carpal spasm (due to hyper excitability of nerves plus galvanic current stimulation).

HYPER PARATHYROIDISM

Increased secretion of parathyroid hormone may be due to a disorder of parathyroid gland (primary hyperparathyroidism) or be a compensation mechanism secondary to low plasma calcium level. This is called secondary hyperparathyroidism.

Primary hyperparathyroidism- all patients with renal stone should be investigated for hyperparathyroidism although only a minority will have excess PTH secretion as hyperparathyroidism is a rare case.

Symptoms:

1. Renal disorder- stone formation
2. Polyuria
3. Inability to concentrate urine

4. Hypocalcaemia and acidosis
5. There is anaemia due to destruction of the bone marrow together with a low and sometime irregular heart rate and cardiac arrest.

Secondary hyperparathyroidism- secretion of parathyroid hormone is increased as plasma Ca concentration is low. Such a condition occurs in renal failure, intestinal malabsorption, vitamin D and calcium deficiencies, pregnancy and lactation.

Tertiary hyperparathyroidism- this is usually applied to the development of an apparently autonomous parathyroid adenoma after long standing hyper activity due to secondary hyperparathyroidism. An adenoma may be developed particularly in the hyper plastic glands secondary to renal failure, malabsorption or chronic vitamin D deficiency.

Plasma calcium, normally reduce in this condition, may therefore still be in the normal range in the presence of parathyroid hormone.

ADRENAL (SUPRARENAL) GLANDS

("suprarenal" means on top of the kidney)

Each is really two endocrine glands

- Adrenal cortex (outer)
- Adrenal medulla (inner)

Histologically, adrenal cortex is divided into three zones;

- Zona glomerulosa which secrets mineralocorticoids (aldosterone)
- Zona fasciculata which secrets glucocorticoids (cortisol or corticosteroids)
- Zona reticularis which secrets sex hormones (mainly androgens)

The secretions of the adrenal gland are steroids; they are synthesized directly from cholesterol in the diet.

ACTIONS

1. **MINERALOCORTICOIDS** e.g. aldosterone.
   - Act mainly on Na^+, K^+, Cl, and water metabolism.
   - They promote reabsorption of Na^+ along with water in the renal tubules, whilst stimulating excretion of H^+, and K^+.
   - On the cardiovascular system, mineralocorticoids increase Na^+ and water retention leading to increase in blood volume, cardiac output and a rise in arterial blood pressure.
2. **GLUCOCORTICOIDS** e.g. cortisol
   - They exert some mineralocorticoid effects i.e. cause salt and water retention like the mineralocorticoids but to a lesser degree.
   - They enhance water diuresis by antagonizing the action of antidiuretic hormones.
   - On carbohydrate metabolism, glucocorticoids are diabeto-genic because they cause gluconeogenesis from amino acids and decrease tissue uptake of glucose (i.e. they cause anti-insulin action).
   - On protein metabolism glucocorticoids stimulate catabolism of proteins into amino acids which are then used for gluconeogenesis.
   - On fat metabolism, glucocorticoids increase mobilization of fats from its stores to supply energy. They also cause centri-pedal distribution of fats (they increase fat deposition in facial and truncal area).

- On blood and lymphoid tissues, glucocorticoids decrease lymphocyte count (anti-immune actions), decrease eosinophil count (anti-allergic), increase red cell count, platelet, and neutrophil counts. They have anti-inflammatory actions. Cortisol inhibit inflammatory response by:-
  i. Inhibiting capillary permeability and fluid exudation.
  ii. Inhibiting fibroblastic activities and the deposition of collagen fibers.
  iii. Stabilizing lysosomal membranes.
- On the stomach, cortisol reduces gastric mucus membrane predisposing to ulcer.
- On stress, cortisol helps to combat stress and shock. Stressful stimulations include trauma, surgical operations, excess heat or cold and infections. (Blood vessels are more sensitive to catecholamine when there is increase concentration of cortisol in the blood).

3. ANDROGENS

- They promote development and activities of sex organs together with hormones of the gonads.
- They are anabolic in functions i.e. they stimulate protein synthesis in the body.

CONTROL OF ADRENOCORTICAL HORMONE SECRETION

a. GLUCOCORTICOIDS – this is affected by ACTH (N.B negative feedback mechanism).
b. MINERALOCORTICOIDS – (aldosterone)
   - Low serum Na leads to renin- angiotensin- system.
   - High K concentration in ECF.
   - Decrease ECF volume.
   - Haemorrhage.

DISTURBANCES OF ADRENAL CORTEX

A. HYPOFUNCTION (Addison's disease).

Manifestations:

a. Hypotension – due to increase Na and water excretion.
b. Hypoglycaemia – due to decrease gluconeogenesis and absence of anti-insulin action of cortisol.
c. Muscular weakness – due to absence of androgens/decrease protein anabolic action of androgens
d. General loss of body weight.
e. Anaemia
f. Bronzing or darkening of the exposed areas of the skin (due to ACTH).
g. Decreased resistance to stress.
h. Loss of appetite; perhaps even diarrhea and vomiting.

B. HYPERFUNCTION (Aldosteronism (Cohn's disease)

That is overproduction of aldosterone (mineralocorticoids).

Manifestations:-

1. Hypertension due to increased blood volume
2. Oedema due to increase Na and water retention.
3. Muscular pains and weakness
4. Metabolic alkalosis due to increased reabsorption of Na along with HCO_3.

C. CUSHING'S SYNDROME (hyper-function of glucocorticoids particularly cortisol).

N.B. females are usually more affected than males.

Manifestations:

1. A). Truncal obesity- moon face and buffalo-neck.
   B). purple striae (lines) - lines on abdomen due to stretching of its skin fat depots.
2. Hyperglycemia
3. Wasting of skeletal muscle due to increased protein catabolism (thin limbs)
4. Atrophy of the gonads (sexual hypo function); amenorrhea in females and importance in males.
5. Systolic hypertension due to Na and water retention.
6. Hirsutism –abnormally excessive hairs on the face and body of females.
7. Acne, muscular weakness.
8. Excessive bleeding and poor wound healing.
9. Loss of minerals from bones- osteoporosis.
10. Blood: (a). lymphocytes decreases, RBC increase, neutrophils increase, platelets increase and eosinophils decrease
    (b). Polycythaemia and cyanosis of face and hand.

D. ANDROGENITAL SYNDROME

This is due to excessive secretion of androgens. This leads to virilism in females.

Features of vilrilism

- Hirsutism
- Voice deepened
- Skeletal muscles are bulky and clitoris enlarged
- Atrophy of external genitals except the clitoris.
- Atrophy of breast.
- Amenorrhoea.

(In young males, androgenital syndrome leads to precocious development of secondary sexual characteristics). Other features include temporal recession of hair lines, akin to male pattern of baldness.

ALDOSTERONE

Mechanism of aldosterone action

The mechanism of aldosterone action involves the penetration of the hormone to target cells and binding with an aporeceptor to form a steroid complex in the cytoplasm. The steroid- complex is translocated into nucleus to interact with chromatin to initiate the synthesis of the so- called “aldosterone-induced-proteins” (AIPS).

Diagram

The following **hypotheses** have been proposed for the functions of AIPS:

i. The **“sodium pump”** hypothesis that contends that the AIPS directly stimulate the activity of the pump on the serosal side of the cell.
ii. The **“metabolic hypothesis”** which suggests that AIPS regulate the supply of ATP which is necessary for the movement of Na^+.
iii. The **“permease hypothesis”** which proposes that AIPS enhance the permeability of the luminal mucosal membrane to Na^+.

The Na^+ pump hypothesis has not been validated because aldosterone has little or no effect on Na transport across the toad bladder lacking precursors of acetyl CoA, but addition of these substrates enhances Na transport. In addition aldosterone does not affect the key enzyme of the Na pump (Na/K ATPase) in isolated toad bladder. However, the antidiuretic activity of aldosterone is associated with enhanced generation of ATP. Aldosterone also

increases the activities of mitochondrial enzymes such as malate dehydrogenase and it would appear that these observations support the metabolic hypothesis.

ADRENAL MEDULLA –

This is a sympathetic ganglia modified into a gland.

SECRETIONS: Adrenaline (80%) and Noradrenaline (20%)

Both Adrenaline and Noradrenalin are collectively referred to as catecholamine.

ACTIONS

1. On Heart – Increase heart rate; Increase cardiac output; Increase BP.
   N.B: Catecholamines act mainly on the β – receptors.
2. On Blood Vessels – Vasoconstriction of skin and gut blood vessels, vasodilation of hepatic, coronary and skeletal muscle blood vessels.
3. On Respiration – Small doses of catecholamine tends to increase respiration; large doses tend to depress respiration.
4. On Metabolism – Increase BMR (plus 20%); stimulate glycogenolysis in liver and skeletal muscles; stimulate release of ACTH which tends to increase secretion of cortisol leading to gluconeogenesis.
5. on smooth muscles –

- GIT smooth muscle; Decrease intestinal motility; causes contraction of sphincters.
- Respiratory smooth muscles; bronchiole dilation and increase tidal volume.
- Urinary bladder; relaxation of walls and contraction of sphincter (internal and external).
- Spleen; contraction of smooth muscles of the spleen leading to increase in circulating blood volume as stored blood is squeezed out.
- Eye; pupil dilation giving rise to improved access to light rays.
- Kidney; Decreases GFR; decrease urine formation due to vasoconstriction of renal arteries.
- On skin; erection of hairs due to contraction of erector pillae muscle (causes heat retention).
- On CNS; causes anxiety and tremors through decrease threshold for the stimulation of reticular formation.

Over-secretion of Adrenaline

Note the consequences:

- Pheochromocytoma; mostly caused by tumour of chromaffin cells.
- In Stressful situation, impulses from CNS stimulate the adrenal medulla to secrete adrenaline. Stressful conditions include;
  a) Haemorrhage
  b) Exposure to cold
  c) Hypoglycaemia
  d) Muscular exercise
  e) Emotional excitement, fear, hypoxia, childbirth etc.

THE PANCREAS

The pancreas is both an exocrine and endocrine gland

(a) **Exocrine functions** – for digestive functions.
(b) **Endocrine functions** –

Histologically the pancreas has two major types of cells –

(a) Acini – secret pancreatic juice
(b) Islet of Langerhans – endocrine function

ISLET OF LANGERHANS

Has four cell types namely;

(i) α-cells (alpha cells); produce glucagon.
(ii) β-cells; produce insulin.
(iii) δ-cells; produce somatostatin.
(iv) F-cells; produce pancreatic polypeptides.

INSULIN

A polypeptide consisting of 51 amino acid residues.

Actions of insulin

1. Actions on Carbohydrates

Insulin lowers the glucose level in the blood by:

(a) Stimulating peripheral utilization of glucose (uptake of glucose into extra hepatic cells).

- Example of typical insulin sensitive cells are; muscle, adipose cells and the heart. Uptake of glucose into the above cells is dependent on insulin.
- Example of insulin insensitive tissues are; the brain, except the satiety center renal tubules, red blood cells, intestinal mucosa, liver and islet cells.

Mechanism of Action

Insulin promotes a carrier – mediated system (facilitated diffusion) by;

(i) Increasing the number of glucose transporters particularly a 509 – amino acids – protein.
(ii) Causing the insertion of more of these transporters in the cell membrane from a pool of molecules in the cytoplasm.

(b) Decreasing glucose entry into blood from glycogen stores in the liver and muscles by;

(i) Facilitating glycogen synthesis (glycogenesis) as glycogen synthase activities are increased.
(ii) Inhibiting the breakdown of glycogen (glycogenolysis) through the depression of the enzyme phosphorylase.
(iii) Inhibiting gluconeogenesis
(iv) Increasing glucose oxidation

Insulin possibly stimulates the activity of hexokinase (glucokinase) which activates the phosphorylation of glucose to glucose-6-Phosphate.

2. Actions of insulin on fat metabolism

(a) Stimulates the uptake of glucose into fat cells to provide energy for adipose tissue.
(b) Inhibits lipolysis by reduction intracellular cAMP.
(c) Activates lipogenesis.
(d) Activates cholesterologenesis.

3. Actions on protein metabolism

(a) It enhances transport of amino acids into cells.
– Overall effect is to stimulate protein synthesis.
– Has a "protein sparing effect" by decreasing protein catabolism.

(b) Insulin facilitates the entry of K^+ into cells to maintain electrochemical gradients across cell membranes.

CONTROL OF INSULIN SECRETION

The secretion of insulin is regulated by blood glucose level acting directly on β-cells to stimulate insulin release.
Normal blood glucose level;

(a) 80 – 120 mg/dL
(b) 75 – 115 mg/dL
(c) 70 – 110 mg/dL

UNDERRODUCTION OF INSULIN

N.B: The TMG (transport maximum for glucose) is 325 mg/min. When exceeded, leads to diabetes mellitus.

DIABETES MELLITUS (DM)

DM is of two types;

1. Juvenile on-set diabetes (insulin-dependent DM) – due to decrease in insulin level in blood – occurs usually before 15 years of age.
2. Maturity on-set diabetes
   - Usually in obese people over 40 years of age.
   - Due to reduction in both affinity and number of insulin receptors in the peripheral tissues.

Features of Diabetes Mellitus

(i) Hyperglycaemia (from reduced glucose entry into cells).
(ii) Glycosuria – presence of glucose in urine when renal threshold for glucose is exceeded i.e. 180 mg%
(iii) Polyuria
(iv) Polydipsia
(v) Polyphagia
(vi) Weight loss and asthenia (muscular weakness).
(vii) Fat metabolism (lipolysis) – Ketone bodies (e.g. aceto-acetic acid)- Acetone breath.
(viii) Severe vascular lesions due to high fat contents in the blood which produce atherosclerosis and subsequent heart disease. Peripheral vascular lesions and blindness.
(ix) Acidosis leading to kussmaul respiration (increase in respiratory rate).

DIAGNOSIS

1. Urinary sugar.
   - In this case, glucose appears in the urine which should not ordinarily happen since the "renal clearance" for glucose is normally zero.
2. Fasting blood sugar level.
3. Oral glucose tolerance test (OGTT).

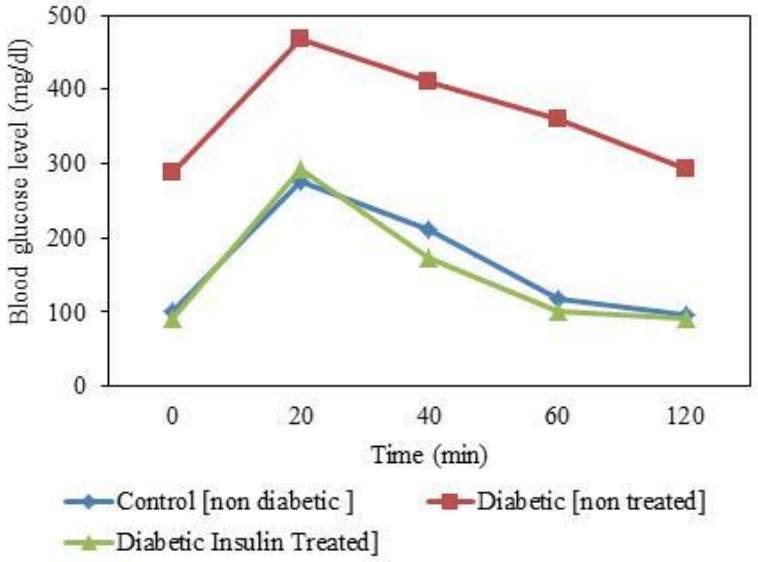


Figure 10.16: OGTT Curve

A glucose tolerance test in which changes in blood glucose are measured in response to oral administration of glucose, provides a definite indication of diabetes mellitus. In diabetes, the blood glucose rises higher in response to a glucose load and returns to base line more slowly than in normal subjects.

4. Acetone breath test.

TREATMENT: diet, exercise and hypoglycaemic drugs or insulin injection

GLUCAGON

Glucagon is produced by the α – cells, a small polypeptide (comprises 29 amino acid residues) MW – 3482

Actions of glucagon

A. Causes elevation of blood glucose.
   (i) Mainly by glycogenolysis (in the liver)
   (ii) Increase gluconeogenesis
B. Stimulates lipolysis in adipose tissue.

Glucagon stimulates the formation of cAMP which in turn activates the normally inactive enzyme phosphorylase in the liver cells.

The active phosphorylase in turn causes rapid glycogenolysis followed by the release of glucose into the blood. However, glucagon does not cause glycogenolysis in extra hepatic tissues.

THE PINEAL GLAND

- It is located at the end of a short stalk on the roof of the diencephalon.
- Pinealocytes with dense calcium particles
- Can be seen on x-ray (because of Ca++)
- Melatonin helps regulate the circadian rhythm
    - The biological clock of the diurnal (night/day) rhythm

- Complicated feedback via retina's visual input

ENDOCRINE CELLS IN VARIOUS ORGANS

The heart: atrial natriuretic peptide (ANP)
- Stimulates kidney to secrete more salt
- Thereby decreases excess blood volume, high BP and high blood sodium concentration

The kidneys
- Juxtaglomerular cells secrete renin
  - Renin indirectly signals adrenal cortex to secrete aldosterone
- Erythropoietin: signals bone marrow to increase RBC production

The skin
- Modified cholesterol with UV (ultraviolet) exposure becomes Vitamin D precursor
- Vitamin D necessary for calcium metabolism: signals intestine to absorb CA++

REPRODUCTION

PHYSIOLOGIC ANATOMY OF MALE AND FEMALE REPRODUCTIVE SYSTEM

MALE REPRODUCTIVE SYSTEM

Physiologic - Anatomy

The male reproductive system consists of the primary sex organs- the testes where the sperm are made, and the secondary or accessory sex organs which are the ducts and glands involved in storage or conveyance of spermatozoa. These include:

(1) Paired epididymis (storage)
(2) Vas deferens (conveyance),
(3) Seminal vesicle (secrets seminal fluid rich in fructose and is necessary for motility of sperm).
(4) Prostate (prostate fluid).
(5) Also associated are ejaculatory duct where the fluid, the semen are emptied.
(6) The urethra is also for the conveyance of sperm to the outside and it is supplied with mucus from the Cowper's or bulbourethral glands.
(7) The Cowper's gland or the bulbourethral gland is located near the origin of the urethra and it secrets mucus into the urethra.
(8) The penis which brings the sperm to the outside or into the vagina.

These various organs associated with the primary sex organ are called secondary accessory organs or secondary sex organs.

The secondary sex characteristics are the physical differences between the sexes which are unrelated to gamete production. These are differences in:

(1) The larynx i.e. enlargement in males but not in females, leading to high pitched voice in males.
(2) In mammary glands.
(3) In hair pattern

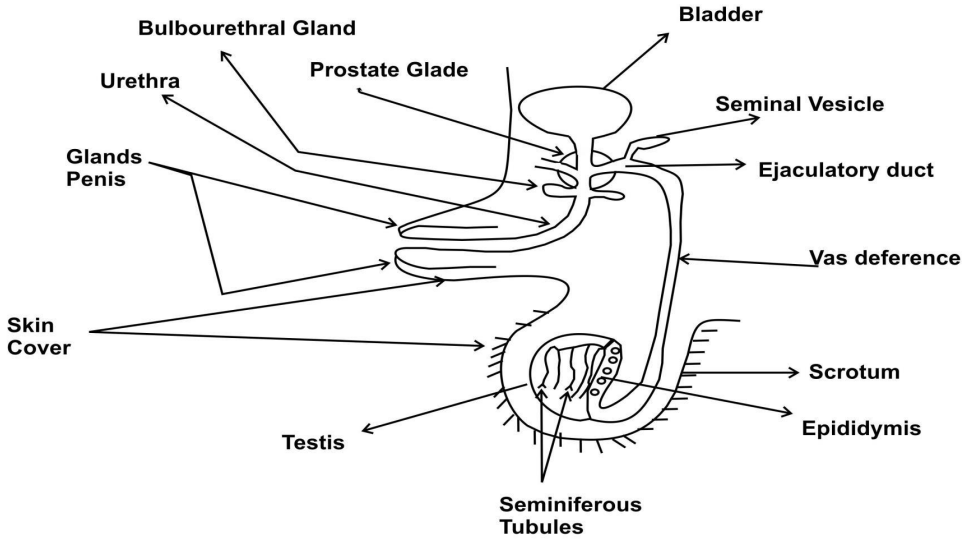


Figure 10.17: The male reproductive system

The morphology of the testis (Primary sex organ)

It is made up of two functional compartments:

1. Seminiferous tubules. 900 coiled, ≃ 0.5m long
2. Interstitial cells (tissues)

The Seminiferous tubules are made up of about 900 coiled tubes and about 0.5 meters long. It has exocrine function thus it is important in the production of gametes in the process of gametogenesis. Germ cells and sertoli cells are found in the seminiferous tubules. The sertoli cells are large cells found inside the seminiferous tubules, they are important for the secretion of estrogen. Germ cells mature into sperm cells. The interstitial tissue (interstitial cells of leydig) performs the endocrine function of the testis. It is also known that the leydig cells are important in the secretion of testosterone the major hormone of the testes.

FEMALE REPRODUCTIVE SYSTEM

The female system consists of:

1. Primarily the ovary and ova.
2. Secondarily:

a) The fallopian tube or oviduct. Penetration of ovum by sperms occurs here. It also produces fluid which increases fertilizing property of sperms. It is lined with cilia that help the ovum to move down to the fallopian tube.

b) The Uterus an extremely muscular organ consisting of strong muscle layer, myometrium and endometrium the inner mucosal layer. Cyclic monthly period occur here and sloughing of the endometrium leads to menstruation. The endometrium is the site of implantation during pregnancy. Thus it is responsible for the proper formation of the placenta.

c) The Vagina, a curved muscular canal. The upper end receives the lower border of cervix. It empties in a cleft between the **Labia Majora.** Its secretions are usually acidic because of the presence of bacteria that

forms its normal flora. These are mostly the ***Lactobacillus Acidophilus*** which keeps the vaginal pH at about 3.5– 4.9 by producing lactic acid that prevents the growth of bacteria.

d) Secretory Glands. These secretes mucus for lubrication.

These secondary sex organs are important for conveyance of eggs and sperm to fertilization site and for foetal development.

The Ovary

The ovary performs the following functions:

(1) Production, growth and maturation of ova or gamete (oogenesis).
(2) Production of hormones.
(3) Production of sex hormones.

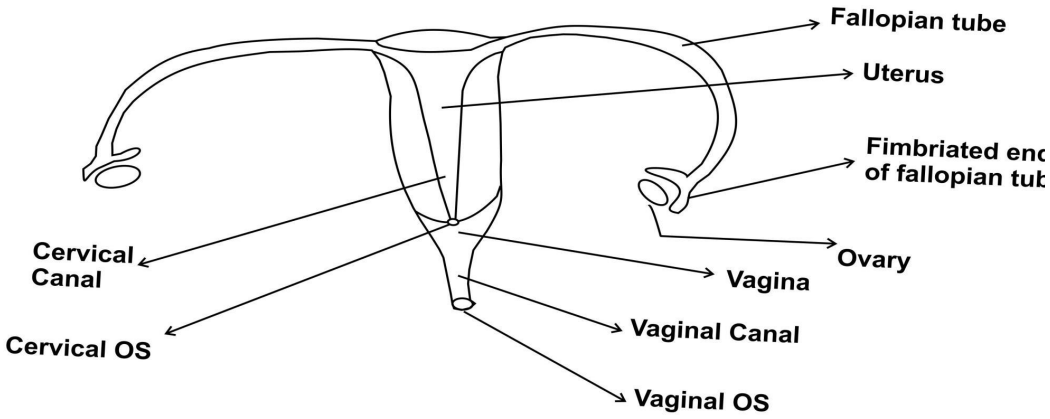


Figure 10.18: the female reproductive system

THE MALE AND FEMALE SEX HORMONES

These are the hormones produced by the sex organs of males and females. They are of two types: (1) Male sex hormones and (2) Female sex hormones.

Male Sex hormones

Also called androgens are produced essentially by the testes while small amounts are produced by the adrenal glands. There are two main circulating androgens, **Testosterone and Androstenedione**. The chief testicular androgen is testosterone. The two are inter-convertible and their syntheses is from cholesterol.

Physiological actions of testosterone

1. Morphogenetic action

These are its actions in-utero. They involve differentiation of male and female external genitalia and duct systems.

2. At puberty

This involves a continuous action as follows:

a. It is required for spermatogenesis at the meiotic division stage and especially the maturation of spermatids into sperms (spermiogenesis).
b. It maintains the integrity of sexual accessory organs and their growth. They are the target cells of testosterone.
c. It is involved in the enlargement of the prostrate.
d. It is involved in the enlargement of seminal vesicle.
e. It is involved in the enlargement of penis.
f. It is involved in the enlargement of scrotum and testis. (e and f about 8 times before the age of 20)
g. It is involved in the respond for sexual drive.
h. It is involved in the increase secretion of these glands.
i. It is involved in the increase protein syntheses of these glands.
j. It causes development of secondary sexual characteristics.
k. Important for distribution of body hair, it causes the growth of hair over the pubis and other areas (i.e. the male hair pattern: -upwards along the **Linea Alba** up to the **umbilicus)**. -the face, chest and the back (less often). -increase proliferation of hairs in other areas.
L. It causes baldness by decreasing the growth of hairs on the top of the head.
l. It has effect on voice by causing larynx enlargement and hypertrophy of mucosa leading to male base voice.
m. It increases skin thickness by increasing ruggedness, melanin secretion, and secretion of sebaceous gland especially on the face leading to development of **acne (pimple)**.
n. It increases muscle development as a result of protein anabolic action. This was used in old age as a **"youth hormone"** to improve muscle strength and vigor.
o. It increases bone matrix by increasing Ca^{2+} deposition leading to increase strength of hone. It is used to prevent osteoporosis in old age. It promotes epiphyseal closure of long bones. If given to a child, it accelerates bone growth, but due to early ossification at epiphysis, there will not be much growth.
   It has specific effects on the pelvis to:
   (1) Narrow the outlet and lengthen it.
   (2) Cause a funnel- like shape instead of the broad ovoid shape of the female pelvis.
   (3) Greatly increase the strength of the pelvis for load bearing.
p. It increases the number of RBC. If injected into a castrated adult, it leads to 15 – 20% increase in RBC.
q. The effect on Na^+ and H_20 balance causes slight increase in Na^+ retention in Distal Tubule (DT). However effect is not comparable to the mineralocorticoids.
r. On Basal Metabolic Rate (BMR), its injection will increase BMR by about 15% as a result of its protein anabolic action which increases the quantity of protein and more especially the enzyme activity of target cell.

FEMALE SEX HORMONES

These are produced in the ovaries**;** hence they are called ovarian hormones and small quantities from the adrenal glands. These include oestrogen, progesterone and a little androgen.

OESTROGEN

It has feminizing actions. There are different types:

1. Oestrone (E1- 17 α hydroxyl progesterone) is the most potent
2. Oestradiol (E2)
3. Oestriol (E3) is the least Potent

Oestrone and oestradiol are inter convertible, they can also be converted to oestriol in the liver and is regarded as degradative product of the two above. Oestriol is excreted in urine and its measurement is an index of foetal viability. High Levels in urine during pregnancy is an indication of good foetal condition and vice versa.
We also have synthetic oestrogens:

1. Ethinyloestradiol. This can be taken orally to bring about oestrogen activity and may be therapeutically very useful.
2. Diethylstilbestrol. This can also be taken orally and has oestrogenic activity. However it is a non-steroidal compound and maybe therapeutically useful. It has wide use in animal industry to bring about female characteristics in male animal. Its use has been discouraged because of possible carcinogenic action.

Physiological Effects of Oestrogen
The primary function of oestrogen is to cause cellular proliferation and growth of the tissues of the sex organs and other tissues related to reproduction.
When produced in the ovaries they have their actions in the sex accessory organs of the female.

(1)Vagina

- Increase thickness and growth of epithelium.
- Changes the epithelium from simple cuboidal to stratified cuboidal which is more resistant to trauma and infection. This explains why some infection are treated which oestrogen in children e.g. gonorrhea vaginitis in children is curable by E2.

(2)Uterus

(1) Increase the thickness and growth of endometrium.
(2) Increase the amount of uterine muscle.
(3) Increase growth of endometrial glands.
(4) Increase vascularization of endometrium.
(5) Increase the tonicity of myometrium.
(6) Increase protein synthesis.

(3)Fallopian Tubes

(1) Increase glandular proliferation.
(2) Increase number of ciliated epithelium which beats towards the uterus causing the ovum to move towards the uterus.

(4) Breast

(1) Responsible for breast development at puberty. This is the basis of applications of oestrogen compound into the breast for enlargement. However it is carcinogenic.
(2) Responsible for areola pigmentation.
(3) Causes fat deposition.
(4) Extensive development of duct system.
(5) Has little effect on milk producing organs.

(5) Electrolyte balance
Oestrogen has slight Na^+ and H_2O retention ability, but not as powerful as the mineralocorticoids. It is very prominent during pregnancy.

Other Effects of Oestrogen
(a) Fat Distribution

Promotes deposition of subcutaneous fat on the buttocks and thighs, leading to hip broadening which is a characteristic female figure.

(b) Skeleton

(1) It increases osteoblastic activity leading to increase Ca^{2+} and H^{+} retention resulting to increase quantity of bone matrix formed.

(2) However at puberty the female growth is very rapid for several years due to E_2.

(3) It however causes early closure of epiphysis. This effect is stronger in females than males leading to general taller males.

(4) Has effect on the pelvis leading to broadening of the pelvis. It changes its outlet from the narrow funnel- like nature into a broad ovoid outlet. This is important for the birth of a baby.

Note: E_2 is also implicated in the development of bone osteoporosis in old age.

(c) Skin

(1) It gives the smooth soft texture of the skin.

(2) However, skin is thicker and more vascular leading to increase warmth of skin and greater bleeding of cut surfaces in females than in males.

(3) It also increases axillary sweat glands. Increased secretion of sebum counters the effect of testosterone, preventing the formation of comedones ("black heads").

Note: Development of acne is by the effects of adrenal androgens in females.

(d) Tissue Growth: It increases mitotic activity. This is correlated to carcinogenic effect.

(e) Protein deposition: It causes a slight increase in total body protein leading to positive nitrogen balance.

(f) Hair distribution: It has a slight contribution. However, this is done mostly by the androgens of female adrenal glands.

(g) Promotes libido and sexual behavior.

(h) Plasma: Promotes salt and water retention, as well as weight gain (anabolic).

(i) Has a cholesterol-lowering action.

(j) Vasodilation property via increase in local production of nitrous oxide (NO).

(k) On Other hormones – Decreases FSH secretion

- Decreases LH secretion (negative feed-back) in some conditions and increase FSH secretion (negative feed-back) in other conditions.
- Increases angiotensinogen and thyroid-binding globulin secretions.

(l) Oestrogen has been associated with:

- Decrease the incidence of heart diseases.
- Decrease the incidence of uterine cancer, breast cancer and osteoporosis.
- Slow the brain cells degeneration associated with Alzheimer's disease.

PROGESTERONE

This is a primary progestagin from ovaries, testes, adrenal cortex and placenta. It is one of the female sex hormones but an important precursor in steroid synthesis. The primary source is corpus luteum but the level in circulation is contributed by all the above organs including the placenta during pregnancy.

Other progestagins includes: (1) 17-α-hydroxy progesterone and (2) 20-α-hydroxy progesterone.

Physiological Effects of Oestrogen and Progesterone

The primary function of progesterone is to promote secretory changes in the uterine endometrium during the latter half of the monthly sexual cycle, thus preparing the uterus for implantation of fertilized ovum. Most times, progesterone does not act alone but sometimes it does act alone.

(1) Vagina: It inhibits oestrogen action thereby producing the thinning of the vaginal epithelium.

(2) Uterus

(1) Increase vascularity of the endometrium.
(2) Increase growth of coiled arteries towards endometrial surface.
(3) Increase growth and secretion of endometrial glands.
(4) It causes decreased frequency of uterine contractions thereby quitens the uterus and prevents expulsion of implanted ovum.

(3) Fallopian tubes:

It increases secretory activity which is important for maintaining the nutrition of the ovum as it divides when passing along the tube.

(4)Breast

(1) Extensive development of milk production organs i.e. lobules and alveoli.
(2) Although it is important in 1 above. It does not cause the alveoli to actually secrete milk. This is done by Prolactin and hence it is its primary action.

(5)Electrolyte Balance

Under normal circumstance, it inhibits aldosterone action by increasing Na^+ and H_2O excretion. However in large quantity it can cause their retention like oestrogen.

RELAXIN

A polypeptide hormone synthesized in the corpus luteum, uterus, placenta and breasts. Also produced in male prostate glands. Its functions are:

(1) It relaxes the pubic symphysis and other pelvic joints during pregnancy.
(2) Promotes rupture of fetal membrane.
(3) Also softens and dilates the cervix, enhancing delivery.
(4) It inhibits uterine contraction.
(5) Helps maintain sperm motility and sperm penetration of the ovum.

PROLACTIN

- Secreted by the anterior pituitary gland.
- Made up of a single chain of 198 amino acids.
- Functions in promoting development of the female breasts and secretion of milk.

Other Ovarian Hormones

The ovary also produces many non-steroidal hormones such as:

- **Inhibin** and **activin** which regulate FSH secretion and ovarian functions.
- **Prostaglandins** - PGF2α induces CL regression,
  - PGF2α and PGE2 required for ovulation.
- **Insulin-like growth factor -** stimulates granulosa cell proliferation; inhibits apoptosis; induces steroidogenesis; induces maturation

SUMMARY OF FEMALE SEX HORMONE EFFECTS

HORMONE	EFFECTS
FSH	• stimulates the growth and development of the follicle • stimulates secretion of oestrogen • enhances effect of LH in stimulating ovulation
LH	• stimulates the final development of the follicle • stimulates ovulation • stimulates the development of the corpus luteum • stimulates production of progesterone
Oestrogen	• stimulates repair of uterine lining • at high conc. inhibits FSH, however during 'pituitary hormone surge', it stimulates further FSH production • as conc. peaks stimulates release of LH
Progesterone	• maintains uterine lining • inhibits release of FSH • inhibits release of LH • fall in conc. results in menstruation • Fall in conc. removes inhibition of FSH and a new cycle begins.

CYCLICITY OF HORMONE SECRETION IN FEMALES

THE FEMALE REPRODUCTIVE CYCLE

The female sex hormones – oestrogen, progesterone, follicle stimulating hormone (FSH), leutinising hormone (LH) – are secreted in a cyclical manner. Each hormonal surge gives rise to a significant event in the different phases of the cycle.

The female reproductive cycle is also termed the menstrual cycle. It is the cycle of events starting from one menstruation to the beginning of another menstruation. In the human females, menstruation occurs at an average of 28-30 days. Cyclic menstruation is an indicator of a normal reproductive phase and extends between menarche and menopause.

The first menstruation occurring at puberty is termed menarche.

The events of the menstrual cycle are categorized into three (3) major

1. The ovarian changes, specifically follicular growth and maturation.
2. The uterine changes – occurring especially within the endometrium.
3. The hormonal changes - Changes in the gonadotropins and the ovarian hormones.

The changes in the ovary and the uterus are induced by changes in the levels of the gonadotropins from the anterior pituitary and ovarian hormones.

The ovarian changes

The ovarian changes occurring in the menstrual cycle are characterized by 3 phases.

a. The follicular phase
b. The ovulatory phase or ovulation
c. The luteal phase

The female reproductive cycle begins with the **menstrual phase**, when menstrual flow occurs and lasts between 3-5 days. The menstrual phase is followed by the **follicular phase**, during which the primary follicles in the ovary grow, through the process of **oogenesis**. In the end, only one ovum ultimately becomes a fully mature **Graafian follicle.**

Rupture of the Graafian follicle and subsequent release of the ovum into the abdominal cavity marks the **phase of ovulation.** It usually occurs at the middle of the cycle, around the 14^{th} day. This phase is followed by the **luteal phase** during which the remaining parts of the Graafian follicle transform into a corpus luteum, in preparation for pregnancy. If fertilisation does not occur, the menstrual phase is recommenced.

Oogenesis: This is the process of formation of a mature female gamete. Oogenesis is initiated during embryonic development, where millions of gametes (**oogonia**) are formed within each fetal ovary. No more oogonia are formed and added after birth.

The oogonia began cell division into prophase-I of the meiotic division and get temporarily arrested at that stage, called **primary oocytes.**

Each \primary oocyte then gets surrounded by a layer of granulosa cells and become **primary follicles.** A large number of these follicles degenerate during this phase between birth and puberty. Only 60,000-80,000 primary follicles are left in each ovary at puberty.

Further proliferation in the layers of granulosa cells and the presence of spindle cells which surround the granulosa cells (theca cells), give rise to the **secondary follicles**. The theca layer is organized into an inner theca interna and an outer theca externa. Transformation into **tertiary or vesicular follicles** is brought about by the appearance of a fluid-filled space called the antrum, with a further increase in size.

At this stage that the primary oocyte within the tertiary follicle grows in size, it completes its first meiotic division. It is an unequal division resulting in the formation of a large haploid **secondary oocyte** and a tiny first polar body. The secondary oocyte retains the bulk of the nutrient-rich cytoplasm of the primary oocyte. At this point, only one follicle grows rapidly to maturity, **Graafian follicle**, while the 5-11 follicles undergo atresia. The Graafian follicle now ruptures to release the secondary oocyte (ovum) from the ovary by the process called ovulation.

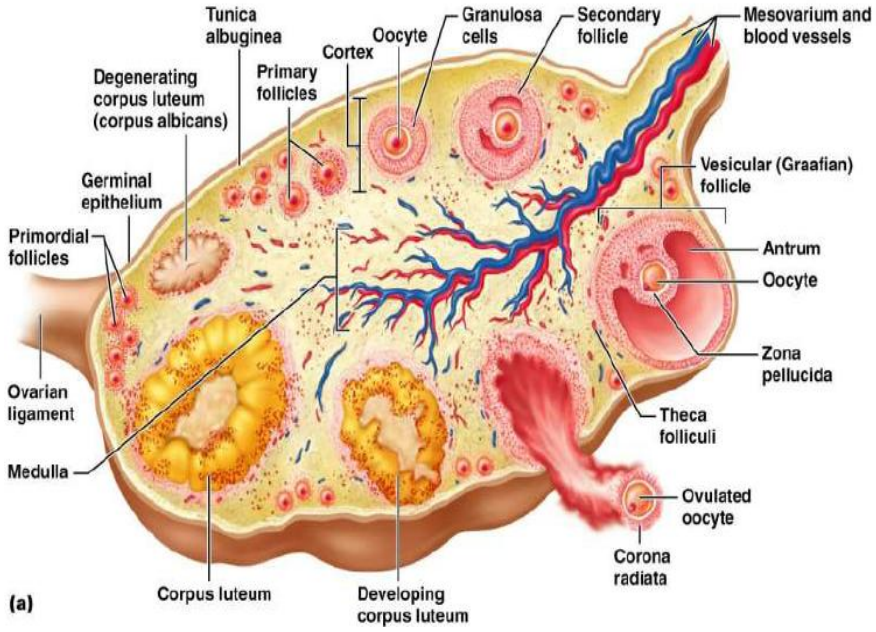


Figure 10.19: Oogenesis and ovulation

The uterine changes

The uterine changes are likewise categorized into 3 phases

a. The menstrual phase or menstruation
b. The proliferative phase
c. The secretory phase

The menstrual flow, lasting about 5 days, results due to the sloughing off of the endometrial lining of the uterus and its blood vessels, forming a bloody discharge through the vagina, termed **menses**. After the menstrual phase, the uterine endometrium undergoes a phase of proliferation (**the proliferative phase**). Under the influence of oestrogen, the epithelial cells of the endometrium (stratum basalis) regenerate to its original premenstrual state. There is also the thickening of the stratum functionalis, increasing the uterine vasculature. This phase is simultaneous with the follicular phase of the ovary. This phase usually occurs between days 6 to 14.

The secretory phase is initiated by the LH surge and subsequent progesterone secretion from the corpus luteum, where there is rapid growth and thickness of the endometrial vasculature, characterized by tortuosity of the uterine arteries. It occurs from days 15 to 28. This phenomenon is done in preparation of pregnancy. Menstruation only recommences if the released ovum is not fertilized. Lack of menstruation may be indicative of pregnancy. However, it may also be caused due to some other underlying causes such as stress, malnutrition, anorexia nervosa, anxiety, etc.

Hormonal changes

The changes in the ovary and the uterus during the menstrual cycle are induced by changes in the levels of anterior pituitary and ovarian hormones.

These female sex hormones, FSH, LH, oestrogen and progesterone, are secreted in fairly constant amounts throughout the female monthly sexual cycle, but at different rates during different parts of the cycle.

The secretion of gonadotropins (LH and FSH) increases gradually during the follicular phase, and stimulates follicular development as well as secretion of **estrogens** by the growing follicles.

Both LH and FSH attain a peak level in the middle of the cycle (about 14th day). Rapid secretion of LH leading to its maximum level during the mid-cycle called **LH surge** induces rupture of Graafian follicle and thereby the release of ovum (ovulation).

Stimulated by LH, the corpus luteum secretes large amounts of **progesterone** which continues the preparation of the endometrium for a possible pregnancy. LH inhibits the contraction of the uterus, as well as inhibits the development of a new follicle. This is essential for the maintenance of the endometrium necessary for implantation of the fertilized ovum and other events of pregnancy.

During pregnancy all events of the menstrual cycle stop and there is no menstruation. If fertilization does **not** occur, the rising levels of progesterone inhibits the release of GnRH which, in turn, inhibits further production of progesterone. As progesterone level drops, the corpus luteum begins to degenerate and the endometrium begins to break down (disintegrate). The inhibition of uterine contraction is lifted, followed by bleeding and menstrual cramps develops, marking a new cycle.

In humans, the cessation of menstrual cycles occurs around 50 years of age, termed **menopause.**

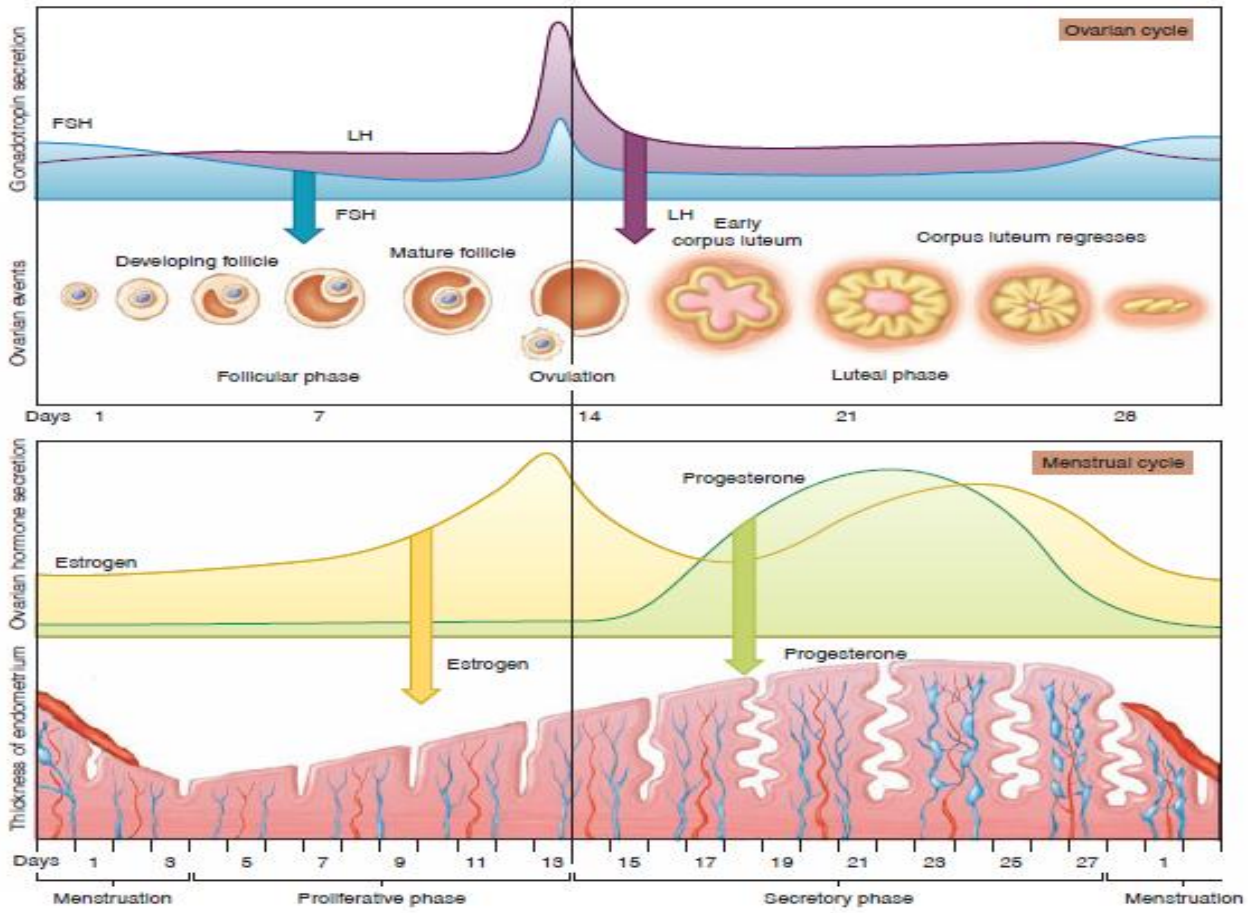


Figure 10.20: The hormonal, ovarian and uterine changes during the different stages of the menstrual cycle.

Summary of the Hormonal Control of the Menstrual Cycle

Follicular Phase: At the start of the oestrous cycle, the **pituitary gland** (in the brain) secretes **follicle-stimulating hormone (FSH)**

↓

FSH triggers development of one or more follicles in the ovary

↓

As the follicle grows in size, **oestrogen** is secreted

↓ ↓ ↓

Inhibits further production of FSH Stimulates the pituitary gland to secrete **LH** Stimulate **growth and repair of the uterine lining**

↓

Ovulatory Phase: As the follicular stage progresses, the developing follicle increases in size and becomes a **mature follicle**

↓

Oestrogen levels increase rapidly

↓

Triggers further release of LH **(high concentration of LH in the blood)**

↓

Ovulation

↓

Oocyte leaves the ovary and passes into the fallopian tube

↓

Female is fertile

Luteal Phase: ↓

The high concentrations of LH that brings about ovulation has an effect on the follicle cells that remain in the ovary

↓

Follicle becomes corpus luteum

↓

Corpus luteum secretes some **oestrogen** and a large amount of **progesterone**

↓ ↓

Progesterone stimulates mammary glands and uterus in **anticipation of pregnancy**

↓

If the Oocyte is not fertilized within 36 hours, it dies

↓

At day 28, a lack of progesterone brings about another **menstruation**

High concentrations of oestrogen and progesterone **inhibit production of FSH and LH**

↓

Without FSH and LH the cells of the corpus **luteum gets smaller** – and **less progesterone and oestrogen is secreted**

↓

With less oestrogen and progesterone, the **FSH is no longer inhibited, and the cycle can start again**

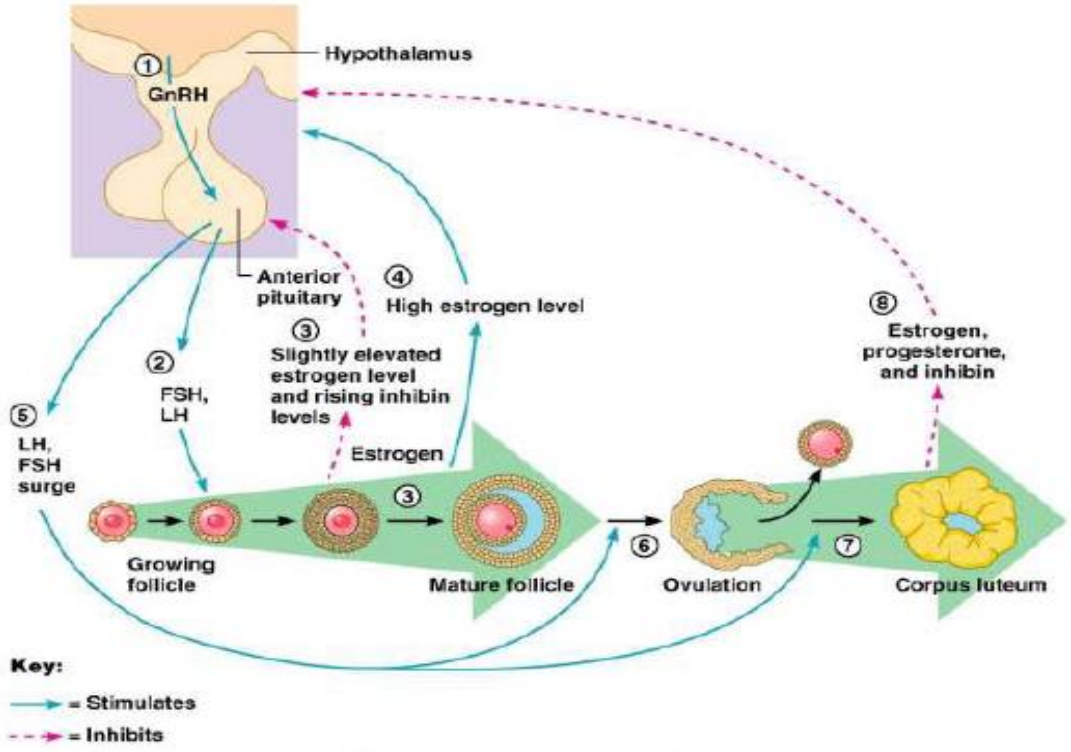


Figure 10.21: Hormonal regulation of the female reproductive cycle

PHYSIOLOGY OF PREGNACY

Fertilization and implantation

During copulation (coitus), semen is released by the penis into the vagina (insemination). The motile sperms swim rapidly, through the cervix, into the uterus and finally reach the junction of the isthmus and ampulla (ampullo-isthmic junction) of the fallopian tube.

The ovum released by the ovary is also transported to the ampullo-isthmic junction where fertilization takes place. Fertilization can only occur if the ovum and sperms are transported simultaneously to the ampullo-isthmic junction.

The process of fusion of a sperm with an ovum is called fertilization. During fertilization, a sperm comes in contact with the **zona pellucida** layer of the ovum and induces changes in the membrane that inhibit the entry of more sperm cells (**acrosomal reaction**). This ensures the fertilisation of an ovum by only one sperm. The secretions of the acrosome enables the entry of the sperm into the cytoplasm of the ovum through the zona pellucida and the plasma membrane. This induces the completion of the second meiotic division of the secondary oocyte. The second meiotic division is also unequal and results in the formation of a second polar body and a haploid ovum (ootid).

Soon the haploid nucleus of the sperm cell and that of the ovum fuse together to form a diploid zygote. The mitotic division, called cleavage, begins as the zygote moves through the isthmus of the oviduct towards the uterus and forms 2, 4, 8, and 16 daughter cells called **blastomeres**. The embryo with 8 to 16 blastomeres is called a **morula**. The morula continues to divide and transforms into **blastocyst** as it moves further into the

uterus. The blastomeres in the blastocyst are arranged into an outer layer called **trophoblast** and an inner group of cells attached to trophoblast called the **inner cell mass.** The trophoblast layer then gets attached to the endometrium, to give rise to the placenta, while the inner cell mass gets differentiated as the embryo.
After attachment, the uterine cells divide rapidly and covers the blastocyst. As a result, the blastocyst becomes embedded in the endometrium of the uterus. This is called implantation, wherein pregnancy is said to be established.

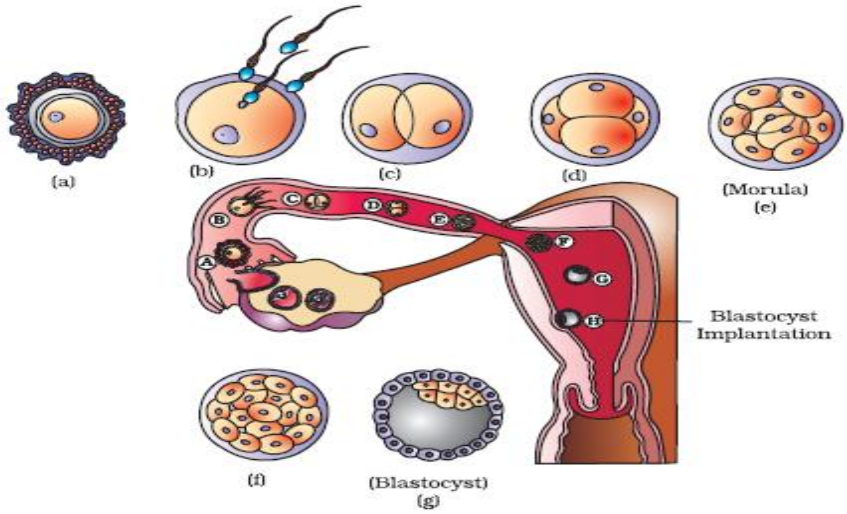


Figure 10.22: Ovum transport, fertilisation and embryonic stages.

Pregnancy and Embryonic Development
After implantation, finger-like projections appear on the trophoblast called **chorionic villi** which are surrounded by the uterine tissue and maternal blood. The chorionic villi and uterine tissue become interdigitated with each other and jointly form a structural and functional unit between the developing embryo (foetus) and the maternal endometrium, called **placenta**.
The placenta facilitates the supply of oxygen and nutrients to the embryo and also the removal of carbon dioxide and excretory/waste materials produced by the embryo. The placenta is connected to the embryo through an umbilical cord which helps in the transport of substances to and from the embryo.
The placenta also acts as an endocrine tissue and produces several hormones

- **Human Chorionic Gonadotropin (hCG),**
- **Human Placental Lactogen (hPL),**
- **Oestrogens,**
- **Progestogens,** etc.

In the later phase of pregnancy, a hormone called **relaxin** is also secreted by the ovary. In addition, during pregnancy the levels of other hormones like estrogens, progestogens, cortisol, prolactin, thyroxin, etc., are increased several folds in the maternal blood. Increased production of these hormones is essential for supporting the fetal growth, metabolic changes in the mother and maintenance of pregnancy.
Immediately after implantation, the inner cell mass (embryo) differentiates into an outer layer called ectoderm and an inner layer called endoderm. A mesoderm soon appears between the ectoderm and the endoderm. These three layers give rise to all tissues (organs) in adults. The inner cell mass also contains certain cells, called **stem cells,** which have the potency to give rise to all the tissues and organs.

SOME PLACENTAL HORMONES AND THEIR FUNCTIONS

Progesterone

- produced by placenta from cholesterol
- maintenance of uterine structure and function
- mammary growth and development
- feedback on gonadotropin
- substrate for cortisol production in fetal adrenal gland

Estrogens

- produced by the placenta from precursors derived from adrenal gland
- important for parturition and lactation

Human Chorionic Gonadotropin (hCG)

- acts at same receptor as LH
- stimulates progesterone production
- regulate development of fetal adrenal and gonad
- It is a marker for pregnancy, by its presence in blood and urine.

Human Placental Lactogen (hPL)

- maternal intermediary metabolism
- fetal growth
- mammary gland development
- steroidogenesis

- **Relaxin**, from the corpus luteum inhibits uterine contraction and relaxes the pelvic ligaments.
- Aldosterone from the adrenal cortex, promotes reabsorption of sodium from the renal tubules, leading to fluid retention.
- **Parathyroid hormone** maintains increased level of maternal calcium (due to high fetal calcium demand).

MATERNAL CHANGES DURING PREGNANCY

- **Total body water (TBW)** increases from about 6.5L to 8.5L. Pregnancy is a condition of chronic volume overload; water retention exceeds sodium retention leading to decreased plasma osmolality (Na ↓ by 3-4mmol/L).

Cardiovascular changes

- Cardiac output (CO) increases by 30 -50% above normal (mean-33%). This may be due to placental circulation, increased metabolism leading to ECG changes, functional murmurs and heart sounds.
- Heart rate (HR) increases up to 90/min.
- Blood pressure (BP) drops, peripheral resistance decreases.
- With multiple pregnancies, CO increases more, BP drops further.

Haematological changes

- Plasma volume increases (50%)
- Erythropoiesis (RBC) increases (25%)
- Red blood cell mass increases by 250-450 cc at term. Increased production is possibly hormonally mediated (oestrogen).
- Decreased haemoglobin (Hb), hematocrit (PCV).
- Iron requirement increases significantly (Iron supplements needed).
- Maternal iron (Fe) requirement is about1000mg. A normal pregnant woman needs to absorb about 3.5 mg/day of iron.
- The goal of iron supplementation is to prevent maternal iron deficiency.
- Iron is actively transported to the fetus.

Respiratory changes

- Oxygen consumption increases 20% above normal.
- Progesterone increases sensitivity for CO_2 in the respiratory centre.
- With growing uterus, all the above changes lead to
  - Increase in frequency.
  - Minute ventilation increases (50%)
  - PCO2 decreases slightly.

Urinary system changes

- Glomerular filtration rate and renal plasma flow increase (up to 30 - 50 %).
- Increased reabsorption of ions and water due to placental steroids and aldosterone secretions.
- Slight increase of urine formation

Maternal weight changes

Changes in the weight of the mother during pregnancy is as illustrated in the figure below.

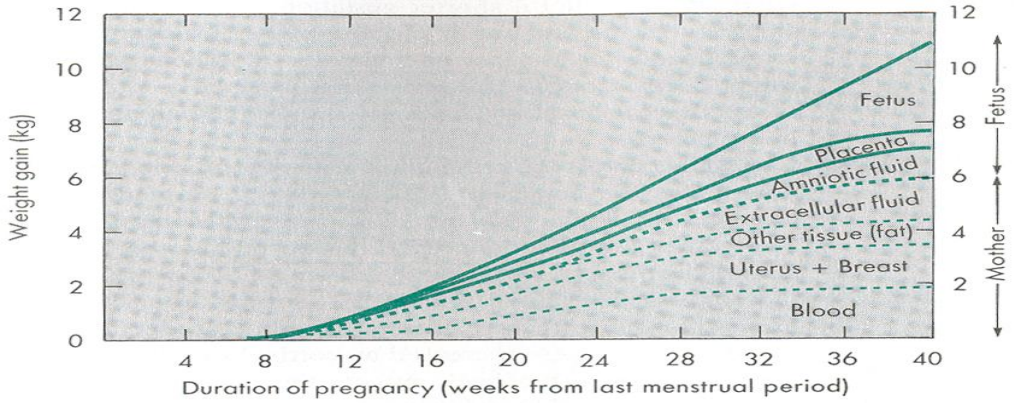


Figure 10.23: Weight changes in pregnancy

Hormonal changes in pregnancy

Increases in the secretion of almost all peptide hormones and all steroid hormones occur during the course of normal pregnancy:

Thyroid, parathyroid, corticosteroids and pituitary hormones are greatly increased. Others are

- Thyrotropin (thyroid-stimulating hormone [TSH])
- Placental-variant growth hormone
- hCS1 and hCS2, also known as hPL (hPL1 and hPL2)
- Placental proteins PP12 and PP14
- TRH
- Corticotropin-releasing hormone (CRH)
- Growth hormone-releasing hormone (GHRH)
- GnRH
- Substance P
- Neurotensin
- Somatostatin
- Neuropeptide Y
- ACTH-related peptide
- The inhibins

PHYSIOLOGY OF CONTRACEPTION

Contraception is a voluntary process of regulating birth. It is any method used in birth control to prevent the fertilisation of the ovum in the female. There are different methods employed in achieving contraception.

Physical methods

a. **Abstinence**: a voluntary decision by both male and female partners to abstain from having sexual intercourse. It is 100% safe.
b. **Withdrawal or coitus interruptus**: it is also called the "pull out" method. The penis is pulled out from the vagina just before ejaculation, so that the semen is not emptied into the vagina. It is about 75% safe, but has the disadvantage of the inability of many men not to achieve 100% interruption in coitus.
c. **The rhythm or Ogino-Knauss method:** The female takes cognizance of her period of ovulation (safe period) after observing the menstrual cycle for at least six months, and avoids engaging in sexual intercourse during such periods. It is known that ovulation occurs in most women fourteen days before the next menstruation. If a woman is very regular (menstruates every 28 days), ovulation will occur on day 14, which makes the method fairly simple, because abstinence from day 9 to day 19 could prevent the majority of pregnancies. Unfortunately, many completely normal women are nonetheless irregular, which makes using this method more difficult (with a failure rate of 25%).
d. **Billings' method:** This method is based on the observation of cervical mucus changes during the normal menstrual cycle. The cervix secretes copious amount of mucus during the proliferative phase of the menstrual cycle (oestrogenic effect), which, is thin and transparent. Under the effect of progesterone, in the secretory phase, the cervical mucus becomes viscous and thick, almost forming a plug to prevent the penetration of spermatozoa. The failure rate of this method ranges from 1 to 20%, due to the difficulty in determining the accuracy of the timing.
e. **Condoms:** These are usually made of latex materials to prevent the permeability of ejaculated sperm cells into the female tract. It can be worn by either the male or female before coitus begins. Condoms also prevent the transmission of sexually transmitted diseases. It has 90% success rate.
f. Diaphragms/foam: with 80% efficiency, it is worn by the female before coitus, to cover the entrance of the cervix, so as to prevent the penetration of semen into the uterus.
g. **Lactational amenorrhoea method**: it has been established that breastfeeding is a form of contraception. This is due to the inhibitory effect of prolactin on oestrogen during lactation, such that the normal menstrual cycle is not initiated. This method can be 98% effective if certain rules for breast-feeding are followed.
    i. The mother must not have recommenced her menstrual cycle while breastfeeding.

ii. The baby must be breast-fed exclusively (i.e. receive no formula), and the interval between feeds must not be longer than 4 hours during the day and 6 hours at night.
iii. In addition, the baby must be less than 6 months old.

Chemical methods

a. **Symptom-thermal method:** This method is based on three signs of fertility. The cervical mucus becomes clearer and more elastic as ovulation approaches. The position of the cervix, at the base of the vagina, the texture and size of the cervical opening, are all changed at the different phases of the reproductive cycle. However, this is difficult to evaluate in most cases. The cervix reaches its highest position at ovulation. Subsequently, the effect of progesterone on the thermoregulatory centre of the hypothalamus increases the female's body temperature by 0.5-1 ^{0}C following ovulation. This method is not highly effective due to inconsistencies encountered, especially in women with irregular cycles. If this method is to be really effective, unprotected sexual activity should not take place until the higher temperature or elastic mucus have been present for 3 days. It is then clear that ovulation has occurred once again. It is advisable to combine this method with the rhythm or other methods.
b. **Ovulation prediction kit:** These test kits are available in pharmacies and are used to detect a particular level of luteinizing hormone (LH) in the urine or saliva, and so predict the moment of ovulation. The main purpose of these tests is to enable conception. However, some other women employ this method for contraceptive purposes but studies have shown that its failure rate is 6% or more.
c. **Oral contraceptive pills:** These are birth control pills taken by the women to prevent pregnancy. It is the method of choice for many women, due to ease of its application. There are 3 types of pills, namely, combined oestrogen-progesterone (COP), progesterone only, and continuous/extended use pills. The most commonly prescribed pill is the combined hormonal pill with estrogen and progesterone. Progesterone prevents pregnancy, and the estrogen component controls menstrual bleeding. Daily moderate intake of these pills confers about 98% effectivity.

Intrauterine devices (IUDs)

IUDs, also called intrauterine contraceptive devices (IUCDs) or coils are devices inserted within the female reproductive tract to act as foreign bodies that attract the migration of leucocytes and activate antibodies in the reproductive canal, preventing sperm viability and subsequent contraception. The coils are usually T-shaped, inserted into the uterus and made to steadily release small quantities of progesterone, like the birth control pill. This further prevents sperm from fertilizing any ovum. It has 95% success rate.

Family planning operations/Surgical methods

a. Tubal ligation: The fallopian tubes of the female is either tied up or cut off, so as to prevent fertilization of the ovum within the tubes. It has 99% success rate, proffering almost perfect contraception.
b. Vasectomy: The vas deferens of the male is likewise surgically removed to prevent sperm transportation. It is also 99% effective.

ASSISTED FERTILITY TECHNIQUES

Infertility is the inability to attain conception after 12 months of regular (≥3 times/week) unprotected sexual intercourse. It is a fast growing gynaecological concern among couples, arising from several factors, ranging from hormonal imbalances, structural defects of the reproductive organs, sterility in males and females, endometriosis, to infections [pelvic inflammatory disease (PID)], etc.

The number of infertile couples has increased over the past few years, mainly because a lot of couples defer pregnancy for professional or personal reasons. The older the woman, the greater the risk that she may be exposed to an infection that can damage her fallopian tubes or that she may develop endometriosis. In addition, fertility diminishes significantly in women as they grow older because of the lower number of ova in the ovaries, unlike men who remain fertile until an advanced age.

The percentage of couples who consult fertility clinics has also increased over the past few years. There is more information out there, couples are better informed, and the success rates of the various fertility treatments have improved.

Assisted fertility techniques or assisted reproductive technology (ART) refers to the various treatment procedures employed to aid conception/fertility in people having problems with conceiving children. In these techniques, there are measures to manipulate the ova, sperm cells or embryos, in addition to modifications in the gonadal hormonal secretions in either the males of females or both.

While the techniques may have favourable success rates, they can be very expensive, rendering a majority of couples or individuals difficult to consider some of these procedures even when in dare need of it. Limited health insurance coverage may also be a constraint to opting for ART for some persons.

Types of ART

There are several types of ART procedures that involve different techniques and reproductive cells. A doctor can advise which ART will be most suitable depending on the circumstances. The most common type is in vitro fertilisation (IVF).

1. In vitro fertilisation (IVF)

IVF involves the extraction of the eggs from the female to be fertilised by a sperm cell outside the body, usually in a special laboratory. It can be done in combination with an **embryo transfer (ET)** – IVF-ET, where the resulting embryo is transferred back into the uterus. The success rate of IVF-ET varies according to age; the higher the age, the lower the success rate.

- 52% for people aged 35 or younger
- 38.1% for people aged 35–37
- 23.5% for people aged 38–40
- 7.6% for those over the age of 40

It may take more than one IVF session to achieve pregnancy, and some people may not conceive with IVF at all. Complications of IVF include:

- Multiple pregnancy, where two or more embryos are implanted at a time.
- Side effects from fertility drugs, such as ovarian hyper-stimulation syndrome.
- Ectopic pregnancy, where the embryo gets implanted outside of the uterus.

2. Intrafallopian transfer (IFT)

This method is similar to IVF but uses laparoscopic surgery to deliver the gametes directly into the fallopian tube. Some people may choose this method for religious reasons, or their insurance may only cover this type of ART.

Similar to other forms of ART, there is an increased chance of multiple pregnancy. Additionally, due to the laparoscopy, there is a risk of complications from the surgery, such as infection, organ puncture, or side effects from anesthesia. Intrafallopian transfers are typically more expensive than IVF. There different subtypes of IFT:

- **Gamete intrafallopian transfer (GIFT):** GIFT involves collecting eggs and sperm in a tube before placing the gametes directly into the fallopian tubes using laparoscopic surgery. As there is no IVF procedure, a person does not have to choose which embryo to transfer.
- **Zygote Intrafallopian Transfer (ZIFT):** ZIFT is a combination of IVF and GIFT. Specialists stimulate and collect the eggs using IVF methods and mix the eggs with sperm in the lab before returning fertilized eggs or zygotes to the fallopian tubes. A benefit of ZIFT is that it may help those with damaged fallopian tubes or severe infertility issues become pregnant.
- **Pronuclear stage tubal transfer (PROST):** PROST is similar to ZIFT but involves the transfer of a fertilized egg to the fallopian tube before cell division occurs.

3. Frozen embryo transfer (FET)

FET involves thawing of previously frozen embryos, via IVF and inserting them into the uterus. A good success rate has been attributed to this technique, however, an increased risk of preterm birth has been reported. Another possible risk of FET is that not all frozen embryos survive the thawing out process. It is also a very exorbitant procedure.

4. Intracytoplasmic sperm insemination (ICSI)

Intracytoplasmic sperm insemination or injection (ICSI) is a procedure that specialists can be perform alongside IVF to help fertilize an egg. An embryologist, or embryo specialist, uses a tiny needle to inject a single sperm directly into the centre of an egg to fertilise the egg.

ICSI fertilizes between 50–80% of eggs. The success rate of ICSI is similar to those of IVF, and it may be an effective method of ART for people with sperm-related infertility. ICSI is typically an add-on procedure to IVF, so it will be more costly than IVF alone.

The probable side effects of ICSI include the following:

- The procedure may damage some or all of the eggs.

- Failure of fertilisation (the egg might not grow into an embryo even after being injected with sperm).
- There is a high risk of congenital defects, even when pregnancy occurs.

5. Third-party ART

Third-party ART is when another individual donates eggs, sperm, or embryos to an individual or couple who desires pregnancy. It can also include surrogate and gestational carriers. These refers to when another person is either inseminated with sperm from the couple using ART or implanted with an embryo from those using ART. Benefits of third-party ART include the following:

- It may work when IVF has repeatedly failed.
- It may help to avoid passing on specific conditions.
- It can help a person who produces healthy eggs but has had difficulty carrying a pregnancy to term.
- It can help those who have difficulty producing an egg or sperm.

Preparation for an ART treatment includes behavioral modifications and healthy lifestyle practices that will enhance a good success rate. These involve dietary changes, such as taking supplements that a recommended by the healthcare professionals, reduction or cessation of alcohol, nicotin and caffeine intakes. It could also involve regular exercise.

Ethics

While there may be no simple answers on the ethical issues regarding ART, the following concerns are still considered:

- Does an individual or couple need ART?
- Who has ownership of stored gametes and embryos?
- Is it ethical for people to donate eggs to a clinic for free or discounted treatment?
- How does a person's religious beliefs align with different ART procedures?
- Should there be age limits on ART?
- Do children born through gamete donation have the right to know about their conception and their genetic parents?
- Are all requests for ART treated equally without regard to relationship status or sexual orientation?
- Is it ethical to use a deceased individual's frozen embryos or sperm?

SUMMARY

- The endocrine system is well developed in the human to augment the functions of the nervous system in controlling the activities of the body.
- Hormones are produced by endocrine glands, some of which perform other functions other than endocrine activities.
- Activities of the endocrine system depend on a variety of characteristics, which will underline the overall action of the hormone.

- Adrenaline reinforces the actions of sympathetic nervous system in preparing the body to meet emergencies. For this reason; its actions are often summed up as the “flight” or “fight” functions of the adrenal medulla.

- The ovarian and uterine changes during the different phases of the menstrual cycle are chiefly under the regulation of the female gonadal hormones in a peculiar pattern.
- Only one ovarian follicle (Graafian follicle) usually gets matured and extruded into the abdominal cavity.
- The menstrual cycle ceases when pregnancy occurs, but can also occur in other disease conditions.
- Many methods of contraception are made available to people who desire to control births, the outcome depends on the choice of the persons concerned.
- Many types of ART are available to treat infertility. The success rates of ART vary according to the type of ART people choose, and factors such as the individual’s age and health.
- A specialist will suggest ART based on an individual or couple’s preferences and type of infertility while also weighing the risks, benefits, and costs.

EXERCISE

1. Classify hormones according to their mechanisms of action.
2. List the endocrine glands and the various hormones they secret.
3. Describe the positive and negative feed-back mechanisms of hormone actions.
4. What are the neurohypophyseal hormones, list their functions.
5. List the hormones and functions of the endocrine pancreas.
6. Describe the mechanism of calcium homeostasis in the blood.
7. Describe why the heart and kidneys are termed endocrine organs.
8. Enumerate the functions of oestrogen and progesterone.
9. Compare the phases of the menstrual cycle according to uterine and ovarian events.
10. Describe the uterine events associated with menstruation.
11. List the effects of estrogen on the accessory sex organs and secondary sex characteristics.
12. List the effects of progesterone on the breasts, cervical mucus, vaginal epithelium, and body temperature.
13. Discuss the effects of hCG and hPL in pregnancy.
14. List the maternal physiologic changes in pregnancy.
15. Enumerate the contraceptive methods you know.
16. Describe the types of assisted reproductive techniques.

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Chapter 11

PHS 305 PATHOPHYSIOLOGY I

Victor D. Dapper, Walter C. Nwafia, Jude N. Egwurugwu,Maisaratu A. Tukur, Ahmed I. Salisu, Aliyu Mohammed, Olawadare Ogunlade, Eze K, Nwangwa, Adesoji A. Fasanmade

Overview

Pathophysiology is the study of abnormal functions in the body and the physiological processes that occur because of injury or disease. This chapter atte.pts to introduce pathophysiology to serve as a basis to understanding pathophysiological changes in disease conditions. It is a deviation from homeostasis. Homeostasis results an equilibrium between the net growth rate and the net rate of cell death. Cellular stressor places this physiological homeostasis under obvious threat. Depending on the type, intensity and duration of the cellular stressors, the cell's response can be manifold. In essence, if the stress stimulus does not go beyond a certain threshold, the cell can cope with it by mounting an appropriate protective cellular response, ensuring cellular survival. Conversely, the failure to activate or maintain a protective response, for example, if the stressful agent is too strong, results in activation of stress signaling cascades that eventually fuel into cell death pathways. This section also focuses on the pathophysiology of palpitation, cardiac arrhythmia, heart block, angina pectoris, myocardial infarction, murmurs, syncope and postural hypotension, heart failure, hypertension, Raynaud's disease, pulmonary embolism, pulmonary oedema, pulmonary hypertension and cor pulmonale. Stroke is a medical emergency which occurs when the blood supply to the brain or part of the brain is reduced or disrupted thereby starving the tissues of oxygen and nutrients. The cells of the brain may die within minutes, if blood supply is not restored. Therefore, early restoration of the blood supply may reduce the damage, complications and restore function.

It is a global or focal disturbance of cerebral function resulting only from a vascular cause with dysfunction lasting more than 24 hours or resulting in death. Included in this definition are: cerebral infarction, intracerebral haemorrhage, subarachnoid haemorrhage, and cerebral embolism.

Stroke is defined as a sudden global or focal neurological deficit resulting from spontaneous hemorrhage or infarction of the central nervous system with objective evidence of infarction irrespective of duration of clinical symptoms. The word stroke is synonymous with apoplexy (to be struck down by violence or paralysis), cerebrovascular accident, cerebrovascular disease, Brain Attack (to highlight the seriousness it deserves and the importance of time in its recovery or otherwise) (Time is Brain)

Pathophysiology is the study of how a disease, injury, or other condition affects a patient, including both the physical and functional changes that occur. This course will focus on the pathological deviation of the normal functioning of the cerebral blood flow.

In Nigeria, a country with over 200 million people, stroke was second to ischemic heart diseases as a cause of death and disability from a non-communicable disease according to the 2019 data.

Stroke unit coverage in Nigeria is still suboptimal, with only a few centers having stroke units. Five (8.6%) out of 58 hospitals had a stroke units (*Babawale et al., 2022).* When normal lung function is compromised by some

abnormalities, the pathophysiology of the problem can easily be deduced by the understanding of the alterations of normal lung homeostasis. A few of the lung function abnormalities are enumerated here

Objectives

At the end of this chapter the student is expected to:

1. Define and understand the terms pathophysiology and pathogenesis
2. Define risk factors and how they affect the onset of diseases
3. Know the various possible causes diseases
4. Understand the pathophysiological basis of patient care
5. Know the importance of clinical diagnosis and types of therapy
6. Define aetiology and disease prognosis
7. Give an overview of cellular stress and the potential stressors to a cell
8. Define the mechanisms of cellular death
9. Differentiate between necrosis, apoptosis and autophagic cell death
10. Explain cell injury
11. Describe 5 causes of cell injury
12. Distinguish between reversible and irreversible cell injury
13. Explain the general mechanism of cell injury
14. Describe Conditions that lead to cellular death
15. Mention Factors that affect the morphologic features of cellular death
16. State the Types of cellular death
17. State the Types of necrosis
18. Describe Mechanism of apoptosis
19. Define cellular senescence
20. Mention seven trigger factors of cellular senescence
21. State 4 beneficial effects of cellular senescence
22. State 4 deleterious effects of cellular senescence.

23. Explain the definition of cellular aging
24. Explain at least six theories of aging processes
25. Describe at least 5 hallmarks of aging
26. Explain the main structural and functional changes in aging
27. explain the cerebral circulation;
28. state the arteries that supply the brain tissues;
29. understand the peculiarities of the cerebral vessels that makes them prone to dysfunction;
30. different types of injury to the cerebral vascular system; and
31. understand the pathological changes that occur in the brain.
32. explain the cerebral circulation
33. explain the meaning of oedema and lymphoedema;
34. understand the causes of oedema and forces responsible for the net movement of fluid
35. State the roles of the lymphatic system
36. highlight the causes of lymphoedema
37. Describe the pathophysiology of
    a. Respiratory Distress Syndrome (RDS)
    b. Haemothorax, hydrothorax and pneumothorax
    c. Bronchial asthma
    d. Hypoxia
    e. Cyanosis

INTRODUCTION TO PATHOPHYSIOLOGY

Introduction:

Pathophysiology or physiopathology a branch of medicine where pathology converges with physiology is the study of the disordered physiological processes that cause, result from, or associated with disease or injury. Pathology is the study of the causes and effects of disease. It deals with the laboratory examination of body tissues for diagnostic and therapeutic purposes. Homeostasis describes process that ensure the maintenance of a near constancy in the chemical and physical conditions of the internal environment. It is the ability of the human

body to maintain stability while adjusting to varying external conditions. Diseases results from changes in homeostasis or when homeostasis is not maintained the result is disease.

Pathologists are medical practitioners who specialize in pathology. It includes:

1. Anatomic pathology
2. clinical pathology
3. medical microbiology
4. Haematology

Pathophysiology, Pathogenesis and Risk factors for diseases

Pathophysiology is the study of abnormal functions in the body and the physiological processes that occur because of injury or disease.

Pathogenesis is the manner of development of a disease. It refers to the sequence of events leading to structural and functional abnormalities in disease including the manifestation and resolution of the disease. In terms of chronicity, a disease may be either acute or chronic. Acute diseases are usually of sudden onset, severe but run a short course, chronic diseases are usually long-term and may reoccur.

Risk factors are basically factors that predispose to particular diseases. The enhance the chances of a particular person getting a particular disease. They include:

1. Age.

Persons at the extremes of life are usually predisposed to particular diseases. These extremes are the newborns and the elderly. Amongst other factors, newborns are predisposed because of an immature immune and other physiological system. The elderly because of aging related decrease in immune function and decline in homeostatic mechanisms

2. Sex.

Some diseases are gender related. For instance, males are more likely to develop gout, while females are likely to develop osteoporosis

3. Genetic factors.

Genetics sometimes plays an important role in the onset of diseases. Some common diseases with important genetic input include: diabetes mellitus, hypertension, asthma, migraines, etc.

4. Stress

Stress by acting to increases the secretion of corticosteroids may depress the immune system and cause the onset of disease.

5. Lifestyle

The lifestyle pattern adopted by an individual may predispose to diseases. Positive life styles for disease avoidance include a good diet, regular exercise, adequate weight control, avoidance of smoking and alcohol consumption, protective sexual practices.

6. Occupation

Occupation may predispose to diseases. For instance, exposure to loud noises and chemical pollutants, unsafe work environments may predispose to disease.

7. Preexisting illness

The presence of preexisting illnesses may reduce resistance to a secondary illness further complicating the health situation.

8. Environmental exposure

Exposure to environmental factors can cause diseases. These factors include allergens and occupational chemicals.

Structural and functional diseases

Disease processes can be either structural or functional.

Structural (organic) diseases usually involve a physical or biochemical cellular change. These cellular structural changes may be initiated by either exogenous or endogenous changes**. Exogeneous changes** are from external sources and include trauma, chemical injury, and microbial infections while ***Endogenous changes arises from*** internal sources and include vascular insufficiency, immunological or autoimmune reactions and diseases resulting from abnormal metabolism. A characteristic of structural disease is the presence of the lesion. *Lesion* describe many types of cellular changes that result in tissue abnormalities. (cuts, fractures, masses, etc. and can be detected by observation with the naked eye macroscopic lesion or with a microscope microscopic lesion.

Functional (physiological) disease usually begins without the presence of any lesion. They result from changes in the physiology and are described as pathophysiologic change. Typical examples include tension headaches and functional bowel syndrome.

Causes of structural diseases

The possible causes of structural diseases are legion but may be conveniently classified into the following:

1. Infectious Diseases are diseases that are caused by invasion and colonization of pathogenic microorganisms. The pathogenic infection may be caused by fungal agents, bacterial agents, viral agents or other types of disease-causing organisms.

2. Neoplasms are new growths and is the uncontrolled growth of abnormal cells. The resultant growth or tumor may be described as benign or malignant (cancerous).

3. Immunologic Diseases arise from abnormalities of the immune system. There are three *immunologic categories: an* overreaction also called immune hypersensitivity, an underreaction of the immune system leading to immune deficiency disease such as AIDS and an autoimmune disease causing the destruction of one's own tissues by antibodies produced by one's immune system.

4. Nutritional Diseases are diseases created by insufficient or excessive nutritional resources for the body. They include protein deficiency leading to difficulty in healing or formation of new body tissue and decreased antibody production, vitamin or mineral deficiencies leading to an interference in biochemical reactions of metabolism and obesity caused by excessive supply of nutrients to the body. Obesity is commonly found in affluent societies.

5. Metabolic Diseases results from disorders in the biochemical reactions in the body. They may be regarded as nutritional because of the connection with carbohydrate, fat, or protein metabolism

6. Genetic Diseases are usually inherited or hereditary diseases due to transmission of defective gene(s) or chromosome(s) from one or both parents. Common examples include diabetes mellitus, Down syndrome, hemophilia and cleft lip.

7. Congenital Diseases arise from a defect in fetal development that may create a functional (physiologic) or structural (physical) abnormality which presents itself at birth. Congenital diseases may be genetic, may be exposure to chemicals, drugs, or viruses during the pregnancy or may arise spontaneously.

8. Trauma is a physical force that mechanically disrupts the structure of the body therefore, disrupts body function. They result in an injury and includes bruises, abrasions, cuts, fractures, burns, etc.

9. Physical Agents can cause diseases. These physical agents include temperature extremes, electrical shock, radiation, and poisons.

10. Inflammatory Diseases are diseases that are usually secondary to primary disease such as infection or autoimmune disease.

Manifestations of Disease

The manifestation of a disease refers to how the disease presents clinically. This is important in the treatment of the disease. Clinical presentation may be via signs and symptoms. ***Signs*** are objective physical observations recorded when the patient is examined. A typical example of a sign include a raised body temperature, blood pressure, respiratory rate, abnormal heart sounds, mass, enlarged organs, edema etc. ***Symptoms* on** the other hand refer to the patient's awareness of abnormalities or discomfort. They are usually not measurable and are based on the patient's subjective perception. Typical examples include pain, nausea, weakness, fatigue, dizziness. A documented description of symptoms in the patient's record is referred to as the ***patient history.***

Patient care

This are measures undertaken to ensure that the patient either recovers from ill health or is able to live a meaningful and functional life despite the presence of disease. Patient care involves three major steps:

1. History taking: Obtaining a correct history to ascertain the patient's symptoms and to review any past or present related medical condition.

2. Physical examination: Performing a detailed physical examination on the patient is an important step in patient care.

3. Laboratory tests including radiologic and other clinical procedures are also important to detect chemical and physiologic abnormalities to aid in establishing the correct diagnosis.

Diagnosis

This is the assignment of a name to a patient's clinical condition. When clusters of findings with more than one disease are found, they are called ***syndromes.*** Diagnosis is needed to determine the treatment and potential outcome of a disease.

Treatment (therapy)

Treatment refers to all measures taken to ensure an improvement in the clinical circumstances of the patient or the stoppage of the progression of the disease. Treatment should be as precise as possible to attempt cure. Possible treatment interventions may include: exercise, nutritional modifications, physical therapy, medications, surgery, and patient education. Three common therapies are:

1. *Supportive therapy* is usually described as conservative and includes rest, optimal nutrition, fluids and possible antibiotics to prevent a secondary infection while the immune system is recovering.

2. *Palliative therapy* provides relief from signs and symptoms of disease and includes include: steroids, pain relievers, possible surgery (removal of tumor, etc.). Palliative treatment is useful for terminal illnesses and other serious chronic conditions for which there is no cure.

3. *Preventive therapy* is aimed at *preventing* disease. Examples include: mammograms, blood pressure screenings, routine dental care, colon cancer tests.

4. *Curative therapy* is therapy aimed at providing a cure to the diseases condition

Etiology

The ***etiology*** of disease refers to its cause. The aetiology is described as ***idiopathic*** if the cause has yet been discovered and is of unknown aetiology and iatrogenic if the disease is as a consequence of a prescribed treatment. A ***nosocomial*** disease is one that was acquired from a hospital environment.

Prognosis

The prognosis of a diseases is the predicted or expected outcome of the disease. Prognosis is often listed as: Good with full recovery; Guarded in which full recovery may or may not occur; and Poor in which the patient is not expected to recover.

Communicable disease are diseases that can be transmitted from one person to another. They may be described as **epidemic** when the disease that affects many people in a given region at the same time; **endemic** when the disease that appears to be indigenous to a particular area or region and is not of epidemic proportions; **pandemic** when the disease occurs in a widespread manner over a country or world over a particular time.

Localized disease are diseases confined to one area of body.

A ***Systemic or generalized disease usually*** spreads throughout the body or to many other systems.

Asymptomatic are usually *sub-clinical* ***diseases*** in which symptoms are not noticeable to the patient but the presence of the disease can be detected via routine physical examination or laboratory tests.

A self-limiting disease is a disease that does not require treatment to be cured and will resolve on its own.

Cellular Response to Persistent Stress

Introduction

Cellular stress response refers to the range of molecular changes that cells undergo in response to environmental stressors including temperature extremes, toxin exposure and mechanical damage. The molecular changes are to adapt and protect the cell against these unfavourable environmental stressors.

Cellular response to persistent stress occurs in a variety of ways ranging from activation of pathways that ultimately promote cell survival to eliciting programmed cell death therefore eliminating those potentially damaged cells. The cellular initial response to a stressful stimulus is geared towards helping the cell to defend against itself and hopefully recover from the insult. However, if the noxious stimulus is unresolved or rather becomes persistent then cells activate death signalling pathways.

There are many different types of environmental stressors including temperature extremes, toxin exposure and mechanical damage. Obviously, the response a cell mounts to deal with these conditions will depend on the type and degree of insult. The adaptive capacity of a cell ultimately determines the fate of the cell. Therefore, depending on the level and mode of stress, a number of defense mechanisms and survival strategies will be mounted; however, if these are unsuccessful, then the cell death programs are activated to eliminate the cells that are damaged from the whole organism. The forms of cellular death include: apoptosis, necrosis, pyroptosis, or autophagic cell death. The particular mechanism by which a cell dies often depends on its ability to cope with the conditions of exposure.

Stress-Induced Cell Death

Cell death has many forms and shapes. Cell death research encompasses not only the study of programmed forms of cell death (both apoptosis and autophagic cell death), necrosis and other modes of cellular demise.

Apoptosis: The term apoptosis describes a particular morphology of cell death common to the vast majority of physiological cell deaths. This morphology includes shrinkage and blebbing of cells, rounding and fragmentation of nuclei with condensation, and margination of chromatin, shrinkage, and phagocytosis of cell fragments without an accompanying inflammatory response. Various types of cellular stressors are known to trigger apoptosis amongst which include chemotherapeutic agents, irradiation, and oxidative stress.

Necrosis: refers to any deaths associated with the loss of control of ionic balance, uptake of water, swelling, and cellular lysis. Lysis causes release of many intracellular constituents, attracting immune cells and provoking an inflammatory response. Necrosis is an accidental mode of cell death. Morphologically, necrosis is characterized by a gain in cell volume, swelling of organelles and plasma membrane rupture, which results in the loss of intracellular contents.

Autophagic Cell Death: This is a multistep process characterized by the vesicular sequestration and degradation of long-lived cytoplasmic proteins and organelles, for example, mitochondria. The resulting double-membrane vesicle formed is called an autophagosome. Although it is still controversial whether autophagy is protective or toxic for the cells, accumulating evidence suggests that it has beneficial roles in the heart under both physiological and pathological conditions. Autophagy was shown to mediate turnover of intracellular proteins and organelles in the heart and protect against hemodynamic stress.

Adaptations Hyperplasia, Hypertrophy, Metaplasia, Atrophy, Intracellular Accumulations

Cellular adaptations

In the study cell and its pathophysiology, cellular adaptation means the changes made by a cell in response to adverse or varying environmental changes. It may be a physiologic (normal) or a pathologic (abnormal) response. The cell can morphologically adapt in four ways: atrophy, hypertrophy, hyperplasia and metaplasia.

(1) Atrophy

This involves a decrease in the size of the cells. If it is extensive in a particular organ, the organ will decrease in size. There are two types of atrophic adaptations:

(a)Physiologic atrophy e.g. the thymus which atrophies during the early stages of development of humans or childhood stage.

(b)Pathologic atrophy e.g. the type that results if the skeletal muscle is not regularly used. This is also called disuse atrophy.

E.g. of tissues and organs that are very susceptible to atrophy includes: skeletal muscles, cardiac muscles, secondary sex organs and the brain.

(2) Hypertrophy

This adaptation involves an increase in the size and volume of the cells. If this is significant in an organ, the whole organ will hypertrophy. The mechanism may involve an increase in intracellular protein as well as cytosol (intracellular fluid) and other cytoplasmic components. Hypertrophy may be caused by:

(a)Mechanical signals e.g. stretch or

(b)Trophic signals e.g. growth factors.

Hypertrophic adaptation can be of two types:

(a)Physiologic hypertrophy e.g. skeletal muscle that undergoes a sustained exercise involving weight bearing

(b)Pathologic hypertrophy e.g. cardiac muscle during hypertension.

(3) Hyperplasia

Hyperplasia is an increase in the number of cells. It is the result of increased cell mitosis or division (also referred to as cell proliferation). It goes via two mechanisms:

(a)Physiologic hyperplasia: This of two types

(i)Compensatory: that permits tissues and organ regeneration. It is common in epithelial cells of the epidermis and intestine, liver hepatocytes, bone marrow cells, and fibroblasts. It also occurs in bone, cartilages, and smooth muscle cells.

(ii)Hormonal: that occurs mainly in organs especially those dependent on oestrogen e.g. uterine cells that depends on oestrogen and undergoes hyperplasia and hypertrophy as a result of pregnancy.

(b)Pathologic hyperplasia: This results from an abnormal increase in cell division. E.g. endometriosis in the female endometrium.

(4) Metaplasia

This involves the replacement of a cell type by another cell type which often times may be less differentiated. It is a reversible process thought to be caused by stem cell reprogramming. E.g. the changes associated with the respiratory tract in response to inhalation of irritants e.g. smog or smoke which converts bronchial cells from mucous- secreting, ciliated, columnar epithelium to non- ciliated, squamous epithelium incapable of secreting mucus. These transformed cells may progress and become dysplastic or cancerous if the stimulus (e.g. cigarette smoking) is not removed.

The most common e.g. of metaplasia is Barrett's oesophagus. If the stressful situation that caused it persists, the metaplasia can progress to dysplasia and carcinoma eventually. In the case of Barrett's oesophagus, it will progress to adenocarcinoma.

Intracellular Accumulations

This occurs when a normal cell accumulate abnormal amount of substance either for temporary or permanently which may be harmful to the cell and may cause injury. The sites of these accumulations are either in the cytoplasm (phargolysosomes) and nucleus. The types intracellular accumulations includes:

(1)Water (hydropic change).

(2)Fatty change: fats may accumulate in the liver as fatty change.

(3)Cholesterol and esters: sphingolipidoses and other lipid accumulations.

(4)Proteins: abnormal protein accumulation is often irreversible.

(5)Glycogen: glycogen storage diseases.

Examples of intracellular accumulations are as follows:

1)Fatty change in the liver because of intracellular accumulation of triglycerides.

2)Appearance of reabsorption protein droplets in renal tubules because of increased leakage of protein from the glomerulus.

Intracellular accumulation of a variety of materials can occur in response to cellular injury e.g. during metamorphosis (fatty change) of the liver in which deranged lipoprotein transport from injury (most often alcoholism) leads to accumulation of lipid in the cytoplasm of hepatocytes.

The mechanisms of intracellular accumulation are as follows:

1)Due to over production

Accumulation occurs due to the overproduction of normal endogenous substances at normal or increased rate but their metabolism is not adequate at the rate e.g. fatty changes in the liver.

2)Due to inadequate metabolism

The accumulation of endogenous substance because they are not metabolized due to lack of enzymes that block the specific pathway.

Cell Injury, Cell Death and Cellular Senescence, Mechanisms of Cell Injury, Programmed Cell Death and Necrosis, Cellular Ageing and Cell Injury

Injury to tissues or organs usually starts at the cellular level. Cell injury disrupts cellular homeostasis. Cellular injury occurs when the cell cannot maintain homeostasis following injurious stimuli or stress; cell cannot adapt or the maximum adaptive response to physiologic or pathologic stimuli is exceeded. Causes of cell injury are numerous and diverse. They can be grouped into:

1. Oxygen deficiency

Hypoxia is the commonest cause cell injury. It can result from inadequate oxygenation of blood(cardiac or respiratory failure), reduction of vascular perfusion(ischaemia), reduced oxygen transport by erythrocytes(as in anaemia or CO toxicosis) or inhibition of respiratory enzymes of the cell(as in cyanide toxicosis).

2. Physical agents

Physical agents that can cause cell injury include mechanical trauma, extremes of temperature, electric shock and radiation. Trauma can damage cells by crushing or tearing of the cell(directly) or interfere with blood supply to the cell or tissues(indirectly). Low grade heat can damage blood vessels, extreme can denature enzymes and proteins. Cold can cause vasoconstriction, thereby limiting blood supply to the tissues and organs. Extreme cold can freeze cells with formation of ice crystals within the cytosol that can disrupt cell membranes. Radiation can also cause cellular damage. Radiation can ionize atoms or molecules which can cause direct cell damage, organelle damage or production of free radicals.

3. **Infectious microbes**

Unlike other injurious agents, infectious microbes can replicate themselves once they can access to the cells or tissues. They injure cells in diverse ways. Many bacteria produce toxins; viruses can subvert the host cell's DNA synthesis in the production of their gene products.

4. Nutritional imbalance

Nutritional imbalances such as excesses and deficiencies can dispose the cells to injury. Man can adapt to short-term dietary deficiencies in protein or calories through glycolysis, lipolysis, and catabolism of muscle protein. Long-term deficiencies can lead to atrophy of cells or tissues. Caloric excess can overload cells with glycogen and lipids leading to obesity with numerous metabolic disturbances. Dietary deficiencies or imbalances such as essential amino acids, fatty acids, vitamins or minerals can result in muscle wasting, metabolic disturbances, increased susceptibility to infection, etc.

5. Workload Imbalance

The cells in the body operate maximally when the workload is balanced. However, the cells can compensate for increased workload with an increase in size(hypertrophy, e.g., muscles), or in number(hyperplasia, e.g., adrenal cortex). Furthermore, cells that are no longer important or or that stopped receiving appropriate stimulus for physical exercise, innervation, hormones, or growth factors may shrink as seen in disuse atrophy or denervation atrophy in skeletal muscles or physiologic atrophy of the mammary gland after weaning.

6. **Chemicals, drugs, and Toxins**

Cellular homeostasis can be altered by chemicals, drugs and toxins.Drugs are beneficial or therapeutic at tolerable doses and harmful at higher doses. Chemicals may negatively affect cells by binding receptors, inhibiting or inducing enzymes, altering metabolic pathways, producing free radicals or increasing membrane permeability. It is worthy to note that the susceptibility of any cell to chemical damage depends on factors such as its mitotic rate and its ability to bind, take up, concentrate, or metabolize the chemical.

7. Immunologic Dysfunction

Immunologic abnormalities can can cause cell injury in many ways such as:

(a) Failure to respond effectively(immunodeficiency) to infectious microbes;

(b) Failure to respond to harmful foreign antigens or through an excessive response (allergic or hypersensitivity reaction to a foreign antigen;

(c) Inappropriate reaction to self-antigen (autoimmune disease) .

8. Aging

As one advances in age, accumulated damage to proteins, lipids and nuclei acids can lead to cell and tissue injury. Much of the cellular damage of aging is attributed to ROS, DNA mutations and cellular senescence.

Irrespective of the cause of cellular injury, the extent of the injury depends on the type, state(including level of cell differentiation and increased susceptibility to fully differentiated cells), and adaptive properties of the cell, as well as the type, severity, and duration of the injurious stimulus.

Again, irrespective of the cause of cellular injury, all of them activate one or more of four final common biochemical mechanisms leading to cell injury. These mechanisms are ATP depletion, permeability of cell membranes, disruption of biochemical pathways, and damage to DNA.

9. Genetic/Epigenetic factors

Genetic factors can alter the cell's nucleus and plasma membrane's structure, shape, receptors, or transport mechanisms. Genetic diseases can cause structural alterations of the red blood cell (e.g., sickle cell anaemia). Cancer can also arise because misregulation of gene expression linked to alterations of epigenetic patterning.

Types of cell injury

There are two types of cell injury: reversible and irreversible cell injury.

Reversible cell injury

In reversible injury, the injurious stimulus is mild and the damage is transient. Elimination of the offending stimuli and /or restoration of the critical needs to the cell, leads to homeostasis. The features of reversible cell injury include:

- Cellular swelling due to water influx(early signs of cell injury)
- Hydropic change or vacuolar degeneration: small, clear vacuoles within the cytoplasm. This follows distended endoplasmic reticulum
- Mitochondrial swelling and appearance of amorphous densities
- Increased cytosol myelin figures(phospholipids from damaged membranes
- Nuclear changes(granular and fibrillar elements disaggregate
- Fatty change from accumulation of lipid vacuoles
-

Irreversible cell injury

The degree of cell injury has reached 'point of no return'; cell homeostasis cannot be restored, leading to cell death. The injurious stimulus is severe and/or persistent. The main features include:

- Mitochondrial dysfunction cannot be reversed (loss of oxidative phosphorylation and adenosine triphosphate(ATP) production
- Significant impaired membrane function
- DNA damage

General Mechanisms of cell injury

The mechanisms responsible for cell injury are numerous and interrelated and depend on a delicate balance between intracellular and extracellular events. The four common biochemical mechanisms are ATP depletion,

permeability of cell membranes, disruption of biochemical pathways and DNA damage.In as much as certain injurious stimuli can solely cause ATP depletion, membrane damage, pathway disruption or DNA damage, there is usually an interplay among the basic mechanisms. Injurious agent, for examople that decreases oxygen supply and other nutrients to the cell or that damages mitochondria directly, can also stop oxidative phosphorylation, resulting in rapid ATP depletion, even in cells that can switch to anaerobic glycolysis. The resultant ATP depletion leads to additional cell injury as it causes failure of energy-dependent enzymes, especially the cell membrane adenosinephosphatase ion pumps that control cell volume and electrolyte balance.

The mitochondiria are the main site of ATP generation as well as one of the most vulnerable organelles of the cell. Therefore, mitochondria injury causes not only ATP depletion but also an increased permeability of mitochondrial membranes with resultant loss of calcium homeostasis and activation of enzymes such as phospholipase, proteases, and endonucleases. This cascade leads to further damage on the mitochondria and other cell membranes, structural and enzymatic proteins, and nuclei acids.

Cellular Death

Severe or persistent injury can overwhelm the cell's capacity to restore homeostasis, in which case potentially reversible acute cell swelling can become irreversible and progress to cell death. The morphologic features of cell death change with the passage of time and depend on the manner of death (oncotic necrosis versus apoptosis) and the type of cell or tissue. *Oncotic necrosis* is a process of cell swelling and thereby distinct from cell death by apoptosis, which is a process of cellular shrinkage and fragmentation. If an acutely swollen cell fails to correct the electrolyte imbalance and loss of volume control, then potentially reversible cell injury can become the initial stage of oncotic necrosis. Once thought always to be unregulated, oncotic necrosis, like apoptosis, can be a programmed process (necroptosis). Programmed cell death, whether by necroptosis or apoptosis, has many extrinsic and intrinsic (acting mainly through mitochondria) triggers. Programmed cell death is a complex and varied process that includes stages of initiation, propagation, and execution. Cells that die by oncotic necrosis tend to do so in groups, whereas apoptosis commonly affects individual cells. Furthermore, oncotic necrosis results in rupture of cell membranes and release of cytoplasmic contents into the extracellular matrix with ensuing inflammation. In contrast, the cell that dies by apoptosis shrinks and fragments, but the fragments remain membrane bound and therefore do not elicit an inflammatory response although they are marked for phagocytosis.

Cell death by necrosis

In cellular death by necrosis, there is uncontrolled cell death after irreversible cell injury. Cell membrane is disrupted, lysosomal enzymes enter and digest cell. Following digestion, cellular contents are released and they circulate into the extracellular space. The circulating contents elicit an inflammatory reaction, recruiting leucocytes to the necrotic site.

The Cytopasmic changes in cell death by necrosis include:

- Eosinophilic cytoplasm: due to denatured cytoplasmic proteins
- Vacuolated cytoplasm: enzymes digest organelles, leaving “moth-eaten”appearance

- Myelin figures: large whorled phospholipid precipitates (from the damaged membrane, which are phagocytosed or degraded to fatty acids

Types of necrosis

a. Coagulative necrosis

- The cell outlines and tissue architecture are maintained for several days
- Tissue injury denatures enzymes, thus, initial tissue proteolysis is blocked
- Ultimately, leukocyte enzymes breakdown the dead cells
- Common in hypoxic and ischaemic injury
- Infarct is localized in area of coagulative necrosis
- Also seen in myocardial and renal infarction.

b. Liquefactive necrosis

- Also called colliquative necrosis
- The tissues are digested and dissolved into a viscous liquid
- Common in bacterial and fungal infections, which stimulate leukocytes and the release of hydrolytic enzymes
- Pus formed is a creamy-yellow necrotic material
- It is a default necrotic mechanism used by hypoxic central nervous system cells
- Liquefactive and coagulative necrosis can lead to one another
- Damaged cardiac myocytes can manifest coagulative necrosis; when leukocytes set in and enzymes are released , liquefactive necrosis occurs.

c. Caseous necrosis

- Caseous necrosis is “cheese-like
- The fragmented cells and debris are surrounded by an inflammatory boarder: granuloma
- Common in tuberculosis and fungal infections
- Mycolic acid from the mycobacterial cell wall induces granuloma formation

d. Fat necrosis

- There are changes in the adipose tissue due to trauma or enzyme release
- Release of pancreatic lipases into pancreatic parenchyma and the peritoneum, leading to destruction of adipocytes
- Liberated fatty cells combine with calcium, producing chalky-white areas(fat saponification)
- Seen in acute pancreatitis, fat necrosis of the breast.

e. Fibrinoid necrosis

Microscopic changes common in fibrinoid necrosis are

i. deposition of immune complexes in vessel walls

ii. Fibrinoid: fibrin combined with immune complexes deposited in vessel walls

f. Gangrenous necrosis

- Not a type of necrosis but a clinical description used when a limb becomes necrotic due to ischaemia
- A form of coagulative necrosis of involving multiple layers of tissue(dry gangrene)
- With superimposed bacterial infection, liquefaction necrosis can occur due to emzymes from bacteria and leukocytes(wet gangrene)

Cell Death by Apoptosis

In programmed cell death(apoptosis), activated enzymes degrade DNA and proteins in cells that are destined to die. The main features include:

- Reduced cell size, eosinophilic cytoplasm
- Chromatin condensation (chromatin aggregates peripherally)
- Cytoplasmic blebs and apoptotic bodies seen
- Phagocytosis of apoptotic cells by macrophages

Apoptosis can occur in different conditions.

a. Physiologic conditions:

i. Fetal development

Cells die off after their purpose has been achieved

Removal of supernumerary cells during development

ii. Involution of tissues with hormone withdrawal

Endometrial shedding in menstrual cycle

Lactating breasts regression(weaning)

Control of cell proliferation , maintaining a constant number of cell populations(immature lymphocytes in bone marrow)

b. Pathologic conditions

- DNA damage: apoptosis prevents survival of cells with DNA mutation(a protective effect)
- Removal of improperly folded proteins
- Ductal obstruction (e.g., kidney, parotid gland: Atrophy occurs by apoptosis
- Infections (especially viral illness): cytotoxic T lymphocytes induce apoptosis to eliminate infected cells

Mechanisms of apoptosis

1. **Caspases:**

- Cystein aspartic acid proteases
- Exist inactive form, requiring enzymatic cleavage to be activated
- Active caspases is a marker for cells undergoing apoptosis
- Phases of apoptosis

Initiation: activation of caspases, leading to cascade of other caspases

Intrinsic pathway

Extrinsic pathway

Execution: terminal caspases, leads to cellular fragmentation

Intrinsic pathway(initiation)

2. **Mitochondrial pathway**

In viable cells, growth factors and survival signals reduce mitochondrial leakage of cytochrome c by producing anti-apoptotic proteins, principal members are BCL-2, BCL-XL and MCL-1

In damaged cells, loss of survival signals, DNA damage, protein misfolding:

Allow cytochrome c leakage from the mitochondria by producing **pro-apoptotic proteins,** main members are BAX and BAK:

Activate apoptosis initiators(BH3-only proteins): BAD, BIM, Puma, Noxa

Events/responses that follow include:

i. Increased permeability of the mitochondrial outer membrane- release of **cytochrome c** into cytoplasm

ii. In the cytoplasm, cytochrome c binds with apoptosis-activating factor-1(**APAF-1**), forming a structure, **apoptosome.**

iii. Apoptosome leads to self-cleavage and activation of caspase-9, the initiator caspase.

iv. Acitvated caspase-9, leads to cascade of caspases.

3. **Extrinsic pathway(initiation**):

Death receptor- initiated pathway

Plasma membrane death receptors initiate this pathway

Death receptors:

Are members of tumor necrosis factor(TNF) family with a cytoplasmic death domain(delivers the apoptotic signals)

Best known death receptors include:

Type 1-TNF receptor(TNFR1)

Fas(CD95

The Events/Responses that follow include:

FasL(Fas ligand on T cells and cytotoxic T lymphocytes) binds to Fas- this gives to the cells, signal for apoptosis.

3 or more Fas molecules combine to form the protein, Fas-associated death domain(FADD).

FADD binds to pro-caspase-8

Caspase-8(Caspase-10) is activated, stimulates executioner caspases.

4. Execution phase

Both intrinsic and extrinsic pathways converge in the execution phase

The Events/responses that follow include:

Starts with sequential activation of executioner caspases

Inhibitor of deoxyribonuclease (DNASE) is cleaved → active DNase → nuclear proteolysis and fragmentation

Cytoskeleton proteins breakdown

Cell fragments → cytoplasmic blebs form → apoptotic bodies

Apoptotic bodies are eaten by phagocytosis

The characteristic differences between necrosis and apoptosis is shown in Table 1

Table 11.1 : Characteristic differences between necrosis and apoptosis

Feature	**Necrosis**	**Apoptosis**
Cell size	Enlarged(swelling)	Reduced(shrinkage
Nucleus	Pyknosis, karyorrhexis, karyolysis	Fragmentation into nucleosome-size fragments
Plasma membrane	Disrupted	Intact but altered structure(orientation of lipids)
Cellular contents	Enzymatic digestion; leak out of the cell	Intact; released in apoptotic bodies
Adjacent inflammation	Frequent	No
Physiologic or pathologic role	Pathologic(result of irreversible cell injury)	Physiologic: elimination of unwanted cells Pathologic: cell injury from DNA and protein damage

Cellular Senescence

Cellular senescence has been defined as a permanent state of cell cycle arrest that occurs in proliferating cells in response to various intrinsic and extrinsic stimuli, as well as, development signals. It is therefore, triggered by stressful stimuli and development signals.

Cellular response to these stimuli depends on the cell type, intensity and nature of the stress. Cellular senescence may be in response to various intrinsic and extrinsic stimuli such as progressive telomere shortening, changes in telomere structure, mitogenic signals, oncogenic activation, radiation, oxidative and genotoxic stress, epigenetic changes, chromatin disorganization, mitochondrial dysfunction, inflammation, irradiation, chemotherapeutic agents and nutrient deprivation. These different types of stressful stimuli produce different types of senescence such as mitochondrial dysfunction associated senescence, epigenetically-induced senescence, etc,. Treatment with anti-cancer agents, chemotherapeutic drugs and ionising radiation can provoke "therapy-induced senescence" in tumor cells.These trigger factors can led to cell injury, senescence and sometimes, death.

The above mentioned various trigger factors give rise to different types cellular senescence such as telomere dependent replicative senescence, programmed senescence or non-telomeric stress-induced premature senescence including oncogene-induced senescence(OIS), unresolved DNA damage induced senescence, epigenetically induced senescence,and mitochondrial dysfunction associated senescence.

Senescence occurs in several tissues during different physiological and pathological processes such as tissue remodelling, injury, cancer, and aging. It has been associated with multiple cellular and molecular changes and distinct phenotypic alterations.Senescence is one of the causative processes of aging and has been implicated in age-related diseases. On the positive side, it can also play a beneficial role. In cancer, senescence works as a potent barrier to prevent tumorigenesis.

Hallmarks

1. Cell cycle arrest correlates with an augmented level of cell cycle inhibitors such as p16INK4a, p21CIP1, and p27.

2. Elevated expression of p19ARF, p53, and PAI-1; used as miscellaneous senescence biomarkers

3. Characterized by an altered cell size with a more smoothed shape compared with proliferating cells.

4. Associated with multiple cellular, molecular changes and distinct phenotypic alterations including a stable and generally irreversible proliferation arrest unresponsive to mitogenic stimuli.

5. Senescent cells remain viable with alterations in metabolic activity and are usually resistant to apoptosis.

6. Exhibit increased lysosomal activity, macromolecular damage, and a temporal cascade in the development of the complex senescene-associated secretory phenotype(SASP)

7. Can also show morphological and structural changes, including an enlarged, flattened, multinucleated morphology with enlarged vacuoles, altered composition of plasma membrane.

8. Upregulation of some microRNAs (miRNAs) and secretion of a large number of factors, including growth factors, cytokines, chemokines, and proteases, known as the senescence-associated secretory phenotype (SASP) or senescence-messaging secretome.

9. They remain metabolically active and able to produce and secrete a plethora of factors that can affect the tissue microenvironment in different modalities

Beneficial effects in different physiological and pathological processes:

Senescence cells play key physiological roles in

a. normal development

b. Maintaining tissue homeostasis

c. Tissue remodeling

d. Tissue repair

e. Wound healing

f. Secretion of insulin by pancreatic beta cells

g. Limits tumor progression by ensuring that potentially dysfunctional, damaged or transformed cells do not perpetuate their genomes to the next generation.

h. Assist in the development of genetic or pharmacological strategies that can extend life span and improve health span.

Deleterious effects

The deleterious effects of cellular senescence include:

1. Can hinder tissue repair and regeneration

2. contribute to tissue and organismal aging due to the accumulation of senescent cells and depletion of stem/progenitor cell compartments and secretion SASP.

3. Leads to many age-related diseases such as atherosclerosis, diabetes mellitus, lung disease and many others.

4. An example of evolutionary antagonistic pleiotropy, has both beneficial and detrimental effects.

Cellular Aging

Aging can be defined as a global, complex, synchronized biological process that occurs across all species at a rate that varies greatly. Aging is associated with increased risk of physical and cognitive decline, decline in the ability to respond to stress, increase in homeostatic imbalance, and affects numerous cells, tissues, organs, and systems in the body. It is a unitary, coordinated and continuous process that take place gradually over time. Its rate and degree of impact on a person depends on the interaction among intrinsic living processes(nature), such as aerobic metabolism; extrinsic factors(nuture) associated with environmental effects; and damage from age-

related diseases. Caloric restriction, is an example of an extrinsic environmental factor that increases longevity in some species by retarding the aging of physiological processes.

Normal biological aging process has many characteristic features such as:

1. Aging process is complex, universal, and developmental, occurring in almost everyone after maturation.
2. It is an individualized and variable process, that is, organ systems within a person age at different rates. Every species has a typical speed of aging.
3. Aging is a predictable, inevitable evolution and maturation until death
4. It is progressive, such that the probability of developing age-associated conditions increases with time.
5. Causes irreversible changes in cells, organs, and systems.
6. There is an increased vulnerability to disease with advancing age.
7. Its detrimental: leads to a progressive loss of function
8. Its intrinsic, not due to environmental modifiable factors..

Hallmarks of cellular aging

The hallmarks of aging include: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

Genomic Instability

Accumulation of genetic damage throughout life is one of the common features of aging. The integrity and stability of DNA are continuously threatened by exogenous physical, chemical, and biological agents, as well as by endogenous challenges, including DNA replication errors, spontaneous hydrolytic reactions, and reactive oxygen species. Some premature aging diseases, such as Werner syndrome and Bloom syndrome, are the result of increased DNA damage accumulation. Defects in the nuclear architecture, known as laminopathies, can also cause genome instability and result in premature aging syndromes.

Mutations and deletions in aged mtDNA can also contribute to aging. MtDNA is a major for aging-associated somatic mutations due to the oxidative microenvironment of the mitochondria, the lack of protective histones in the mtDNA, and the limited efficiency of the DNA repair mechanisms compared to those of nuclear DNA.

Telomere attrition

The telomeres are some of the parts of chromosomes that are highly susceptible to ageing-related deterioration. Telomere shortening is seen in normal aging process. Telomere deficiency in humans have been associated premature development of diseases,such as pulmonary fibrosis, dyskeratosis congenita, and aplastic anaemia, which involve the loss of regenerative capacity of different tissues. Telomere uncapping and chromosome fusions may also result from deficiencies in shelterin components. Genetically, casual links have been established between telomere loss, cellular senescence, and organismal aging. Mice with shortened or lengthened telomeres exhibit decreased or increased lifespans , respectively.

Epigenetic alterations

Epigenetic alterations affect all cells and tissues throughout life. Epigenetic changes include alterations in DNA methylation patterns, post-translational modification of histones, and chromatin remodeling, increased histone H4K16 acetylation, H4K20 trimethylation, or H3K4 trimethylation, as well as decreased H3K9 methylation or H3K27 trimethylation, constitute age-associated epigenetic marks.

Loss of Proteostasis

Aging and aging-related disorders are associated with impaired protein homeostasis or proteostasis. Evidences abound that proteostasis is altered with aging. Furthermore, chronic expression of unfolded, misfolded, or aggregated proteins contribute to the development of some age-pathologies, such as Alzheimer's disease, Parkinson's diseases, and cataracts.

The activities of the autophagy-lysosomal system and ubiquitin-proteasome system, the two main proteolytic systems that control protein quality, decline with aging, supporting the notion that collapsing proteostasis constitutes a common feature of old age.

Mitochondrial dysfunction

As cells, tissues and organisms age, the efficiency of the respiratory chain tends to decline, thus increasing electron leakage and reducing ATP generation. The mitochondrial free radical theory of aging posits that the progressive mitochondrial dyfunction that occurs with aging results in increased production of ROS, which in turn causes further mitochondrial deterioration and global cellular damage. Mitochondrial dysfunction can also contribute to aging independent of ROS. For example, mitochondrial deficiencies can affect apoptotic signalling by increasing the propensity of mitochondria to permeabilize in response to stress, and trigger inflammatory reactions by favouring ROS-mediated and /or permeabilization-facilitated activation of inflammasomes.

Stem cell exhaustion

One of the main characteristics of aging is reduction in the regenerative potential of tissues. Examples include: (a) haemtopoiesis declines with age, resulting in a diminished production of adaptive of immune cells- a process called immuno-senescence- and increased incidence of anaemia and myeloid malignancies. Furthermore,

functional attrition of stem cells has been demonstrated in almost all adult stem cell compartments, including the bones, and muscle fibers.

Altered intercellular communication.

Aging involves not only cell-autonomous alterations but also changes at the level of intercellular communication, be it endocrine, neuroendocrine,, or neuroral. Moreover, neurohormonal signalling(e.g., renin-angiotensin, adrenergic, insulin-IGF1 signalling) is usually deregulated in aging as inflammatory reactions increase, immunosurveillance against pathogens and premalignant cells declines, and the composition of the per- and extracellular environment changes.

A typical example of aging-associated alteration in intercellular communication is 'inflammaging', i.e., a smoldering proinflammatory phenotype that accompanies aging in mammals. Inflammaging can arise from many causes including: accumulation of proinflammatory tissue damage, failure of dysfunctional immune system to effectively clear pathogens and dysfunctional host cells, increased ability of senescent cells to secrete proinflammatory cytokines and the occurrence of a defective autophagy response. Inflammation has also been implicated in the pathogenesis of obesity and type-2 diabetes. Defective inflammatory response is also involved in atherosclerosis.

Theories of Cellular Aging

There are many theories with multiple perspectives on the aging processes. Evolution, environmental factors, technological advances, and public health considerations have impact on the aging process and hence the theories of aging.

Table 11.2: Some theories of Aging and their tenets.

Theory	Tenets
1. The "Wear and Tear" Theory	Body and its cells were damaged by overuse and abuse.
2. The Neuroendocrine Theory	Based on the wear and tear theory by focusing on the neuroendocrine system
3. The Genetic Control Theory	Genetic inheritance says about how quickly we age and how long we live
4. Hayflick Limit Theory	Human cells have a limited life span
5. Death Hormone Theory (DECO)	We age because the pituitary begins to liberate DECO that increases the metabolic rate by accelerating the aging process
6. Mitochondrial Theory	Mitochondria are one of the easiest targets of free-radical injury
7. Autoimmune Theory	With age the system's ability to produce antibodies declines, as does its ability to distinguish between antibodies and

	proteins
8. he Telomerase Theory	very time our cells divide, telomeres are shortened, leading to cellular damage and cellular death associated with aging
9. The free radical Theory	Enhancement of the antioxidative defence system to attenuate free-radical-induced damage will counteract the aging process
10. Antagonistic pleiotropy Theory	Natural selection has favoured genes conferring short-term benefits to the organism at the cost of deterioration in later life

Structural and Functional changes in Aging

Most structural and functional changes associated with aging are strongly specific to the individual and the organ system, hence the rate of decline varies across the individuals.

1. Body configuration and composition

i. Loss of body water or decline in the proportion of body weight attributable to water

ii. Aging processes have been associated with reduction in lean body mass, in protein synthesis and protein degradation rates and in the amount of potassium in the body.

iii. Bone mineral density reduces as we move from middle age to old age

iv. By age 75, about 30% of the cells in the body are lost.

2. Changes in appearance and body temperature

i. Gradual decrease in height and weight.

Reductions in height may be to changes in the skeleton, including calcification of tendons and ligaments; thinning of vertebral discs associated with osteoporosis; and weakening and shrinkage of muscle groups.Normally, as people age, they assume a more stooped posture with the head and neck bent slightly forward and hips and knees flexed.The observed changes in height may contribute to the instability and increased prevalence of fall among older persons.

ii. Reductions in weight may be due to a decline in lean tissue mass, a decrease in total body water, a decline in muscle mass, and bone loss.

iii. Aging has also been linked with continuous decline in the ability to sense absolute temperatures (e.g., hot and cold), and in the ability of the body to generate heat and dissipate heat. The deficits in temperature regulation makes the elderly vulnerable to the effects of extreme temperatures.

3. **The skin**

a. There is significant reduction in the turn over time of epidermal cells as we age, this decreases the rate at which wounds heal.

b. Melanocytes decrease with each decade of life, this occurs in both sun-protected and sun-exposed skin. The elderly therefore, have less protection against the negative effects of ultraviolet radiation. Graying of the hair is a typical example of the manifestation of loss of functions of melanocytes.

c. During normal aging, the epidermis becomes structurally thinner, there is a flattening of the dermo-epidermal junction, and the corneocytes adhere less to one another, reducing water-binding capacity, which leads to dry skin. Hair graying is also a result of aging of the epidermal layer of the skin.

d. Generally, the skin becomes dry and itchy, and its integrity decreases over time.

e. With aging, dermal thickness decreases by about 20%, this may account for the paper-thin appearance of the skin of some elderly persons. There are also changes in the collagen and elastic fibers, which degenerate, resulting in less bulk and structure to the dermis.

f. During aging, changes in the dermis, may account in part, for the wrinkle formation common in old age.

g. Dermal collagen, elastin, and glycosaminoglycans are altered.

4. Changes in the nervous system with aging

1. Neurons may shrink with age, but there is no significant loss of neurons with age.

2. During aging, there is significant loss of white matter. This leads to an increase in the sizes of ventricles, gyral atrophy, and causing sulci to be become wider.

3. There is breakdown of myelin sheaths with age. This breakdown of the myelin sheaths may partly explain cause of cognitive decline with age. Breakdown of myelin sheath affects the timing in neuronal circuits, which in turn could affect memory.

4. aging leads to motor cortex atrophy, reduced motor cortical excitability, and plasticity, thus leading to accumulation of denervated muscle fibers

5. During aging, the magnitude of force generated by the neuromuscular apparatus, its transmission along the myofascial chain, joint mobility, and movement coordination are impaired

BLOOD PATHOPHYSIOLOGY

Pathophysiology of prolonged bleeding time, purpura, haemophilia, hemoglobinopathies, pathophysiology of sickle cell disease, thalassemia, hypersplenism

Pathophysiology of Prolonged Bleeding Time

Prolonged bleeding is typically caused by an abnormality in the clotting system such as deficiency of certain coagulation factors (e.g. factor VIII or IX). It can be either genetic or acquired. The genetic factors can be due to hemophilia and thrombocytopenia can cause prolonged bleeding, in addition to clotting factors and platelet disorders, vascular disorders can also cause abnormal bleeding which include vascular malformations, such as arterio-venous malformations. The acquired can be as a result of vascular occlusions, such as deep vein thrombosis and pulmonary embolism, medications and acquired conditions such as vitamin K deficiency, or secondary to liver and chronic kidney diseases. These conditions can lead to a decrease in clotting factors or platelet function, which can cause excessive bleeding.Treatment of prolonged bleeding depends on the underlying cause and may include the use of anti-fibrinolytic agents, anticoagulants, or medications that stimulate clot formation.

Purpura

This is the leakage of blood from the blood vessel usually small vessels in to the skin, presents as spots under the skin, mucous membrane or other organs usually large in size. This can be due low level of platelets (thrombocytopaenia), also called thrombocytopaenic purpura, due to some medical conditions like transplant bone marrow or stem cell, HIV infection or chemotherapy. The skin of the individual displays many small purplish blotches, giving the disease the name thrombocytopaenic purpura. Thrombocytopaenia can be idiopathic in which the cause is unknown, but the individuals develop antibodies against their own platelet cells.

Haemophilia

Haemophilias are heterogenous group of coagulation disorders caused by deficient /defective factor VIII or IX and characterized by bleeding into joints and muscles. They may be inherited as x-linked or arise from spontaneous mutation. There are two types; Haemophilia A (Classic) due to deficiency of factor VIII or Haemophilia B (Christmas Disease) due to deficiency of factor IX.

Males are affected almost exclusively, female are carriers but do not manifest the disease as they have a normal allele on the complementary X chromosome. They may have sufficiently low levels of factor VIII or IX to require treatment prior to invasive procedure or following major trauma. About one third (1/3rd) is sporadic (resulting from new mutations). Gonadal mosaicism has been reported in both Haemophilia A and B and this increases the chance of passing on the disease to future children.

Pathophysiology: extrinsic pathway controls bleeding through interaction of tissue thromboplastin with activated factor VII after injury, Tissue factor VIIa complex activates factors IX and X and to initiates a rapid but limited generation of thrombin on tissue injury. The initial formation of thrombin is subsequently amplified by a feedback mechanism in which thrombin activates factor IX and VIII of intrinsic pathway. In factor VIII deficiency, in adequate amounts of thrombin are generated. But increased amount of thrombin is required for the activation of thrombin activated fibrinolysis inhibitor (TAFI). So factor VIII deficiency is associated with insufficient clot formation as well as rapid clot removal.

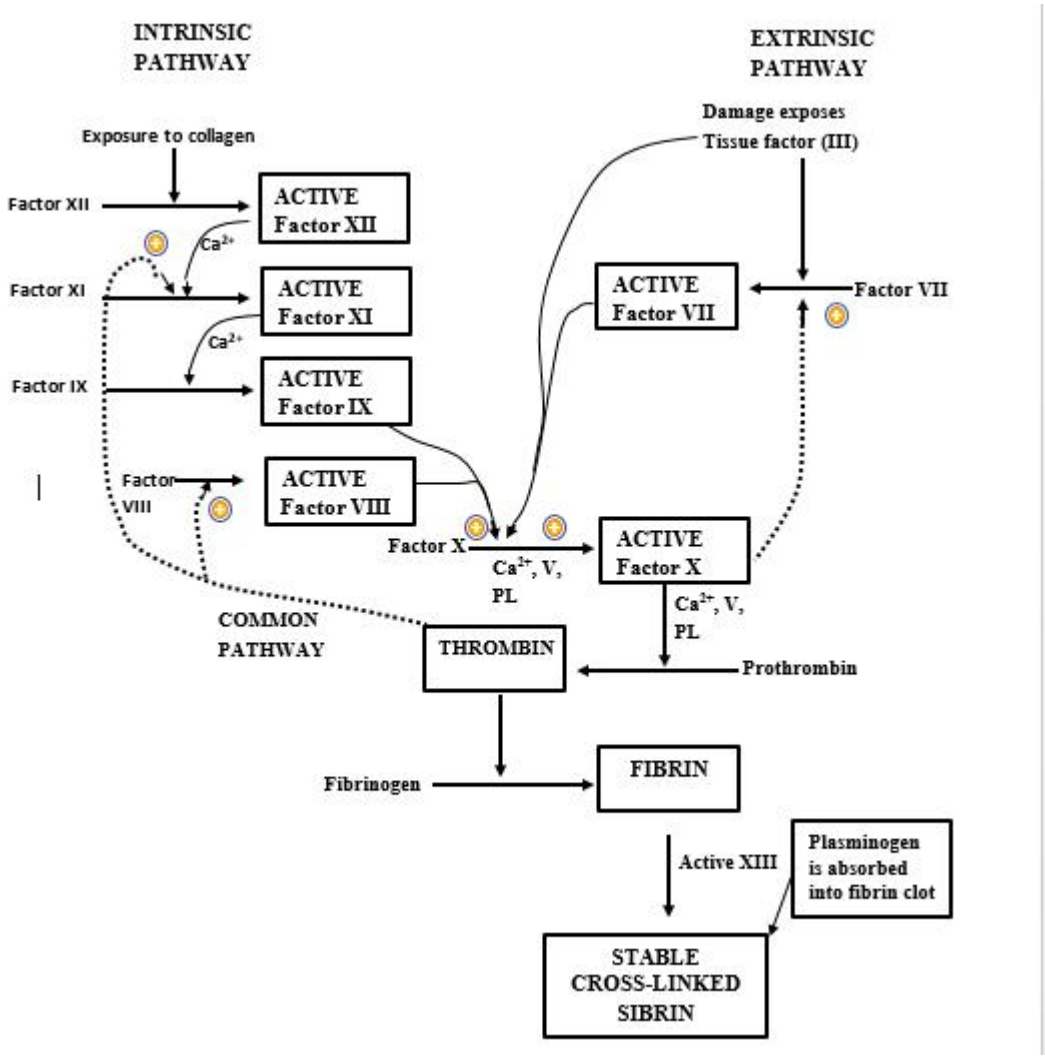


Fig. 11.1. Clotting pathway

Haemoglobinopathies

These are the most common inherited red cell disorders worldwide. Among these disorders, sickle cell syndromes and thalassaemias constitute major public health problems.

Pathophysiology of Sickle Disease

The normal haemoglobin molecule consists of four globin chains; two α chains and two β-globin chains. When α and β chains are normal, this is abbreviated as HbA. Abnormality is designated by the type of defect present in

the globin chain. Homozygous sickle cell disease is designated as HbSS. Sickle cell disease is usually the result of an abnormality in the β-chain (not α). It is formed when the amino acid valine is substituted for glutamic acid at position six of the β-chain. This is the result of a point mutation in the gene coding for β-chain synthesis. This abnormal haemoglobin has unusual tendency to bind with other HbS when deoxygenated. Deoxygenated Hb tends to polymerize into long strands that deform the erythrocyte, giving it characteristic sickle cell morphology. Initially the sickled RBC can revert to normal shape (i.e. unsickle when arterial oxygen tension increases. It may undergo a series of sickling and unsickling before it becomes irreversibly sickled. Irreversibly sickled cell (ISC) is the pathogenic hallmark of sickle cell disease. Irreversible Sickle Cells have deformed membranes that have lost the capacity to return to a normal shape even on exposure to oxygen. The cycles of sickling and unsickling of HbS during their passage through the circulation, and owing to loss of membrane permeability, the cells become irreversibly sickled. In this state, aggregates of sickled haemoglobin molecules arrange themselves in parallel, rod-like fibers, called polymerization. Normal haemoglobin molecules tend to line up in a similar way when in the deoxy configuration, but in sickle cells the ß6 valine substitution arranges these molecular in stacks. Sickled RBC have increased mechanical fragility and hence a shortened survival, leading to chronic haemolytic anaemia. Because of relative rigidity of sickled cells, and because they form aggregates, particularly in the microvasculature, the viscosity of the blood increases, which leads to vascular stasis, blockage of small vessels and tissue infarction. Sickle cell anemia is also considered as chronic inflammatory state punctuated by acute increase in inflammation wherein the endothelium, neutrophils and monocytes, platelets, coagulation pathways, several plasma proteins, adhesion molecules, and derangements in nitrogen oxide (NO) metabolism interact in concert with the abnormality in Hb polymerization described several decades ago. Abnormal adenosine signaling and activation of invariant natural killer T (iNKT) cells have been implicated in the disease pathophysiology.

Thalassaemia

Disease was first recognized in 1925 by Thomas B. Cooley. Many patients with this disease are from Mediterranean descent. There is reduced rate of production or total absent of one or more of the globin chains in haemoglobin. Types include: α, β, δβ, and γδβ thalassaemia depending on the affected globin chain. If there is no production of globin, it is referred to as α^o, β^o, $\delta\beta^o$. If there is reduced production it is referred to as α^+, β^+, $\delta\beta^+$. Thalassemia are also classified according to their clinical severity into major (blood transfusion-dependent), intermediate which is characterized by anaemia and splenomegaly but not transfusion-dependent and minor (asymptomatic carrier) type.

Pathophysiology of β-Thalassaemia

β-Thalassaemia causes excess of α –chains. Excess α –chains are unstable and precipitate inside the immatured RBC. Precipitate forms inclusion bodies interfere with RBC maturation, causing severe ineffective erythropoiesis erythropoiesis. Mature RBC that escapes ineffective erythropoiesis has inclusion bodies and easily destroyed in the spleen. Anaemias of β-Thalassaemia are therefore caused by ineffective erythropoiesis and haemolysis. Anaemia stimulates erythropoietin production causing marrow expansion leading to deformities of the skull and long bones. Splenomegaly results from constant supply of abnormal RBC in the spleen and extramedullary haemopoiesis, further aggravating the anaemia. Excess α –chains may also combine with δ -and γ chains to form increased level of fetal hemoglobin (HbF) and HbA_2. Increased level of HbF causes oxygen dissociation curve to be shifted to the left and induces further anaemia. Anaemia is also caused by increased

plasma expansion and hypersplenism. Regular blood transfusion reverses the pathophysiology, but causes iron overload which may eventually be fatal.

Hypersplenism

Hypersplenism is a characteristic triad of splenomegaly, variable degrees of cytopaenia (anaemia, leucopaenia and thrombocytopaenia). In other words, it is a group of syndromes that involves splenomegaly and peripheral cytopaenia of various causes. It can be caused by infections commonly of viral origin e.g. hepatitis, parasitic e.g. Malaria, excessive alcohol intake, autoimmune disease such as systemic lupus erythromatosis, or drug induced. Hypersplenism can occur with moderate or minimal splenic enlargement as a result of exaggerated removal of physically abnormal red blood cells (e.g hereditary spherocytosis) or antibody coated erythrocyte (auto-immune haemolytic anaemia). Hypersplenism can be divided into three; primary, secondary and occult.

Pathophysiology: This involves the destruction and pooling of RBCs, WBCs and platelets inside the spleen, leading to splenic enlargement with concomitant anemia, decrease immunity and reduction in platelets counts. In patients with primary hypersplenism, the spleen can increase 8–10 times its normal size. Splenic blood volume increases due to the increased venous pressure leading to congestive splenomegaly, or because of the increased splenic arterial blood flow induced by a variety of diseases, resulting in hyperemic splenomegaly. Consequently, there is retention of a large number of leukocytes, erythrocytes and platelets in the spleen, thus facilitating capture, phagocytosis or destruction of blood cells by phagocytes resulting in peripheral cytopaenias. In hypersplenism the macrophages are overactivated with significant increased phagocytosis, cytokine secretion, antigen processing and presentation. Excessive activation of macrophages is an important cause of hypersplenism. Significantly increased counts of macrophages in the spleen and their enhanced phagocytosis have been reported in patients with primary hypersplenism. The number of erythrocytes and platelets phagocytosed was also significantly increased.

Pathophysiology of anaemia, megaloblastic anaemia, pathophysiology erythroblastosis fetalis, incompatible blood transfusion.

Pathophysiology of Anaemia

Anaemia is defined as a reduction in the concentration of circulating haemoglobin or oxygen-carrying capacity of blood below the level that is expected for healthy persons of the same age and sex in the same environment.

WHO definition of anaemia – Hb <11.0g/dl for non-pregnant females

- Hb < 8.2g/dl for pregnant females

- Hb < 13g/dl for males

Clinical features of anaemia depend on how rapidly the anaemia develops. Most cases caused by nutritional deficiencies are of gradual onset, and physiological adaptations of the associated symptoms are usually mild. In contrast, anaemia of acute onset (acute haemorrhage or haemolytic anaemias) where the lack of physiological adaptations permits symptoms at a less marked level of anaemia, typical symptoms include lassitude, fatigue, dyspnea on exertion, palpitations and headache. Anaemia can be classified according to two major group's base on aetiological or morphological characteristic changes in the size of red cells; (mean corpuscular volume, MCV)

and their degree of haemoglobinization (mean corpuscular haemoglobin, MCH). The classification base on size of the RBCs includes;

i. Microcytic (MCV < 80fl)

ii. Macrocytic (MCV >98fl)

iii. Normocytic (MCV 80-98fl)

Aetiological Classification

Anaemia due to impaired red cell production

i. Insufficient erythropoiesis

ii. Ineffective erythropoiesis

Anaemias due to increased red cell destruction

i. Intrinsic red cell abnormalities e.g. membrane defects, enzyme deficiency (G6PD deficiency) and haemoglobin structural defects e.g. hemoglobinopathies.

ii. Extrinsic red cell abnormalities- Auto-immune disorders e.g. Rh incompatibility, infections, hypersplenism etc.

Anaemia due to excess blood loss

i. Road traffic accidents

ii. Post-partum haemorrhage

Morphological Classification

Microcytic hypochromic

i. Iron deficiency anaemia

ii. Thalssaemia

iii. Sideoblastic anaemia

iv. Lead poisoning

v. Anaemia of chronic disease (late stage)

Macrocytic

Megaloblastic

i. Vitamin B_{12} deficiency

ii. Folate deficiency

iii. Defects in other pathways of DNA metabolism

Non-megaloblastic types of anaemia include; Alcohol consumption, Liver disease, Myxoedema, Myelodysplastic syndromes, antimetabolite drugs, e.g. hydroxyl carbamide, aplastic anaemia, Smoking, Reticulocytosis, Myeloma and paraproteinemia, pregnancy, neonatal age group.

Normocytic normochromic

i. Acute blood loss

ii. Anaemia of chronic disease

iii. Some haemolytic anaemias

Megaloblastic Anaemia

This is a group of anaemias in which the erythroblasts in the bone marrow show a characteristic abnormality in which maturation of the nucleus being delayed relative to that of the cytoplasm. The underlying defect accounting for the asynchronous maturation of the nucleus is defective DNA synthesis in all proliferating cells. Usually cause by deficiency of vitamin B_{12} or folate. Vitamin B_{12} is an extrinsic factor that requires an intrinsic factor for absorption. Intrinsic factor is a glycoprotein secreted by parietal cells of the gastric mucosa. In humans, it has an important role in the absorption of vitamin B_{12} (cobalamin) in the intestine, and failure to produce or utilize intrinsic factor results in the condition called megaloblastic anaemia. This occurs as a result of an autoimmune attack against parietal cells. In all mammals, vitamin B_{12} is necessary for maturation of erythrocytes, and a deficiency of this vitamin leads to development of anemia. Since efficient absorption of vitamin B_{12} in humans depends on intrinsic factor, diseases which decrease the secretion of intrinsic factor (e.g. atrophic gastritis), interfere with cleavage of the binding proteins e.g. decrease binding and absorption of the intrinsic factor-vitamin B_{12} complex (e.g. ileal disease or resection) can result in this type of anaemia.

Erythroblastosis Foetalis or Haemolytic Disease of the Newborn

Although the Rh factor is important in transfusion, it is also of great importance in pregnancy especially when an Rh-negative mother has an Rh positive foetus (inherited from the father). Some red cells may enter the maternal circulation and stimulate the production of anti-Rh antibodies in the mother. Normally, there is no mixing of foetal and maternal blood, the two being separated by placental membranes. The mixing of maternal and foetal blood may occur only during labour. After the first pregnancy, the mother slowly develops antibodies against the Rh antigens. However, by the second pregnancy the well-developed antibodies slowly diffuse through the placental membrane into foetal blood and cause agglutination. As a result, the agglutinated red cells become hemolyzed causing the release of haemoglobin and hence bilirubin. Thus causes yellowish discolouration of the foetal skin

and conjunctivae to cause jaundice (icterus). The antibodies can also attack and damage other organs of the body especially the brain.

In an attempt by the foetal haemopoietic system to replace the lost cells (RBCs), the liver and spleen become greatly enlarged due hyperactivity to produce red cells. This becomes so rapid that many incompletely formed, erythroblast become noticeable in the foetal blood hence the disease erythroblastosis foetalis. If the anaemia becomes so severe, there may be death in utero or the foetus may develop severe oedema. This condition is known as hydrops foetalis. Bilirubin may also find its way into the brain tissues causing their destruction and permanent mental impairment (because the blood brain barrier does not develop in foetus). This condition is known as kernicterus.

Incompatible Blood Transfusion

The practical importance of the blood groups is that cells from one person transfused into another must be matched so that, they are not agglutinated by the antibody present in the recipients plasma. It should be noted that the donors serum has little effect on the recipient cell because of the large dilution which takes place, thus the effect of transfusion are tested for directly by testing the donors cell with recipients serum before transfusion. This is called **cross matching**. The severity of symptoms of a mismatch blood varies into immediate and delayed.

Immediate transfusion reaction: this occurs immediately when the transfusion is on process, such as haemolytic transfusion reactions and can be fatal involves massive intravascular haemolysis as a result of complement-activating antibodies of IgM and IgG classes, usually with ABO specifity, febrile non-haemolytic transfusion reaction, allergic reactions, transfusion associated lung injury and circulatory overload. Individuals who have been sensitized earlier to certain red cell antigens by previous transfusion or pregnancy e.g. Rhesus negative individuals that received Rh positive blood on exposure to the same antigen will have an immediate transfusion reaction because of the building up of antibodies slowly over time.

Delayed transfusion reaction: this occurs usually Individuals who have been sensitized earlier to certain red cell antigens by previous transfusion or pregnancy. On exposure to the same antigen will have secondary immune response that causes the destruction of the transfused red cells bearing the particular antigen. The patient will develop fever, anaemia, jaundice five to ten days after transfusion.

Others are transmission of infection like HIV, hepatitis, rickettsia, and malaria, post transfusion purpura.

RENAL PATHOPHYSIOLOGY

Pathophysiology of albuminuria, nephritic and nephrotic syndrome, acute tubular necrosis. Glycosuria, pathophysiology of kidney stone.

Pathophysiology of Albuminuria

This is a condition of having too much albumin in the urine which results from damage within the kidney. It is not a disease in and of itself but a symptom of certain conditions affecting the kidney. Under physiological conditions, almost all albumin filtered at the glomerulus is reabsorbed by the renal tubular epithelial cells, and only 1% is excreted in the urine. The pathophysiology indicates that albuminuria may not only be a consequent or sign of vascular disease at a later age.

Albuminuria, a component of proteinuria is consequent of two mechanisms:

(1)The abnormal transglomerular passage of proteins due to increased permeability of glomerular capillary wall.

(2)Subsequent impaired reabsorption by the epithelial cells of the proximal tubuli.

There are three pathophysiologic mechanisms of proteinuria:

(1) Glomerular abnormalities.

(2) Tubular abnormalities and

(3) Overflow.

However, glomerular abnormality is the most common and usually corresponds to a urinary protein excretion of more than 2g per 24 hours.

Albuminuria is classified in the KDIGO classification as :

(1)A1 (UAE< 30 mg/ day or urine ACR [uACR] < 30 mg/g creatinine).

(2) A2 (previously termed “microalbumuniria”; urinary albumin excretion, 30- 300 mg/day, or urine ACR [uACR] 30- 300 mg/g creatinine).

(3) A3 (previously termed “macroalbuminuria”; urinary albumin excretion of > 300mg/day or urine ACR [uACR] > 300mg/g creatinine).Those at risk include: people with diabetes, high blood pressure and family history of kidney failure.

Pathophysiology of nephritic and nephrotic syndrome

Nephritic syndrome also called glomerulonephritis is a clinical syndrome that presents as haematuria, elevated blood pressure, decreased urine output, and edema. The underlying pathology is inflammation of the glomerulus that results in nephritic syndrome. The main difference between this and nephrotic syndrome is that there is haematuria in nephritic syndrome. There is also proteinuria, hypertension, uraemia and possibly oliguria. The two standout features are hypertension and RBC casts. Proteinuria is less in nephritic syndrome because inflammatory glomerular injuries are so advanced that total glomerular filtration is reduced, thus lead to reduction in total amount of filtered proteins. That’s why in these cases albuminuria and globulinuria are comparatively less in nephritic syndrome. Common symptoms of nephritic syndrome are: blood in the urine (urine appears dark, tea-coloured or cloudy), decreased urine output (little or no urine may be produced), swelling of the face, eye socket,

legs, arm, hands, feet, abdomen, or other areas. There is also hyperlipidaemia, thromboembolism and an increased rate of infection. Complications include infections, thromboembolism, cardiovascular disease, hypovolemic crisis, anaemia, and acute renal failure.

Nephrotic syndrome is usually caused by damage to the clusters of blood vessels in the kidney that filter waste and excess water from the blood. The condition causes swelling, particularly in the feet and ankles, and an increases the risk of other health problems. It causes the loss of significant volumes of protein via the kidneys (proteinuria- ≥ 3.5g/day) which results in hypoalbuminaemia (serum albumin ≤ 30g/L). There is also hyperlipidaemia (hypertrigliceridemia and cholesterolemia), lipiduria, and edema.

Pathophysiology of Acute Tubular Necrosis (ATN)

This is a kidney disorder involving damage to the tubular cells of kidney, which can lead to acute kidney failure. The most frequent causes of acute tubular necrosis are stroke or heart attack, conditions that reduce oxygen to the kidneys, chemicals like X-ray contrast dyes, anaesthetic drugs, antibiotics and other toxic chemicals. ATN causes marked arteriolar vasoconstriction; the degree is related to the severity of the ATN. It is usually suspected when serum creatinine rises ≥ 0.3mg/dl/day (26.5 micromol/ liter [µmol/ L]) above baseline or a 1.5- to 2.0- fold increase in serum creatinine from baseline after an apparent trigger (e.g., hypotensive event, exposure to a nephrotoxin); the rise in creatinine may occur I to 2 days after.

There are 2 types:

(1)Ischaemic ATN occurs when severe hypotension leads to decreased renal perfusion.

(2)Toxic ATN occurs when a nephrotic drug decreases renal perfusion and/ or causes injury.

The course of ATN can be divided into three phases:

(1)Onset or initiating phase. This lasts hours or days, this is then time from onset of the precipitating event (e.g. toxin exposure) until tubular injury occurs.

(2)Maintenance phase.

(3)Recovery phase.

It clinically typically progresses through four phases:

(1) Initiation: This phase usually lasts hours to days.

(2) Extension: The GFR continues to decrease or remains low.

(3) Maintenance: Typically lasts 1-2 weeks.

(4) Recovery: Marked by tubular cell repair and regeneration.

It may be classified as either toxic or ischaemic. Toxic ATN occurs when the tubular cells are exposed to a toxic substance (nephrotoxic ATN), while Ischaemic ATN occurs when the tubular cells do not get enough oxygen, a

condition that they are highly sensitive and susceptible to, due to their very high metabolism. This is the most common cause.

Symptoms includes:

(1) A small amount of urine.

(2) Swelling and fluid retention.

(3) Nausea and vomiting.

(4) Trouble waking up/ drowsiness.

(5) Feeling sluggish.

(6) Confusion.

The risk factors includes:

(1) Taking certain medicines.

(2) Using certain illegal drugs.

(3) Having certain health problems such as : kidney, heart, liver, or lung disease, blood pressure that is too high or low, diabetes, cancer.

(4) Blood loss from surgery.

Common complications include:

(1) Electrolyte imbalance (e.g. hyperkalemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis).

(2) Platelet dysfunction.

(3) Uremia.

(4) Altered consciousness or coma.

Prognosis depends on the underlying aetiology and severity of kidney damage.

Pathophysiology of Glycosuria

It is a term that defines the presence of reducing sugars in the urine, such as glucose, galactose, lactose, fructose etc. It occurs when the glomerulus filters more glucose than the proximal tubule can reabsorb. In normal individuals, a small amount of glucose in urine is normal. If a random urine sample shows more than 0.25mg/ml, this is considered glycosuria and can be caused by too high blood glucose level, a problem with your kidney filters, or both.

Types of Glucosuria

It is typically caused by an underlying condition that affects the blood sugar level. Type 2 diabetes is the most common cause of glycosuria. Other causes includes hyperthyroidism, acute tubular interstitial nephritis (ATIN), global dysfunction of proximal tubule called Fanconi syndrome, acute tubular necrosis (ATN), chronic kidney disease, eating more sugar than the body can process and physiologically during pregnancy.

Glycosuria can be of 3 types:

(1)Type A: This is the most common where there is a decline in both glucose threshold and maximal glucose reabsorption rate.

(2)Type B: Here, the rate of reabsorption is normal but there is a decline in renal threshold.

(3)Type O: Here, glucose reabsorption does not happen in the kidneys.

The symptoms include:

(1)Extreme hunger.

(2)Extreme thirst or dehydration.

(3)Accidental urination.

(4)More frequent urination.

(5) Nighttime urination.

Pathophysiology of Kidney Stone

These are hard deposits of minerals and acid salts that stick together in concentrated urine. They can be painful when passing through the urinary tract, but usually don't cause permanent damage. Globally, approximately 80% of kidney stones are composed of calcium oxalate (CaOx) mixed with calcium phosphate (CaP). It can also be composed of uric acids (9%), struvite (10%) and cystine (1%) respectively.

The single most important determinant of stone formation is low fluid intake. A low fluid intake results in the production of concentrated urine, causing supersaturation and crystallization of stone- forming compounds. Also, low urine flow rates favour crystal deposition on the urothelium.

Causes of kidney stone include:

(1) Drinking too little water.

(2) Exercise (too much or too little).

(3) Eating food with too much salt or sugar.

(4) Infections.

(5) Family history.

The symptoms include

(1)Severe, sharp pain in the side and back, below the ribs.

(2)Pain that radiates to the lower abdomen and the groin.

(3)Pain that come in waves and fluctuates in intensity.

(4)Pain or burning sensation while urinating.

Hydronephrosis, pyelonephritis and haemonephrosis. Causes of haematuria, causes of urine retention, dehydration and over-hydration.

Hydronephrosis: is the dilatation of the renal pelvis and calyces due to partial or intermittent obstruction to the flow of urine. It can be unilateral or bilateral.

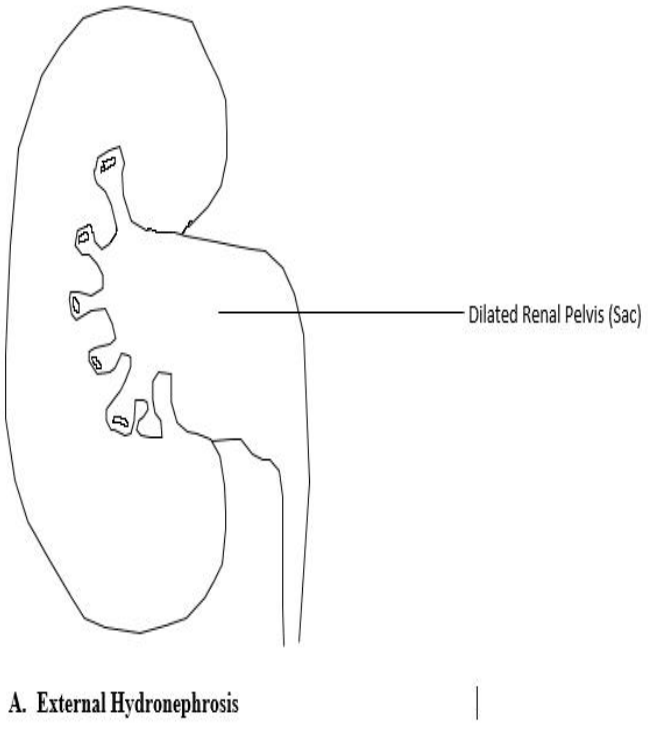


Fig.11.2a. External hydronephrosis

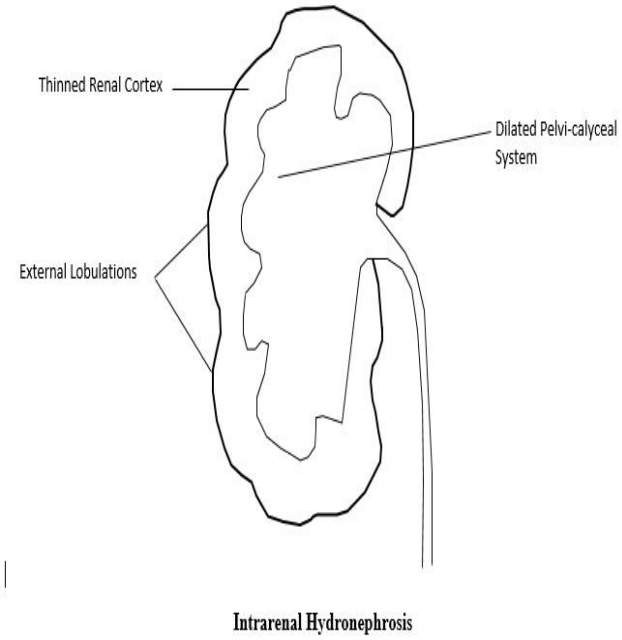


Fig. 2b Internal hydronephrosis

Unilateral hydronephrosis can occur due to ureteral obstruction at the level of pelvi-ureteral junction causes can be:

a. Extramural e.g. tumours from adjacent structures e.g. cervix, prostate, idiopathic retroperitoneal fibrosis

b. Intramural e.g. congenital stenosis, physiological narrowing of the pelvi-ureteric junction

c. Intra luminal e.g. calculus in the ureter or pelvis, diabetics, analgesic abuse etc.

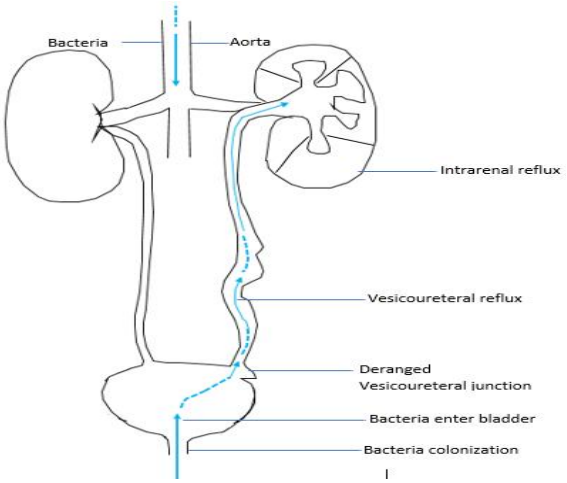
Bilateral hydronephrosis usually occurs as a result of bilateral ureteral obstruction. It can be

- Congenital e.g. atresia of the urethral meatus, posterior urethral valve
- Acquired e.g. bladder tumour, prostatic enlargement, cancer of the prostate and urethral stricture

Pyelonephritis: is a renal disorder affecting the tubules, interstitium and renal pelvis. It is among the most common kidney diseases. It can be acute or chronic. Acute pyelonephritis mainly is caused by bacterial infection, while chronic pyelonephritis is a more complex disorder and bacterial infection is still more dominant in causation, but other factors like vesico-urethral obstruction can also cause. Pyelonephritis is a serious complication of urinary tract infection (UTI).

Haematogenous Infection

Common Agents;
Staphylococcus
E. Coli



Ascending Infection

Common Agents;
E. Coli
Proteus
Enterobacter

Fig. 11.3:. Pyelonephritis

Pathogenesis: major aetiological agents that cause pyelonephritis are gram negative bacteria that are normal flora of the gastrointestinal tract. Most common are E.coli, proteus and enterobacter, others are streptococcal faecalis, staphylococci and other bacterial and fungal agents. In immunocompromised patients' e.g. those with transplanted organs, HIV and cytomegalovirus can also cause UTI.

There two routes by which infecting agents reaches the kidneys; ascending infection from the lower urinary tract by reflux from the vesico-urethral junction or haematogeneous from a focus somewhere not in the urinary tract, causing septicaemia. Although, the haematological is less common than the ascending infection through the lower urinary tract. Normal human bladder and bladder urine are sterile. In pyelonephritis there is loss of demarcation between the cortex and medullar as well as multiple abscesses with widespread interstitial infiltration with polymorphonuclear leucocytes.

Haemonephrosis

Haemonephrosis is a condition in which blood leaks into the renal tissues resulting into swelling and inflammation. It manifests with abdominal pain, nausea, vomiting, and dark coloured urine.

Causes are:

1. Kidney damage caused by kidney disease, such as glomerulonephritis, pyelonephritis, nephrotic syndrome, etc.
2. Obstruction of the urinary system, such as kidney stones, foreign bodies, and urinary tract tumours,
3. Congenital malformations, such as narrow renal pelvis, renal cysts, etc.
4. Severe dehydration, shock and other serious systemic diseases
5. Immune diseases, such as systemic lupus erythematosis, vasculitis, etc.
6. Excessive intake of drugs, such as non-steroidal anti-inflammatory drugs, antibiotics.
7. Trauma and acute infection of the urinary system

Treatment: be directed towards controlling bleeding, surgery may be necessary or medication like anticoagulant, antibiotics, intravenous fluid (IVF) to help maintain hydration and electrolyte balance.

Haematuria

Haematuria is the passage of blood in the urine. Presence of three or more red blood cells in centrifuged urine per high power field microscopy (> 3 RBC/HPF) signifies haematuria. Normally, urine does not contain blood cells as the glomerular membrane does not allow the passage of more than 3 red blood cells. Blood in urine can be microscopic seen only under the microscope or macroscopic seen with the naked eye appears as cola pink or red coloured. It is one of the most common presenting signs of parenchymal renal disease and cancer of the urinary tract. It can be nephrologic or urologic in origin.

Causes:

The causes of haematuria can be congenital or acquired

Congenital: Congenital anomalies of the genitourinary system especially renal malformations and embryonic tumours.

Acquired: Traumatic, inflammatory, metabolic, haematological, neoplastic, medical, miscellaneous, or idiopathic.

Medical causes: can be renal or non-renal in origin.

Renal origin: acute glomerulonephritis, tubule-interstitial, renovascular or systemic disorders.

Non- renal: anticoagulants, thrombosis and embolization of renal fistula, AV fistula, surgical cyst, stones, benign prostatic hyperplasia etc.

Haematuria: due to other pigments like myoglobin, drugs like Rifampicin etc.

Urine Retention:

Urine retention is defined as inability to completely empty the bladder or inability to voluntarily void urine. It is also called ischuria. It can be acute, acute on chronic on-chronic type.

Causes of urine retention: Can be;

i. Obstructive benign prostatic hyperplasia, urethral strictures bladder calculi, faecal impaction, benign or malignant pelvic masses, uterine fibroid or ovarian cyst, retroverted impacted gravid uterus or foreign body.

ii. Infectious and inflammatory causes like prostatitis, prostatic abscess bilharziasis, herpes simplex.

iii. Pharmacologic: drugs that have anticholinergic propertiese.eg antidepressants like amitriptyline, Opioids, sympathomimetic drugs e.g. oral decongestants, NSAIDS in men, antipsychotic, anti-Parkinsonian, and muscle relaxant

iv. Neurologic: autonomic or peripheral nerve; diabetes mellitus, Guillain-Barre syndrome, radical pelvic surgery, cerebrovascular accident Parkinson's disease, haematoma, spina bifida occulta

v. Other causes are post-op complications, pregnancy associated retention, trauma e.g. penile fracture or laceration, idiopathic detrusor failure

Dehydration

Dehydration is a state of pure deprivation of water leading to Na^+ retention and hence a state of hypernatraemia. In this situation there is only loss of water without loss of Na^+.

Causes of Dehydration

- GIT excretion, severe vomiting, and diarrhea,
- Renal excretion as in acute renal failure in the diuretic phase, extensive use of diuretics,
- Endocrine diabetes insipidus,
- Blood loss as in severe injuries, burns and during delivery.
- Loss from the skin: excessive perspiration, hypothermia, excessive sweating as in heavy exercise,
- Accumulation in third space like sudden ascites, sudden intestinal obstruction.

Overhydration

Overhydration is the increase extravascular fluid volume due to pure water excess or water intoxication.

Causes of Overhydration

- Excessive unmonitored intravascular infusion: Normal saline, Ringer lactate
- Renal retention of sodium (Na^+) and water e.g. in congestive cardiac failure, acute glomerulonephritis, chronic renal failure
- Liver cirrhosis

CARDIOVASCULAR PATHOPHYSIOLOGY

Pathophysiology of Palpitation

Palpitation refers to awareness of heartbeats. It is described as a thumping, pounding, or fluttering sensation within the chest or around the neck. Communications occur between the heart and the brain bidirectionally through neural (nervous impulses), biochemical (hormones and neurotransmitters), or biophysical pathways(mechanoreceptors). The neural networks include the sympathetic and parasympathetic system, brainstem, subcortical nuclei, and cerebral cortex (modulation of awareness). Disturbances in these pathways as a result of alteration in cardiac impulse generation and or propagation. Palpitation may be intermittent or persistent, regular or irregular. Pathophysiological mechanisms involved in palpitation include;

1. Cardiac arrhythmia (abnormal heart rhythms); atrial, junctional or ventricular premature beats, supraventricular tachycardia, atrial flutter, atrial fibrillation.
2. Conduction defects such as heart block
3. Hyperdynamic states such as excessive catecholamine release, thyrotoxicosis, hypoglycaemia, anaemia and aortic regurgitations.
4. Ischaemic heart disease resulting in tissue hypoxia and resultant arrhythmias
5. Alterations in heart rate due to stimulants such as caffeine, alcohol, energy drink usage, tobacco, thyroxine, bronchodilators such as Ventolin
6. Mental health disorders such as insomnia and emotional disturbances; depression, anxiety, panic attacks, and somatization.

Pathophysiology of Cardiac Arrhythmia

Cardiac arrhythmia refers to an abnormal rhythm. A cardiac arrhythmia occurs due to a disturbance either in the origin, rate, regularity or conduction of cardiac electrical impulses. It occurs with a slow or fast heart rate.

Pathophysiological Mechanisms

A cardiac arrhythmia occurs due to a disorder in impulse formation and or propagation. The

pathophysiological mechanisms for cardiac arrhythmia include altered automaticity, triggered activity and reentry. Arrhythmias with slow heart rate (bradyarrhythmia) may be due to slow automaticity or interruption of conduction through the atrioventricular node or the conducting fibres beyond the atrioventricular node. For instance, sinus bradycardia is due to abnormally slow automaticity while bradycardias due to atrioventricular block are due to conduction abnormalities. The pathophysiological mechanisms for tachyarrhythmia include;

i. Enhanced automaticity

ii. Triggered activity and

iii. Re-entry

i. Enhanced Automaticity

Enhanced automaticity refers to the acceleration of the generation of an action potential by pacemaker tissue within the heart (enhanced normal automaticity) or by non-pacemaker tissue (abnormal automaticity).

ii. Triggered Activity

Triggered activity results from the oscillation of transmembrane potentials occurring during or immediately after a preceding action potential is called afterdepolarizations. There are two types of afterdepolarizations; early afterdepolarization (EAD) occurs during phase 2 or 3 of myocardial action potential and delayed afterdepolarization (DAD) occurs at the end of the action potential. Both EAD and DAD may reach a threshold and produce arrhythmia. Examples of arrhythmia due to triggered activity include atrial fibrillation and ventricular arrhythmia

iii. Re-entry

Re-entry occurs when an activation wavefront propagates around a structural or functional obstacle and re-excites the site of origin. An example of arrhythmia due to re-entry is the Wolff-Parkinson-White pattern.

Conditions for Re-entry

- An initiating trigger.
- A substrate: myocardial tissue of varying electrophysiological properties.
- Presence of area of a block (structural or functional obstacles, usually unidirectional block)
- Localized slow conduction or abnormally fast conduction pathway.
- A critical mass to sustain re-entrant wavefront.

Heart Block

Introduction

In the cardiac conduction system, cardiac electrical impulses are propagated from the sinus node to the atrioventricular node to the bundle of His to bundle branches to fascicles to Purkinje fibres at the ventricular walls. Heart block refers interruption of the propagation of electrical impulses along the cardiac conduction system. It can be classified according to the level of the interruption. Heart block can be congenital or acquired. Heart block includes; sinoatrial exit block, atrioventricular block, bundle branch block, and fascicular block.

Sinoatrial Exit Block

Sinoatrial exit block occurs when the cardiac electrical impulses failed to propagate beyond the sinoatrial node, the pacemaker of the heart. With this, not all sinus impulses result in atrial depolarization.

Atrioventricular Block

Atrioventricular block occurs as a result of a partial or complete interruption of impulse conduction from the atria to the ventricles through the atrioventricular junction. AVB is a cause of clinically significant bradycardia, syncope, and sudden cardiac death.

Bundle Branch Block

Bundle branch block occurs as a result of a partial or complete interruption of impulse conduction along the bundle branches. When the right bundle is blocked, the right ventricle fails to be excited by impulses propagating along the right bundle but will be excited from the impulses receives from the left bundle after left ventricular excitation. In the left bundle branch block, the left ventricle cannot be excited by impulses along the left bundle branch but will be excited by impulses received from the right bundle branch after excitation of the right ventricle. These results in the prolongation of ventricular activation time.

Fascicular Block

With a fascicular block, there is an interruption of propagation along the left anterior fascicle or left posterior fascicle resulting in a change of direction of propagation of the cardiac electrical impulses. This manifests electrocardiographically as significant left axis deviation or right axis deviation respectively.

Pathophysiology of Heart Block

Heart block may be linked with a variety of cardiac and extracardiac disorders such as drug usage, cardiac diseases, hypoxemia, and electrolyte imbalance. The major pathophysiological mechanisms include the affectation of the cardiac conduction pathway by one or more of the following; drugs, ischaemia, infarction, inflammation, fibrosis, infiltration, and immune-mediated injury. Interruption of electrical impulses propagation along the cardiac conduction system may result in failure of cardiac excitation, bradycardia, decreased cardiac output, and decreased tissue perfusion with resultant hypoperfusion of organs such as the brain and kidney. Hypoperfusion of the brain may result in syncope and seizure. Hypoperfusion of the kidney may result in the activation of the renin-angiotensin-aldosterone system culminating in hypertension in the background of bradycardia and kidney injury.

Pathophysiology of Ischaemia Heart Disease; Angina Pectoris and Myocardial Infarction

Ischaemic heart disease is a spectrum of cardiac disorders in which the imbalance between myocardial oxygen supply and demand (demand > supply) results in ischaemic injury to the myocardial tissue. Ischaemic injury may be reversible (*myocardial ischaemia*) or irreversible (*myocardial infarction*). Myocardial ischaemia manifests clinically as angina pectoris presenting as chest pain whereas myocardial infarction manifests as an acute coronary syndrome.

The imbalance between oxygen supply and demand may also result from increased demand by myocardial tissue or inadequate capacity of the blood to deliver sufficient oxygen to meet the demand of the tissue. Reduction of blood flow to the myocardium may be due to atherosclerosis, plaque or thrombus formation, arterial embolism, and or arterial spasm causing partial or total occlusion of the vascular supply to the myocardial tissue. Partial occlusion of the blood supply to a particular region of the heart muscle results in hypoxia, myocardial ischaemia, inflammation, and oxidative stress causing myocardial dysfunction and chest pain. Total occlusion of the blood supply to the heart muscle results in severe tissue hypoxia, myocardial necrosis(infarction), inflammation, apoptosis, fibrosis, and myocardial dysfunction culminating in decreased cardiac output, hypotension, altered heart rate, arrhythmia, and heart failure. Both myocardial ischaemia and infarction manifest with chest pain. While myocardial ischaemia may occur without major haemodynamic compromise, acute myocardial infarction is usually associated with a major haemodynamic collapse.

Pathophysiology of Murmurs

Murmurs are audible vibrations due to turbulent blood flow within the heart or its great vessels. Murmurs are classified according to the phase of the cardiac cycle when the sound is perceived. These include systolic, diastolic, or continuous murmur. Systolic murmurs are perceived during ventricular systole, diastolic murmurs are perceived during ventricular diastole whereas machinery or continuous murmurs are perceived both in ventricular diastole and systole. Pathophysiological mechanisms of murmur include the following; increased turbulence of blood flow across a cardiac valve or intracardiac shunt. Increased turbulent blood flow may also occur when there is hyperdynamic circulation. Cardiac lesions resulting in increased turbulence include valvular stenosis, incompetence, or prolapse while intracardiac shunts include atrial septal defects, ventricular septal defects, and patent ductus arteriosus. Hyperdynamic states resulting in turbulent blood flow include anaemia, fever, thyrotoxicosis, beriberi, and arteriovenous fistula.

Pathophysiology of Syncope

Syncope refers to a transient loss of consciousness and postural tone secondary to cerebral hypoperfusion. Syncope is characterized by rapidity of onset, short duration and spontaneous recovery. It is often described as fainting. Syncope can be classified into three major categories; reflex syncope, orthostatic syncope, cardiac syncope and neurologic syncope.

1. Reflex Syncope

Reflex syncope is due to autonomic dysfunctions resulting in cardioinhibitory and/or cardiodepressor responses. Reflex syncope includes neurocardiogenic syncope, situational syncope, and carotid sinus syncope.

a. Neurocardiogenic syncope

Neurocardiogenic syncope embraces vasovagal or vasodepressor responses culminating in decreased cardiac output, cerebral hypoperfusion, and transient loss of consciousness. Vasovagal syncope is associated with both sympathetic tone withdrawal resulting in vasodilatation and an increase in vagal (parasympathetic) tone resulting in bradycardia but vasodepressor syncope is characterized by only sympathetic tone withdrawal. It is related to initial increased sympathetic discharge and venous pooling (erect posturing) which trigger reflex activation of myocardial mechanoreceptors and increased vagal afferent discharge resulting in the withdrawal of sympathetic tone and overwhelming parasympathetic discharge. Precipitants of neurocardiogenic syncope include; a crowded or hot environment, pain, hunger, fear, fatigue, prolonged standing, stress, or emotional condition.

b. Situational syncope

This is a type of neurocardiogenic syncope involving cardioinhibitory and or cardiodepressor responses but the precipitants are situations such as swallowing, coughing, micturition, defaecation or straining (Valsava maneouvre).

c. *Carotid sinus syncope*

Carotid sinus syncope occurs as a result of carotid sinus hypersensitivity manifesting as an exaggerated response to pressure applied to the carotid sinus. Conditions triggering such a reflex include turning of neck to one side, wearing a tight collar, or shaving the hair around the neck. Among susceptible individuals, activation of carotid sinus baroreceptors triggers exaggerated cardioinhibitory responses resulting in bradycardia and or exaggerated cardiodepressor responses resulting in vasodilation. Both responses result in decreased cardiac output and cerebral hypotension.

2. Orthostatic Syncope

Orthostatic syncope refers to transient loss of consciousness due to a postural decrease in blood pressure. Orthostatic syncope is precipitated by a sudden rise from a supine position. There is a failure of autonomic adjustment to the assumption of erect posturing. Upon assumption of erect posture, there is gravitation-induced venous pooling of blood to the extremities and splanchnic vascular system with a consequential fall in systolic blood pressure. This induces reflex normalization of the blood pressure. But in individuals with orthostatic syncope, blood pressure drops resulting in cerebral hypoperfusion and fainting spell. Factors associated with orthostatic syncope include antihypertensive drugs, vasodilators, peripheral neuropathy, pure autonomic failure, and decrease blood volume.

3. Cardiac syncope

Cardiac syncope refers to transient loss of consciousness as a result of sudden reduction of cardiac out primarily due to cardiovascular disorders. Pathophysiological mechanisms include obstruction to either left or right ventricular outflow, impaired left ventricular systolic or diastolic function, cardiac arrhythmias or massive pericardial effusion.

4. Neurologic syncope

Neurologic syncope occurs when neurological disorders cause transient loss of consciousness. It is usually associated with vertebrobasilar insufficiency. The vertebrobasilar arteries supply blood to the medulla, midbrain, cerebellum, and cerebral cortex. So, occlusion of these arteries results in inadequate blood flow through the posterior circulation of the brain, thereby causing cerebral hypoperfusion and fainting spells.

Pathophysiology of Postural Hypotension

Postural hypotension is defined as a fall of systolic blood pressure of at least 20 mm Hg and/ or of diastolic blood pressure of at least 10 mm Hg within 3 minutes of standing from supine position or head-up tilt to at least 60° on a tilt table. Physiologically, upon assumption of erect posture, there is the pooling of about 500-1000mls of blood to the veins of the legs and trunk. This transiently reduces venous return, cardiac output and blood pressure to activate cardiac autonomic responses aiming at restoring the blood pressure to normal. With decrease in blood pressure, information from the baroreceptors in the aortic arch and carotid sinuses send signals to activate sympathetic discharge to increase heart rate, myocardial contractility, increases vasomotor tone of the capacitance vessels and vasoconstriction. Simultaneous inhibition of parasympathetic discharge also increases heart rate and facilitates vasoconstriction, thereby increasing blood pressure. With prolonged standing, the renal responses consisting of the renin-angiotensin-aldosterone system is also activated resulting in sodium and water retention and increase circulating blood volume. Physiologically, this cardiac autonomic reflex results in an increase in heart rate by 10 to 20 beats per minute, and diastolic blood pressure by 5mmHg, but systolic blood pressure may not change significantly. In patients with impaired cardiac autonomic response, there is a decrease in blood pressure leading to persistent hypotension.

Pathophysiology of Heart Failure

Introduction

Heart failure is a condition in which the heart is not able to pump blood to maintain the metabolic demand of the body or is able to do so at a higher filling pressure. Aetiology of heart failure includes hypertension, coronary artery disease, valvular heart diseases, cardiomyopathy, endocarditis, myocarditis, arrhythmias, congenital heart disease, degenerative diseases and extracardiac disorders suchanemia, thyrotoxicosis, fluid overload, Beriberi, and Paget's disease.

Types of Heart Failure

A. Depending on the ventricle(s) involved;

Left Heart Failure: Inability of the left ventricle to pump blood into the systemic arteries, resulting in increased left ventricular end-diastolic pressure, left atrial pressure, pulmonary venous congestions, decrease tissue perfusion and culminating in cough, dyspnoea, orthopnoea, paroxysmal nocturnal dyspnoea. There is also a decrease in tissue perfusion resulting in hypoxaemia(Fig 5).

Right Heart Failure: Inability of the right ventricle to pump blood into the pulmonary arteries, resulting in increased right ventricular end-diastolic pressure, right atrial pressure, and systemic venous congestion culminating in pedal swelling, abdominal swelling, right upper abdominal pain, early satiety, prominent jugular venous pulsations(Fig 5).

Congestive Heart Failure: This is biventricular failure, resulting in both systemic and pulmonary venous congestion

B. Classification of Heart Failure based on phase of cardiac cycle involved;

1. ***Diastolic Failure***: Impairment of ventricular filling

2. ***Systolic Failure***: Impairment of ventricular contractility and ejection

Pathophysiological Mechanisms

1. Abnormality of the heart muscle, vessel or valve results in systolic dysfunction (impairment of ventricular ejection) and or diastolic dysfunction (impairment of ventricular relaxation and filling)
2. Pressure loaded or volume loaded ventricles
3. Impairment of Frank-Starling mechanisms
4. Ventricular hypertrophy and or dilatation
5. Altered gene expression resulting in re-expression of embryogenic forms of contractile protein.
6. Loss of myocyte, increase collagen deposit, fibrosis
7. Inflammation
8. Decrease in cardiac output and tissue perfusion
9. Stimulation of neurohormonal compensatory mechanisms to increase cardiac output;

i. Increase sympathetic adrenergic drive

ii. Decrease vagal discharge

iii. Stimulation of renin-angiotensin-aldosterone system

iv. Increase release of catecholamines

v. Increase antidiuretic hormones

vi. Release of nitric oxide

vii. Release of endothelin from the vascular bed

10. Increase of cardiac output at the expense of increasing impairment of myocardial contractility, vasoconstriction, increasing afterload, increasing heart rate, left ventricular hypertrophy and or dilatation.

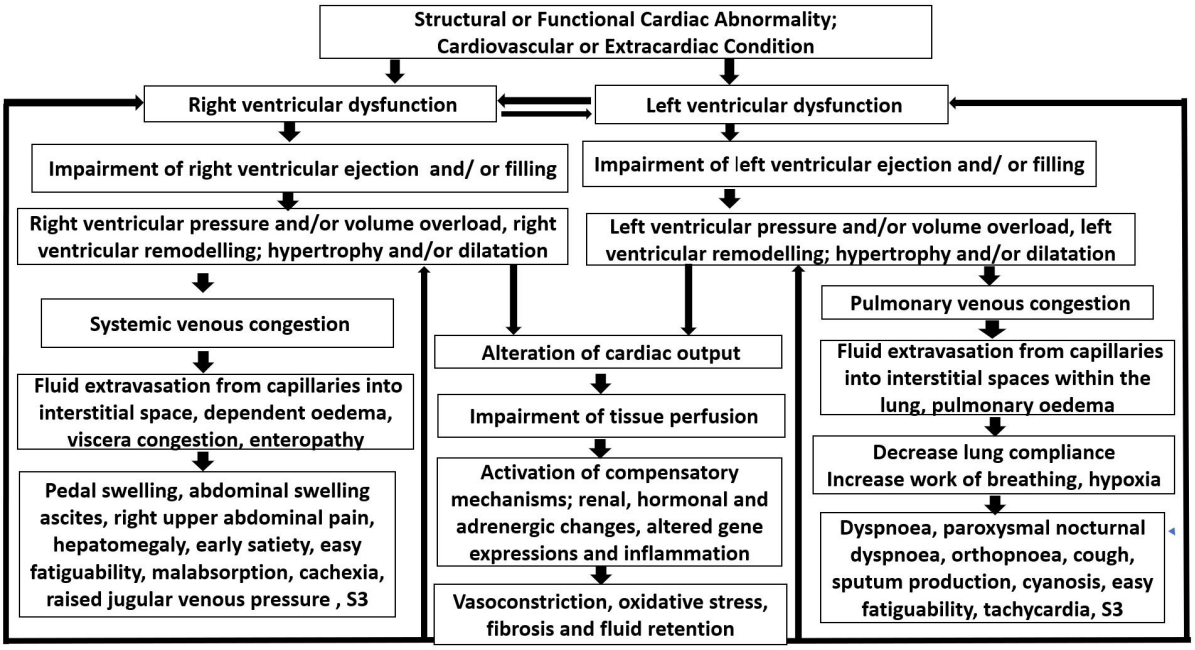


Fig. 11.4. Pathophysiolgy of Heart Failure

Pathophysiology of Hypertension

Hypertension is persistent elevation of systemic arterial pressure. Hypertension is a leading cause of death world worldwide. Hypertension results from interplay of many factors including genetics, diet, environmental and organ dysfunction. Hypertension is classified into two; primary hypertension and secondary hypertension. Primary hypertension is otherwise known as essential hypertension. It is the most common form of hypertension, responsible for 95% of cases among adults. The aetiology of primary hypertension is unknown but risk factors

include, excess salt intake, increasing age, genetic predisposition, intake of stimulants, smoking, sleep deprivation, obesity, and drug use and abuse. The causes of secondary hypertension are known. These include kidney diseases, endocrine disorders, cardiovascular diseases such as coarctation of aorta, and neurological disorders such as sleep apnoea syndrome and raised intracranial pressure. Blood Pressure is the product of cardiac output and peripheral vascular resistance. Hypertension results from an increase in cardiac output and or total peripheral vascular resistance (Fig. 6)

The cardiac output is a product of stroke volume and heart rate (Fig 6).

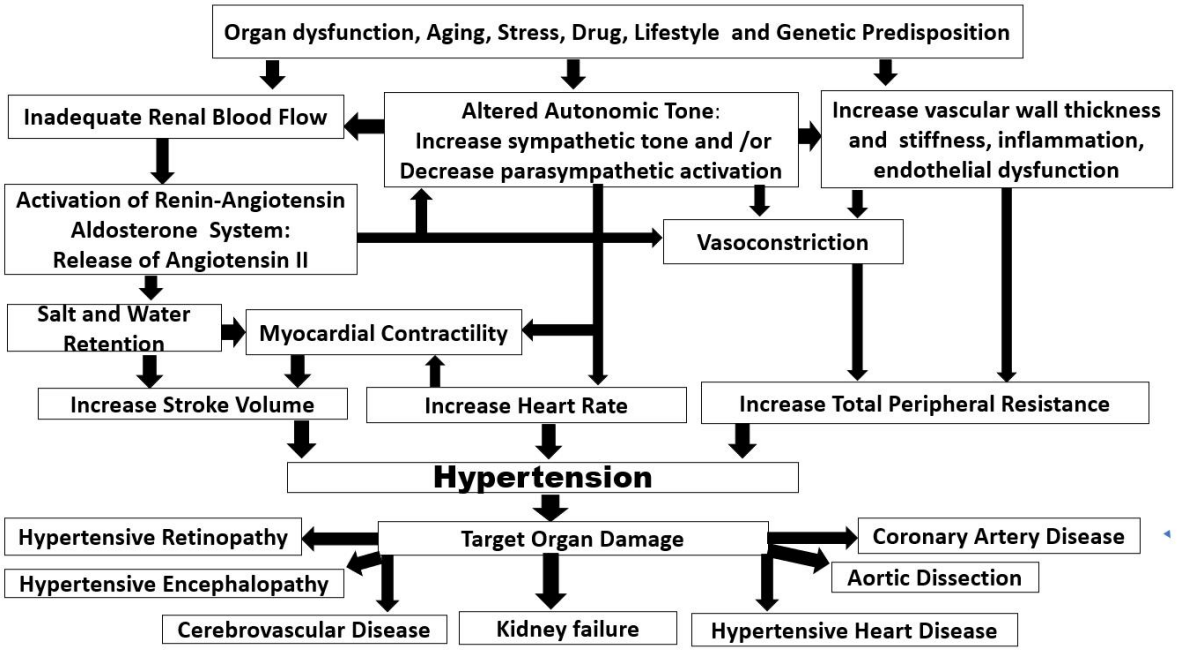


Fig. 11.5:. Pathophysiology of Hypertension

Pathophysiological Mechanisms for Hypertension

1. Altered autonomic tone: This is characterised by imbalance between sympathetic and parasympathetic tones. There is sympathetic overactivity and /or low parasympathetic activity resulting in vasoconstriction and total peripheral resistance. Sympathetic overdrive also contributes to increase heart rate and myocardial activity. Decrease blood flow to the kidney as a result of vascular narrowing also triggers renin-angiotensin-aldosterone system.

2. Renin-Angiotensin-aldosterone-system

A reduction in renal blood flow and/ or reduction in extracellular fluid results in release of renin from the juxtaglomerular apparatus of the kidney. Renin cleaves angiotensinogen (produced by the liver) to angiotensin I, thus triggering the classical and alternate pathways of renin-angiotensin-aldosterone system (RAAS) for blood volume and blood pressure regulation. Angiotensin Converting Enzyme (ACE) produced in the lung cleaves angiotensin I to angiotensin II in the classical pathway. On the other side, Angiotensin Converting Enzyme

2(ACE2) mainly produced by the endothelial cells of the heart and kidney metabolizes angiotensin I to angiotensin-(1-9), which in turn is converted to angiotensin-(1-7) by ACE. ACE2 also metabolizes angiotensin II to angiotensin-(1-7). Angiotensin II increases total peripheral vascular resistance by facilitating vasoconstriction. It stimulates adrenal cortex to release aldosterone, thereby promoting salt and water retention. Angiotensin II promotes release of antidiuretic hormone by the posterior pituitary, thereby decreasing water excretion by the kidney. It also promotes increase in sympathetic tone, fibrosis, thrombosis and myocardial hypertrophy. Angiotensin-(1-7) is a vasodilator. It is also anti-inflammatory and anti-proliferative, thereby modulating the effects of angiotensin II. An imbalance in this system, favouring persistent production of angiotensin II and or impairment of production of angiotensin-1-7) results in hypertension. This explains why some kidney diseases present with elevated blood pressure. It also explains while hypertension is a feature of affectation of the function of ACE2 in disease such as Corona Virus Disease 2019(COVID-19). The causative agent of COVID-19, Severe Acute Respiratory Syndrome Coronavirus-2(SARS Cov-2) which utilizes ACE2 receptor for its pathogenesis, thereby impairing its physiological role of regulating angiotensin II activity.

3. Increase Total Peripheral Resistance

Increase arterial wall thickness and stiffness due to smooth muscle hypertrophy, the aging process, metabolic derangement, oxidative stress, inflammation, and endothelial dysfunction increase total peripheral resistance. Other factors contributing to increased peripheral resistance include the release of vasoconstricting agents such as endothelin and a decrease in the availability of vasodilating agents such as nitric oxide.

Pathophysiology of Raynaud's Disease

Raynaud's phenomenon was first described by Maurice Raynaud in 1862 and later in 1930, the concept was also studied by Thomas Lewis. Raynaud's phenomenon is characterized by episodic vasospastic ischemia of the digits. Each episode is triggered by cold and emotional stress. It manifests with the reversible change of colour of the digits. The colour sequentially changes from white to blue and to red indicating phases of arteriolar spasm, reduced blood flow (cyanosis), and reactive arteriolar dilatation respectively. The idiopathic form is known as Raynaud's disease. In Raynaud's phenomenon or disease, cold or emotional stress triggers sympathetic nervous system activation and the release of vasoconstricting neuropeptides and norepinephrine leading to vasoconstriction of arteriolar smooth muscle and decreased blood flow to the skin of the digits. There is subsequent tissue ischaemia, reperfusion, and reactive hyperaemia. In severe form, trophic changes such as ulceration or gangrene may occur.

Pathophysiology of Pulmonary Embolism

Pulmonary embolism occurs when a thrombus formed in the systemic venous network or deep veins of the leg or pelvis or right side of the heart dislodges to block the pulmonary arterial network. The occlusion of the pulmonary vascular network is enabled because of the progressive narrowing of the vascular lumen from pulmonary arteries to the capillaries. Hence, an embolus that emanated from the deep veins in the leg or pelvic veins travels freely through the vena cava into the right atrium to get stuck at the pulmonary tree network. So also, an embolus generated from the clot in the right atrium can also get stuck within the pulmonary arteries or their branches.

The blockage of the pulmonary arterial system may not be restricted to an embolus but it could also be due to air bubbles, amniotic fluid, fat, tissue fragment, foreign body or tumour. Pulmonary embolism is a leading cause of cardiac arrest and sudden death. In the mid-19th century, Rudolph Virchow identified three risk factors for thrombosis. These are stasis of blood flow, vascular endothelial damage, and hypercoagulability. Blockage of pulmonary artery by large embolus results in hypoxaemia, right ventricular ischaemia, decrease preload to the left ventricle, decrease cardiac output and haemodynamic collapse or cardiac arrest. Blockage of small vessels results in hypoxaemia, reactive vasoconstriction and pulmonary hypertension culminating in right ventricular dilatation, tricuspid regurgitation and right ventricular failure. A decrease in right ventricular cardiac output reduces left ventricular preload leading to decrease in left ventricular output and decrease in systolic blood pressure. Occlusion of the pulmonary arteries results in hypoxaemia, pulmonary infarction and lung parenchymal inflammation. Hypoxaemia results in arrhythmia. Right ventricular failure is manifested with features of systemic venous congestion. In addition, with decrease cardiac output, the renin-angiotensin aldosterone system and other neurohormonal changes are triggered with resultant vasoconstriction and salt and water retention.

Pathophysiology of Pulmonary Oedema

Pulmonary oedema refers to the accumulation of fluid in the interstitium of the lung and or alveoli. It can be classified into cardiogenic or non-cardiogenic. Cardiogenic pulmonary oedema results from haemodynamic dysfunctions resulting from elevated pulmonary venous pressure and subsequent, capillary hydrostatic pressure. With elevated capillary hydrostatic pressure, fluid accumulates in the lung interstitium and later in the alveolar spaces (alveolar oedema) and in the pleural spaces (pleural effusion). There is ventilation-perfusion mismatch resulting in hypoxaemia. Causes of cardiogenic pulmonary oedema include hypertension, left ventricular failure, congestive heart failure and mitral stenosis. In non-cardiogenic pulmonary oedema, there is injury to the lung resulting in an increase capillary permeability despite normal capillary hydrostatic pressure. There is leakage of proteins into the lung interstitium. Increase oncotic pressure within the interstitium results in fluid accumulation within the interstitium and subsequent in the alveoli. Non-cardiogenic pulmonary oedema is associated with dysfunction of surfactant and increased intrapulmonary shunting resulting in hypoxaemia. There is inflammation, pulmonary fibrosis and decreased lung compliance. Causes of non-cardiogenic include sepsis and high altitude. Both cardiogenic and non-cardiogenic pulmonary oedema are characterised by dyspnoea, orthopnoea, cough and sputum production.

Pathophysiology of Pulmonary Hypertension

Pulmonary hypertension refers to elevation of pulmonary arterial pressure. It is diagnosed when the mean pulmonary arterial pressure ≥ 25mmHg at rest. It may be due to one or more of the following; left heart failure, mitral valve disease, pulmonary vascular, interstitial or parenchymal disease, thromboembolism and haemoglobinopathy. Genetic predisposition and drugs usage also play role in the occurrence of pulmonary hypertension.The development and progression of pulmonary hypertension involve interplay of two or more of pathophysiological mechanisms occurring within the pulmonary vascular network and/or within the lung parenchyma. These include chronic hypoxic vasoconstriction, vascular remodelling, vascular destruction, inflammation, progressive parenchymal fibrosis, perivascular fibrosis and thrombotic angiopathy. The outcome of these interplay is a persistent increase in pulmonary vascular resistance, elevation of pulmonary arterial pressure,

raised right ventricular afterload, tricuspid regurgitation, right ventricular dysfunction and ultimate right ventricular failure triggering neuroendocrine release, salt and water retention and systemic venous congestion.

Pathophysiology of Cor pulmonale

Cor pulmonale refers to right ventricular structural or functional abnormality due to primary pulmonary vascular disease and or lung parenchymal disease. The structural right ventricular abnormality includes right ventricular dilatation and or hypertrophy and the functional abnormality is right ventricular failure.

There are two forms of cor pulmonale; acute and chronic. The acute cor pulmonale occurs following a severe and strong insult to pulmonary vascular network resulting in rapid onset of ventricular dilatation and failure without ventricular hypertrophy. Chronic cor pulmonale occurs with slowly involving increase in pulmonary vascular resistance and progressive pulmonary hypertension culminating in right ventricular dilatation, hypertrophy and failure. Cause of chronic cor pulmonale include chronic obstructive airway disease,

Pathophysiological mechanisms in cor pulmonale includes; occlusion of pulmonary vasculature from massive embolus, pulmonary vascular smooth muscle proliferation, hypoxia induced-vasoconstriction. Release of vasoconstrictive mediators such as endothelin and decrease release of vasodilatory mediators such as nitric oxide. The interplay of the mechanisms play role in increase pulmonary vascular resistance culminating in right ventricular dilatation, hypertrophy and failure with resultant in systemic venous congestion and peripheral oedema. Carbon dioxide retention (hypercapnia) also contributes to vasodilation and peripheral oedema.

PATHOPHYSIOLOGY OF CEREBRAL BLOOD FLOW DISTURBANCE (STROKE)

Pathophysiology of Stroke

The central nervous system consists of the brain and the spinal cord. The brain is made up of different parts- the cerebrum, the cerebellum and the brain stem (medulla oblongota, the pons and the mid brain). Cerebral blood flow disturbances may come in different forms and for it to be considered as stroke it has to be of vascular origin, rapidly developing, focal or global in nature and may lead to death.

To understand the pathophysiology of stroke, it is very germane to first appreciate the cerebral blood flow.

Blood supply to the brain is via two pairs of major blood vessels (arteries): the carotid arteries and the vertebral arteries:
Carotid Arteries: This is divided into a right carotid and a left carotid arteries. The course of this vessels is along the anterior part of the neck.

Vertebral Arteries: These vessels run along the posterior part of the neck. It is divided into the right vertebral and a left vertebral artery. The right and left vertebral arteries join to form one basilar artery.

The circle of Willis is formed below the hypothalamus at the base of the brain from the basilar artery and the carotid artery which gives origin to the six large vessels supplying the cerebral cortex. This is a circle of arteries that provide many paths for blood to supply oxygen and nutrients to the brain. The branches from the circle of Willis supply different parts of the brain.

Some branches from the circle of Willis are affected by stroke.

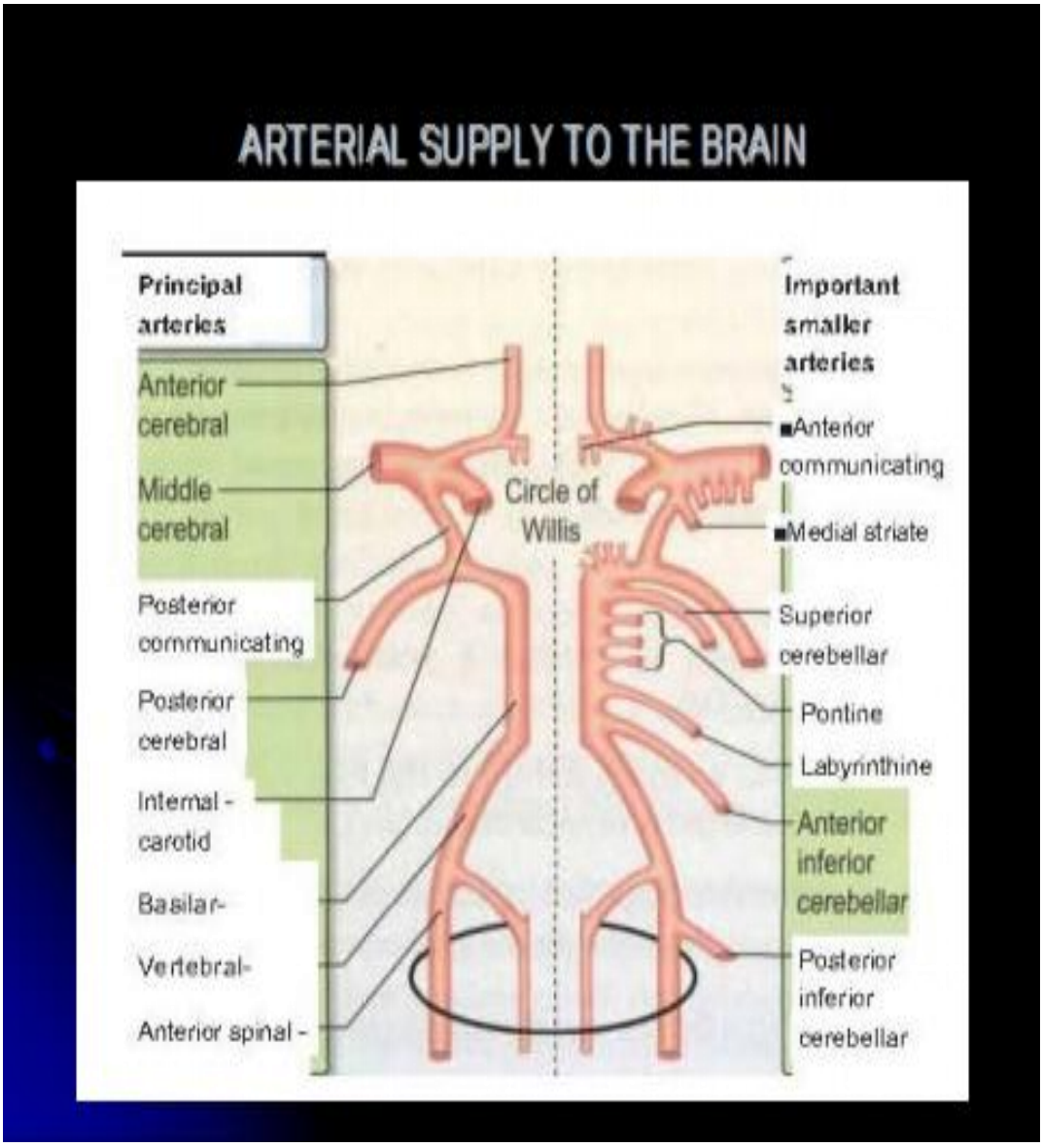


Figure 11.6: Arterial blood supply to the brain

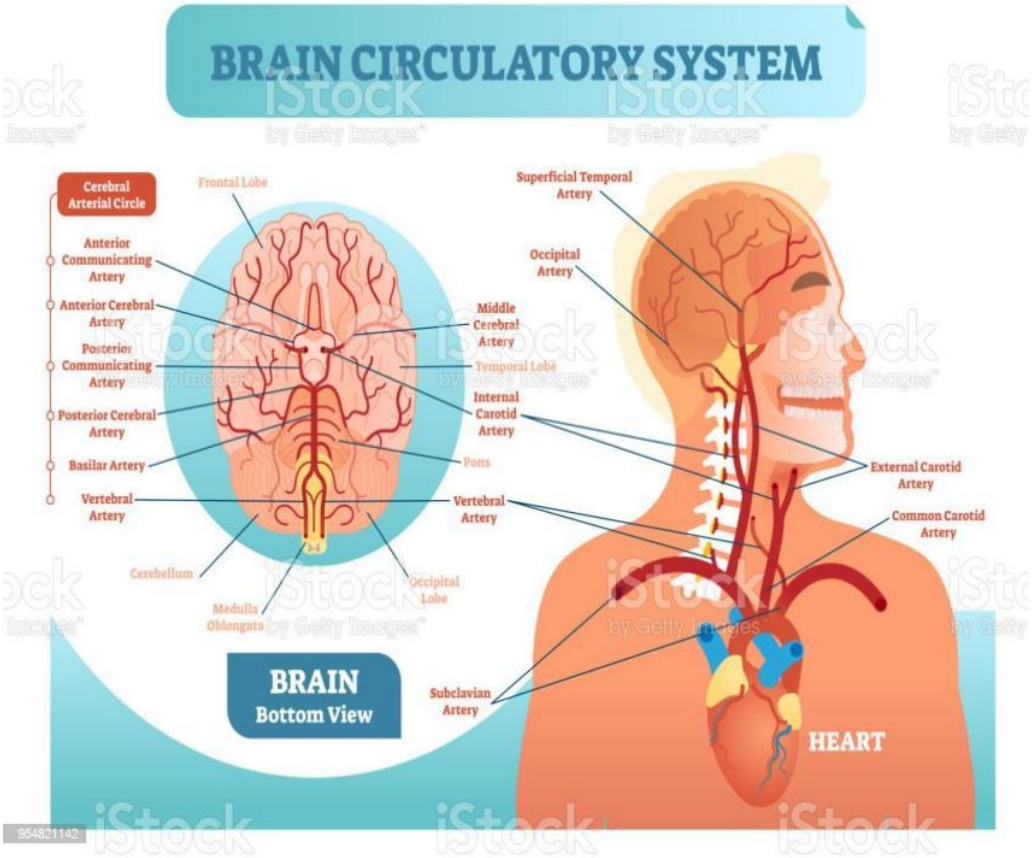


Figure 11.7: Brain circulatory system (Source: iStock 2018)

Anterior cerebral Artery (ACA)- This is the terminal branch of the internal carotid artery. It supplies a large portion of cerebral hemisphere (corpus callosum. frontal, parietal and cingulate cortex. Through the anterior communicating, it anastomoses with its contralateral counterpart. This anastomosis makes the anterior/rostral components of the circle of Willis which is the most important anastomosis between the cerebral vessels. There is a right sided ACA and a left sided ACA. If a stroke occurs in this area, individual may present with weakness of the leg and/or cognitive dysfunction. There could also be change in personality.

Middle Cerebral Artery (MCA): This is the largest branch and the second terminal branch of the internal carotid artery. It is the part of the circle of Willis that is within the brain, found between the frontal and temporal lobes through the lateral sulcus. It is the most common pathologically affected blood vessel in the brain hence called the 'artery of stroke'. It supplies most of the lateral aspect of the cerebral hemisphere and basal ganglia. The stroke from MCA is characterized by a large core of severe ischaemia and a relatively small penumbra.
There is a right sided MCA and a left sided MCA.
If a stroke occurs in this vessel, individual may present with:

- Hemiparesis or hemiplegia of the contralateral upper and lower limbs
- Hemiparesis or hemiplegia of the lower half of the contralateral face
- loss of sensation on the contralateral face, arm and leg.

- Blindness (either on the left or right side)
- Language problems, such as difficulty with forming words and sentences or difficulty with understanding what others are saying.
- Ataxia of contralateral extremities

Posterior Cerebral Arteries (PCA): This is a terminal branch of basilar artery. It supplies oxygenated blood mainly to the occipital lobe, the inferomedial surface of the temporal lobe, midbrain, thalamus and choroid plexus of the third and lateral ventricle. It anastamosis laterally on each side with posterior communicating artery. The main branches are anterior temporal artery, parietoocipital artery and calcarine artery
These vessels supply blood to the back of the brain. There is a right sided PCA and a left sided PCA.
If a stroke occurs in this area, one may present with:

- Headache
- Mild visual changes such as loss of vision, diplopia, inability to see half of vision
- Difficulty recognizing familiar faces

In the brain, no crossing over occurs in the two hemispheres of the cerebral cortex probably because of equal pressure on both sides. There is presence of anastomotic channel which help as alternative supply but generally insufficient to maintain the circulation and prevent infarction when a cerebral artery is occluded. The vessels are very thin, the veins have no valves and blood flow reduce by 15% in the erect posture. Variations in blood flow to the brain occur in sleep, wakefulness, talking and cognitive activities and different other activities.

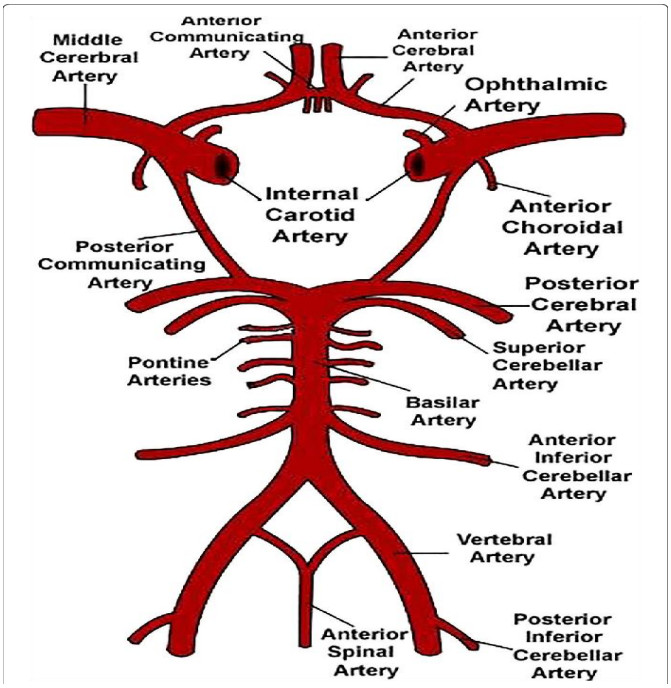


Figure 11.8: Circle of Wills (Source: Vrselja et al., 2014).

The causes of stroke are: cerebral infarction, intracerebral haemorrhage, subarachnoid haemorrhage, and cerebral embolism.

Stroke can be classified into

- Ischaemic Stroke - comprising thrombotic and embolic stroke. About 80% of all strokes are in this category
- Haemorrhagic Stroke – comprising intracerebral (intraparenchymal) and subarachnoid haemorrhage. About 15 – 20% of all cases.
- Cryptogenic stroke- that sums up 5% of cases It may be difficult to identify a definite cause .

The mechanisms by which stroke may occur is usual:

■ arterial embolism from a distant site (usually the carotid, vertebral or basilar arteries) and subsequent brain infarction

■ arterial thrombosis causing occlusion in atheromatous carotid, vertebral or cerebral artery with subsequent brain infarction

■ haemorrhage into the brain (intracerebral or subarachnoid).

Causes of Stroke

The causes of stroke include

- Thrombosis-in-situ (presence of thrombus at the site of vessel injury and or a site of disturbance of flow
- Heart emboli from atrial fibrillation, infective endocarditis, myocardial infarction
- Atherothromboembolism from the carotids
- CNS bleeding from elevated blood pressure,trauma, aneurysmal rupture
- Prosthetic valves,cardiac surgery
- Others - which may include sudden drop in blood pressure greater than 40mmHg, vasculitis, thrombophilia, venous sinus thrombosis

Risk Factors for Stroke

- High Blood pressure
- Smoking
- Obesity
- High cholesterol level/ hyperlipidaemia

- Diabetes mellitus
- Excessive alcohol intake
- Polycythemia
- Blood clotting abnormalities
- Sedentary lifestyle -poor diet, physical inactivity
- Age (> 65 yrs)
- Transient ischaemic attack
- Sickle cell disease
- Oral contraceptive pills/ Hormone replacement therapy
- Others- which include dehydration, congestive cardiac failure, severe anaemia, low Socio economic status, black race, male sex, positive family history. Hypothyroidism, Hyperuricaemia, Hypercoagulable states e.g. protein C or S deficiencies (natural substances in blood that help prevent blood clots)

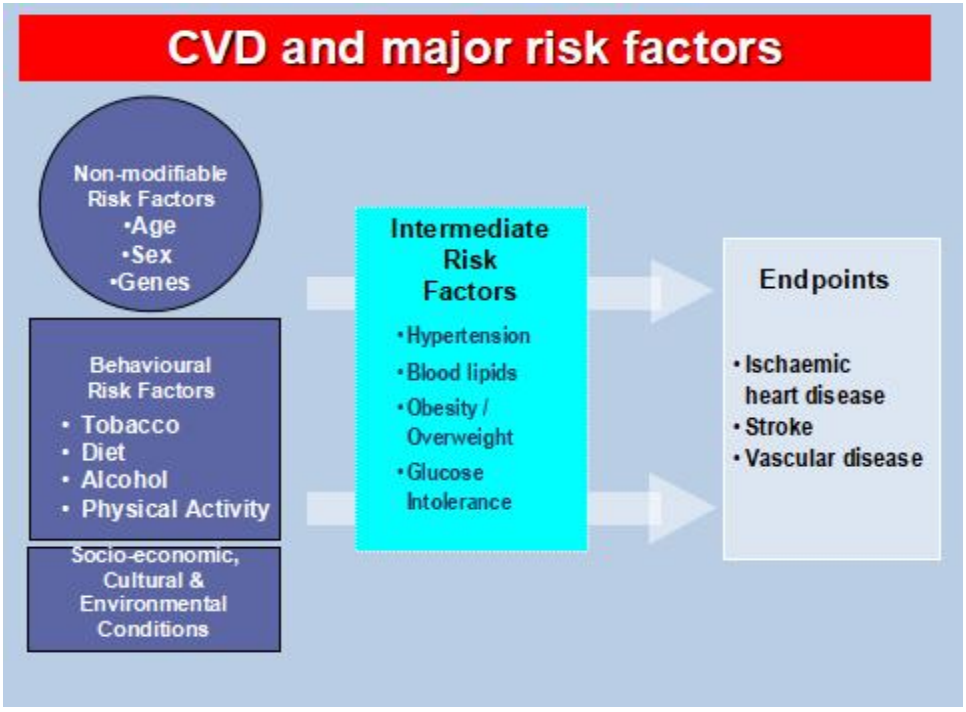


Figure 11.9: Risk Factors for Stroke

Stroke in the Young

There is an increasing incidences of stroke occurring in the young adults. Stroke occurring at age < 40 years. The possible aetiologies - mitral valvular prolapse, patent foramen ovale, fibromuscular dysplasia, migraine, cocaine use, oral contraceptive pills, haemoglobinopathy, carotid artery dissection (usually traumatic) etc.

Therapeutic strategies for stroke have been developed with two main aims: restoration of cerebral flow and the minimization of the deleterious effects of ischemia on neurons. The key to achieving this is a rapid assessment of brain attacks just like heart attacks and thrombolysis. Additionally, post-stroke management exerts a significant impact on families, the healthcare system and the economy. Emphasis should be placed on prevention, treatment, recovery and rehabilitation.

The manifestation of the neurological deficits in stroke is a function of the vessel involved and the part of the brain that is affected

PATHOPHYSIOLOGY OEDEMA AND LYMPHEDEMA

Pathophysiology of Oedema

Oedema simply means the abnormal accumulation of fluid in the interstitial spaces. The fluid in the intracellular and extracellular compartments of the body are in constant communication. Oedema results due to excess fluid accumulation in the body tissues, or an imbalance in the regulation of the distribution of the body fluids. It can occur in any part of the body but more frequently at the dependent parts of the body. The fluid is predominantly water, but protein and cell-rich fluid can accumulate in cases of infection or lymphatic obstruction.

Oedema may be

- Generalized also called Anasarca, which is an extreme generalized swelling of the body. It mostly results from systemic disorders.
- Localalized when it is limited to a single extremity or part of an extremity. Mostly results from local causes. It may result from deep vein thrombosis (DVT) or venous occlusion due to tumour.

It sometimes appears abruptly, which may be sudden but more often edema develops slowly, beginning with weight gain, puffy eyes at waking up in the morning, and tight shoes at the end of the day or after a long distance journey. Slowly developing edema may become massive if not attended to promptly.

The dynamics of edema shows it may results from increased movement of fluid from the intravascular to the interstitial space or decreased movement of water from the interstitium into the capillaries or lymphatic vessels. Any factor that may cause or hinder this movement will ultimately cause oedema.

An understanding of the mechanisms involved in fluid filtration and reabsorption explains the causes of oedema which may include one or more of the following

- Increased capillary hydrostatic pressure (filtration pressure)
- Decreased plasma oncotic pressure (osmotic reabsorption force)
- Increased capillary permeability
- Lymphatic obstruction

Increased capillary hydrostatic pressure - there is a difference in the intracapillary pressure at the arterial and venous ends. An increase in this pressure at the venous end impedes fluid reabsorption potential. This may result from venous outflow obstruction or impeded venous outflow as a result of increased blood pressure or heart failure. There are occasions where one leg becomes apparently bigger than the shoes after a long distance travel or sitting for a long time. The heart inability to generate enough pressure as in heart failure is also to be considered.

Decreased plasma oncotic pressure- Any condition that affects the concentration of protein in the body may cause oedema., Oedema also results from decreased movement of fluid out of the interstitial space into the capillaries due to lack of adequate plasma oncotic pressure or plasma osmotic pressure. These conditions are found in cases of nephrotic syndrome (increased loss of proteins through urine- proteinuria), protein-losing enteropathy, liver failure like in cirrhosis due to deficient synthesis of albumin which is essentially responsible for the oncotic pressure, starvation as in protein energy malnutrition (Kwasiokor).

Increased capillary permeability- Increased capillary permeability occurs in inflammations eg cellulitis and allergic reactions, or as the result of toxin that damage the capillary walls. In angioedema, mediators, including mast cell–derived mediators (eg, histamine, leukotrienes, prostaglandins) and bradykinin and complement-derived mediators, cause focal edema. The vasodilators increase capillary permeability and permits increased capillary filtration.

Lymphatic obstruction- The lymphatic system removes proteins and white blood cells from the interstitium. Lymphatic obstruction allow these substances to accumulate in the interstitium. The common cause of lymphatic obstruction is tropical worm *Wuchereria bancrofti* which usually cause swollen legs and scrotum (hydrocele - wheelbarrow scrotum). it may also be caused by malignant tumors, radiations, surgical obstruction or pregnancy that occlude the lymphatic drainage. Oedema caused by lymphatic obstruction is known as lymphoedema.

Oedema can also result from fluid overload, excessive salt intake or sodium retention. Myxoedema also called Graves' dermopathy of thyroid dermopathy is the swelling of the skin and underlying tissues giving a waxy consistency, results from excessive production of a particular glycoprotein (mucin) in the interstitial space caused by hypothyroidism.

The forces/factors regulating the ionic and fluid distribution may have effect on the direction of flow of fluids and then, oedema. The capillary hydrostatic pressure is about 10 mmHg while plasma oncortic pressure is about 25mmHg. The inward gradient of 15mmHg serves to keep fluids within the capillary space. At the arteriolar end, oncotic pressure is greater than capillary pressure and fluid moves into capillary spaces, while at the venular end hydrostatic pressure is greater and fluids moves into interstitial space. The fluids is returned back to the vascular space via the lymphatics.

Oncotic pressure is critically dependent on the plasma proteins, principally albumin; thus in chronic liver disease or nephrotic syndrome where there is decreased synthesis of plasma proteins and increased renal loss respectively, there is a fall in oncotic pressure and fluid shifts into the interstitial space creating oedema.

Thus, the inwardly directed gradient due to oncotic, hydrostatic pressure differences maintains vascular volume. The ECF volume is regulated by the Na^+ content and the kidney maintains homeostasis of this ion by varying the osmolality and volume of urine. The ICF/ECF ionic gradient is maintained by the Na^+-K^+ ATPase pump activity.

Certain red flag findings should prompt a more serious assessment of the etiology of edema.

- Sudden onset
- Pain
- Breathlessness or difficulty breathing
- Fever
- Previous history of a cardiac disorder or an abnormal findings on cardiac examination
- Haemoptysis, dyspnea, or pleural friction rub
- Hepatomegaly, jaundice, ascites, splenomegaly, or haematemesis
- Unilateral leg swelling with tenderness

The presence of oedema with these findings my be a guide to the organ that is affected. Oedema could be bilateral, unilateral, pitting or non pitting.

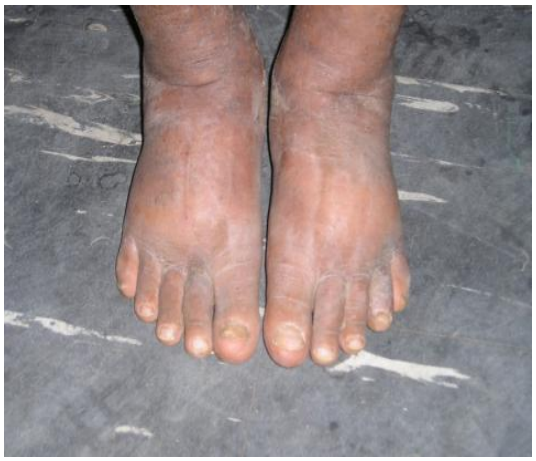


Figure 11.10: Bilateral Pedal Oedema (Nwangwa 2023)

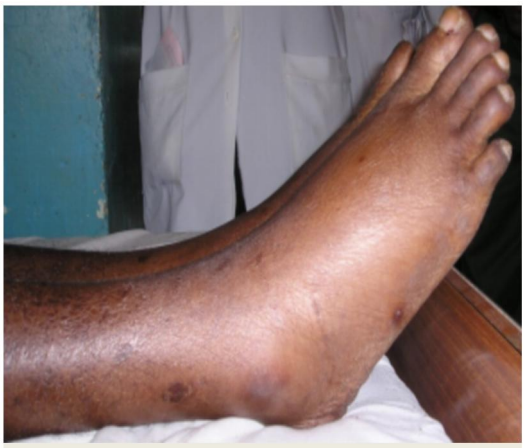


Figure 11.11: Unilateral pedal oedema (Nwangwa 2023

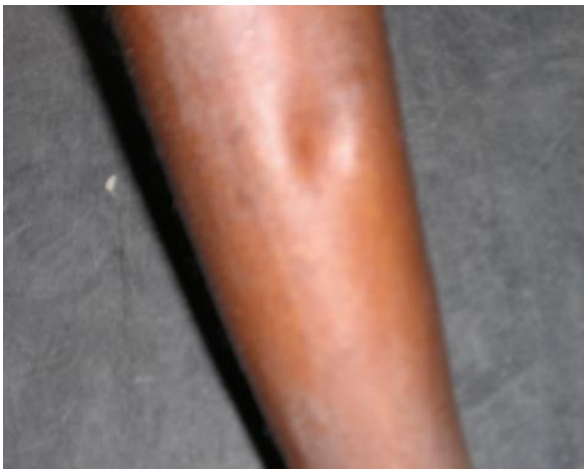


Figure 11.12: Pitting oedema (Nwangwa 2023

Lymphatic System

The lymphatic system is found in the same area as the capillaries and are blind-ended vessels with single layer of epithelium. The lymphatics come together to empty into the thoracic duct and right lymphatic duct both ultimately empty into the large veins (jugular and subclavian veins). Structurally, lymphatics are similar to veins having three walls- tunica interna, media and adventitia with nerve supply and numerous valves which ensures unidirectional flow. Along the lines of the lymphatic system are lymph nodes. Lymphatic vessels collect the small amount of plasma proteins that escape into the interstitial space and return them to the blood circulation via the thoracic duct.

Lymphatic capillaries are more porous compared to blood capillaries and allow the passage of particles as large as plasma proteins with great ease. They are absent in the bones, CNS, cartilage, teeth and placenta.

The forces that help in venous returns also help in lymphatic flow, which include:

- ✓ Pumping action of skeletal muscles (calf muscle nicknamed second heart)
- ✓ Intrathoracic pressure which is usually negative
- ✓ Rhythmic contraction of the smooth muscle walls of the lymphatics
- ✓ Suction effect of fast flowing venous blood

Functions of the lymphatic System

i. It is the means of transportation of long-chain fatty acids

ii. Returns filtered fluid by blood capillaries which were not completely reabsorbed back into circulation

iii. It is the pathway for some large enzymes such as lipases, histaminases secreted from cells into the interstitial fluid enter blood circulation

iv. The lymph nodes are sites of concentrated mononuclear-phagocytic cells which help to remove bacteria and foreign bodies from circulation. This is a protective function and is the reason for enlargement of lymph nodes as a sign of infection.

The lymphatic vessels transport lymph. The composition of lymph consist of white blood cells, bacteria, triglycerides, cell debris, water, and protein. It has a composition comparable to blood plasma.

Lymphoedema

This is the swelling of the arm or the leg as a result of the blockage of the lymphatic system.. it is most frequently caused by the removal of lymph nodes or damage due to cancer treatment.

Primary lymphoedema may be congenital or inherited condition which results in malformation of the lymphatics system, most often because of genetic mutation.
Primary lymphoedema - can be divided into

- ✓ Congenital lymphoedema- usually present at birth or recognized early, may be within first two years of birth
- ✓ Lymphoedema praecox- occur in puberty or third decade
- ✓ Lymphatic tarda- which begins around the mid 30s

Secondary Lymphoedema- results from injury, insult, or obstruction of the lymphatic system. most secondary lymphoedema cases are due to malignancy or related to the treatment of malignancy

What do you see in someone with lymphoedema?

- ✓ Oedema: which is more at the extremity
- ✓ Hyperkeratosis: thickened and scaly skin
- ✓ Lymphangioma: development of small blisters and bumps on the skin
- ✓ Lymphorrhea: lymph fluid leaks from the skin

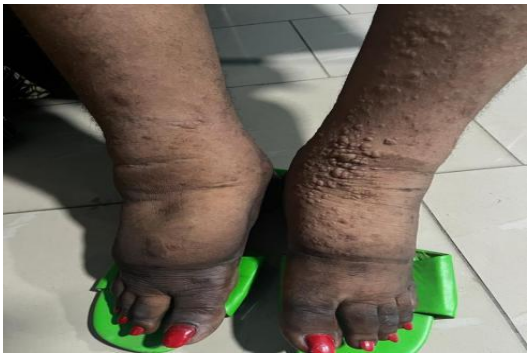


Figure 11.13: Lymphoedema (Nwangwa 2023)

RESPIRATORY PATHOPHYSIOLOGY

Respiratory Distress Syndrome

Respiratory Distress Syndrome (RDS) is also called Hyaline Membrane Disease in children. It is due to lack of surfactant.

Surfactant is a phospholipid, dipalmitoyl lecithin *(*dipalmitoylphosphatidylcholine*)* and other proteins and lipids. It is a detergent-like substance – reduces surface tension of fluid in the alveoli, thus reducing the force of expansion of the alveoli. Its production is facilitated by thyroid hormones and maturation by glucocorticoids. This is usually during the end of the third trimester of pregnancy. Prostaglandin is useful in the treatment of RDS, due to its maturation effect on surfactant.

Respiratory distress syndrome (Hyaline membrane disease) of newborn is usually seen in premature infants, usually with gestation of less than 37 weeks. Cigarette smoking results in decrease of surfactant and lung collapse is a consequence of reduced surfactant. Infants that died of RDS have characteristic hyaline membrane appearance of the lungs at post mortem.

Acute respiratory distress syndrome (ARDS) is a form of respiratory failure characterized by excessive leakiness of the respiratory membrane and severe hypoxia. It is seen in near-drowning, aspiration of acidic gastric juice, drug reaction and allergic reactions, inhalation of irritant gases, lung infection and pulmonary hypertension.

Pneumothorax, haemothorax and hydrothorax

The pleural cavities are sealed off, preventing them from equalizing their pressure with that of the atmosphere. Chest wall injury can result in air entry into the intrapleural space, either from outside or from the alveoli. Air in the intrapleural space is called pneumothorax, and can give rise to tension in the intrapleural space. The tension can be great enough to result in lung collapse.

Haemothorax is collection of blood in the intrapleural space, in which the haematocrit of the fluid is more than 50% of the peripheral haematocrit of the individual. It is usually due to trauma or occasionally due to coagulation defect or rupture of the aorta or the pulmonary artery. Presence of large amount of fluid in the pleura cavity can lead to lung compression and atelectasis.

Hydrothorax is a non-inflammatory collection of serous fluid within the pleural cavities. It may be unilateral or bilateral. It may be caused by heart failure, renal failure and liver cirrhosis. The effect is to compromise lung function and cause hypoxia.

Bronchial asthma

Asthma is a diffuse airway disease caused by chronic airway inflammation, hypersensitivity to a variety of stimuli and airway obstruction which is partially reversible. The airway obstruction may be due to airway smooth muscle spasm, excessive mucus production in the airway or oedema of the mucosa of the airways. Epithelial damage may also be responsible for the increased airway resistance. It is more common in children than in adults.

Majority of those who suffer from asthma react to low levels of agents that do not normally affect normal people. The trigger is usually an allergen such as pollen, food, house dust mite or molds. Cigarette smoke inhalation, exercise or cold air may be the trigger in some people. Characteristic changes, like fibrosis and necrosis, occur in the lungs and airways after some time.

The consequence of bronchial and bronchiolar constriction is increased resistance to airflow in the airways. The airway resistance is more during expiration than during inspiration. Periodic attacks occur in sufferers, and relief can be effected by bronchodilation using appropriate bronchodilators.

Hypoxia

Hypoxia is reduced oxygen tension at the tissue level. There are typically four types of hypoxia. **Hypoxic hypoxia** occurring in low oxygen tension environment, airway obstruction, lung collapse, increased anatomic dead space or in situations where the diffusion of oxygen into the blood from the alveoli is impeded. **Anaemic hypoxia** occurs in situations of low oxygen-carrying capacity of the blood (all forms of anaemia) and in carbon monoxide (CO) poisoning, in which case, the proper oxygenation of haemoglobin is inhibited by competitive attachment of CO to haem. In **Stagnant hypoxia**, blood flow to the tissues is impeded, causing reduction in the amount of O_2 being delivered to the tissues. This is typically seen in heart failure. In **Histotoxic hypoxia**, mechanism for the transfer of O_2 from the blood to the tissue is inhibited. Poisoning by cyanide can rapidly cause death due to histotoxic hypoxia. The blood of those dying of histotoxic hypoxia appears cherry red due to full oxygenation of the blood.

Cyanosis

Cyanosis is a bluish discolouration of the skin and mucous membranes due to increased arterial deoxyhaemoglobin level (>5g/dL). Central cyanosis is seen in cardiac and lung diseases which reduce proper blood circulation and arterial blood oxygenation. In Peripheral cyanosis, blood circulation to the extremities is reduced. It is typically seen in the hands and feet of people with arterial vasoconstriction due to cold exposure. Cyanosis is not seen in patients with anaemia, as the condition would have resulted in death before the deoxyhaemoglobin level could be more than 5mg/dL. Cyanosis is usually due to diseases of heart and/or lungs. Congestive heart failure, chronic obstructive airway disease and asthma may lead to chronic cyanosis with evident clubbing of the digits, especially the fingers.

Ondine's curse, pathophysiology of respiratory acidosis. Pathophysiology of tachypnoea, apnoea and asphyxia. Pathophysiology of cough and sneezing, hiccup and yawning

~~**Professor Salisu Ahmed Ibrahim**~~

Ondine's Curse

Ondine's curse is a rare and severe form of central sleep apnea syndrome caused by lack of automatic control of respiration during sleep. It is associated with a serious deficit in central respiratory control during sleep, while voluntary control of breathing is usually unaffected. Once afflicted by Ondine's curse, the victim cannot breathe if he falls asleep. Therefore must choose between sleeping and remaining alive. Respiratory chemosensitivities to

O_2 and CO_2 are also markedly reduced or absent. Those with the syndrome, usually hypoventilate resulting in a shortage of oxygen and a buildup of carbon dioxide in the blood. It is genetic in origin but can also occur as a result tumor infiltration of the brain stem. The patient lost automatic control of his respiration at night and became increasingly hypoxemic and hypercapnic. Despite advances in diagnosis, treatment of Ondine's curse continues to rely on respiratory support, with mechanical ventilation, and sometimes tracheostomy.

Respiratory Acidosis

Respiratory acidosis typically occurs due to failure of ventilation and accumulation of carbon dioxide. The primary disturbance is an elevated arterial partial pressure of carbon dioxide (pCO2) and a decreased ratio of arterial bicarbonate to arterial pCO2, which results in a decrease in the pH of the blood. Respiratory acidosis can be acute or chronic; the chronic form is asymptomatic, but the acute form causes headache, confusion, drowsiness and tremors. Causes of respiratory acidosis include; Severe diarrhea and vomiting, lactic acidosis, asthma, pulmonary fibrosis, scoliosis, muscular dystrophies etc.

Tachypnoea

Tachypnea is an increase in respiratory rate manifesting as a rapid and shallow breathing that results from a lack of oxygen or too much carbon dioxide in the body. It is the appropriate response to increasing carbon dioxide production in the body. Tachypnea can be a symptom of sepsis or acidosis, such as diabetic ketoacidosis or metabolic acidosis. Patients with lung problems such as pneumonia, pleural effusion, pulmonary embolism, COPD, asthma, or an allergic reaction also present with tachypnea.

Apnoea

Apnoea is the temporary cessation of breathing. Apnea can be **central or obstructive**. The most common of these is obstructive sleep apnea (OSA). Symptoms of apnoea include; excessive daytime sleepiness, loud snoring, observed episodes of stopped breathing during sleep, abrupt awakenings accompanied by gasping or choking, awakening with a dry mouth or sore throat, morning headache and difficulty in concentration during the day. Central sleep apnea occurs because the brain does not send proper signals to the muscles that control breathing, but in obstructive sleep apnea, the person cannot breathe normally because of upper airway obstruction. Central sleep apnea is less common than obstructive sleep apnea. A test to detect sleep apnea is called Nocturnal Polysomnography. During this test, the equipment monitors the functions of the heart, lung and brain activity, breathing patterns, arm and leg movements, and blood oxygen levels while the patient is asleep. Treatment is by a breathing device, such as a CPAP machine, which provides constant air pressure in the throat to keep the airway open when person breaths in.

Asphyxia

Asphyxia is a breathing impairment that occurs when there is insufficient oxygen in the body which results in decreased delivery of oxygen to the brain and other vital organs. Asphyxia can result from drowning, asthma, choking, strangulation, seizure, drug overdose, or inhaling chemical substances. Asphyxiation can lead to loss of consciousness, brain injury, and death. Symptoms of asphyxia include; difficulty of breathing, bradycadia, hoarseness of breath sound, confusion and loss of consciousness.

Cough

Cough is defined as a reflex action of the respiratory tract that is used to clear the upper airways. The reflex occurs as a result of chemical irritation of the peripheral nerve receptors within the trachea, bronchi and more distal smaller airways. These receptors respond to both mechanical and chemical stimuli, thereby making the

airways cleared. Cough involves three-step processes; first is inhalation of air, which is followed by the closure of the epiglottis as the chest constricts, thereby compressing the air within the lungs. Third, the epiglottis opens, and allows the expulsion of air through the mouth. Cough occurs as a result of exposure to cigarette smoke, environmental pollutants especially particulate matters and various diseases such as asthma, gastro-esophageal reflux disease, chronic pulmonary diseases and pulmonary fibrosis.
Effect control of cough requires not only controlling the disease causing it but also desensitization of cough pathways.

Sneezing
Sneeze is a coordinated protective respiratory reflex which arises due to stimulation of the upper respiratory tract, particularly the nasal cavity. Actually, activation of the central and peripheral nervous system plays a major role in the pathophysiology of this process.

Yawning
Yawning is a semi-voluntary action and partly a reflex controlled by neurotransmitters in the hypothalamus of the brain. It is also associated with increased levels of neurotransmitters, neuropeptide proteins and certain hormones. Yawning helps us bring more oxygen into the blood and move more carbon dioxide out of the blood. Watery eyes can occur when yawning pulls on and stimulates the lacrimal glands, which produces tears. In some cases, the eyes may also be dry from fatigue, causing them to tear off. Yawning can be spontaneous when it occurs on its own or contagious as a result of seeing someone else doing it as part of humans natural empathic response. Typically, yawning is a response to fatigue or lack of stimulation and serves a social function to communicate boredom or fatigue. The brain needs oxygen to function properly and when it does not get sufficient oxygen in conditions such as when we feel drowsy or sleepy, yawning helps to gather a large amount of oxygen for the brain, to help it function faster and control drowsiness.Yawning helps the body to wake itself up. The motion helps stretch the lungs and tissues, and allows the body to flex its muscles and joints. It also forces blood toward your face and brain to increase alertness. Trying to stifle those involuntary stretches only makes the urge to yawn even stronger.

Hiccups
A hiccup occurs due to an involuntary, intermittent, spasmodic contraction of the diaphragm and intercostal muscles. This causes sudden inspiration that ends with abrupt closure of the glottis, generating the “hic” sound. The left hemidiaphragm is involved in approximately 80 percent of cases. Common causes of hiccup include; eating too much or too quickly, feeling nervous or excited, carbonated beverages or too much alcohol and physical Stress. The hiccup reflex consists of the afferent limb that travels through either the phrenic, vagus or the thoracic sympathetic fibres to the spinal cord and then back to the diaphragm through the efferent limb of the phrenic nerve. Treatment of hiccup include; breathing in and holding the breath for about 10 seconds, then inhaling two more times before exhaling, breathing into a paper bag but taking care not to cover the head with the bag or bringing the knees to the chest and hugging them. Drugs used to treat long-term hiccups include baclofen, chlorpromazine and metoclopramide.

Summary
Pathophysiology is the study of abnormal functions in the body and the physiological processes that occur because of injury or disease. A knowledge of pathophysiology is critical to medical practice. Cellular stress response refers to the range of molecular changes that cells undergo in response to environmental stressors including temperature extremes, toxin exposure and mechanical damage.

Cell death has many forms and shapes. Forms of cell death include necrosis, apoptosis and autophagic cell death. When exposed to injurious stimuli or stress, cell injury occurs due to its inability to maintain homeostasis, cannot adapt to stressful stimuli. Common causes of cell injury include oxygen depletion, nutritional imbalance, work overload, physical agents, infectious microbes, chemical, genetic factors and aging. There are two types of injury: reversible and irreversible injury. Cell death occurs when a cell's capacity to maintain or restore homeostasis is over whelmed. The morphologic features of cellular death depends on passage of time, type of death(necrosis or apoptosis) and type of cell or tissue. Types of necrosis include liquefactive necrosis, caseous necrosis, fat necrosis, fibrinoid and coagulative necrosis. Mechanisms of apoptosis include caspases, mitochondrial pathway, extrinsic pathway and combination of intrinsic and pathways(execution phase). Cellular senescence is a stable state of cell cycle arrest that occur in stressful challenges and development signals. Senescent cells exhibit morphological changes,altered gene expression and secretion of many factors called senescence-associated secretory phenotype, which is responsible for the paracrine effects of senescent cells.Senescence processes happen in physiological and pathological conditions. Its beneficial effects include roles in embryogenesis, tissue repair, and tissue remodeling.Cellular senescence also has deleterious effects such as cellular aging,age-related diseases, hindrance of tissue repair.Aging is a complex, universal biological processes that affect all species at varying rates and intensity. Many theories have proposed to explain the many varied processes involved in aging. Hallmarks of aging include genome instability, telomere attrition, epigentic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication. Aging affects every part of the body such as the skin, muscles, nervous system, special senses and motor activity. Pathophysiologic mechanisms of a few of the problems with the airways and lung homeostatic abnormalities have been discussed in this sub-section of the chapter

Exercises

1. What do you understand by the following terms pathophysiology and pathogenesis?
2. Define risk factors. How do they affect the onset of disease?
3. Classify the various possible causes disease
4. What is the importance of clinical diagnosis and what are the available types of therapy?
5. Define aetiology and disease prognosis
6. Define cellular stress what are potential stressors to a cell?
7. Describe the mechanisms of cellular death
8. Differentiate between necrosis, apoptosis and autophagic cell death
9. Mention the factors that cause cell injury
10. State two conditions that make a cell vulnerable to injury.
11. Describe the features of reversible injury
12. Describe the features of irreversible injury

13. Briefly explain the general mechanism of cell injury.
14. What is cellular death?
15. State the two main types of cellular death
16. Outline the mechanisms of apoptosis
17. Explain 5 types of necrosis.
18. What is cellular senescence?
19. State five trigger factors of cellular senescence
20. Mention beneficial effects of senescence
21. State the deleterious effects of cellular senescence
22. Define aging
23. Describe 5 theoretical frameworks of aging
24. Explain 7 hallmarks of aging
25. Describe 4 structural and functional changes associated with aging
26. Write a short note on the pathophysiology of palpitation,
27. State the pathophysiological mechanisms of cardiac arrhythmia,
28. Describe the pathophysiology of heart block,
29. Discuss the pathophysiology of ischaemic heart disease
30. Describe the pathophysiology of murmurs,
31. Highlight the pathophysiology of types of syncope,
32. Describe the pathophysiology of postural hypotension.
33. Write a short note on the pathophysiology of heart failure
34. With the aid of an annotated diagram, describe the pathophysiology of hypertension
35. Describe the pathophysiology of Raynaud's disease
36. Write a short note on the pathophysiology of pulmonary oedema
37. Discuss the pathophysiology of pulmonary hypertension
38. Describe the pathophysiology of cor pulmonale

39. Describe the arteries that form the circle of Willis?
40. What are the peculiarities of cerebral circulation?
41. What are the common presentations of stroke?
42. Discuss the causes of oedema?
43. What are the factors responsible for the movement of fluids in the body compartments?
44. What is lymphoedema?
45. What is the physiological role of lymphatic system?
46. What are the causes of lymphoedema.?
47. Describe the functions of the airways
48. Write short notes on the pathophysiologic mechanisms that interplay in the following:
    a. Respiratory Distress Syndrome (RDS)
    b. Haemothorax, hydrothorax and pneumothorax
    c. Bronchial asthma
    d. Hypoxia
    e. Cyanosis

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Chapter 12

PHS 307 LABORATORY TECHNIQUES AND INSTRUMENTATION

Maisaratu A. Tukur, Ahmed I. Salisu , Adesoji A. Fasanmade, Alhassan Abdulwahab, Aliyu Mohammed, Samuel O. Odeh, Victor D. Dapper, Fortune S. Amah-Tariah

Overview: The goal is to introduce the students to specialized tools, set of equipment and techniques to systematically conduct blood experiments. The student is expected to be analytical, preparative and interpretive in the use of various techniques that include pipetting, colorimetric, chromatography, spectroscopy, microscopy, flow cytometry and immunoassays. These techniques measures cells, DNA, proteins and other biological characteristics in blood. Careful adherence to the protocol of each technique will enhance precision, accuracy and reliability of experimental results.

Objectives of Instrumentation for Blood and Body Fluids

The basic objectives of Instrumentation for Blood and Body Fluids are for:

i. Information generation
ii. Diagnosis
iii. Monitoring
iv. Evaluation
v. Control

Instrumentation for Blood and Body Fluids

It is concern with measurement of blood properties or phenomena as well as the recording, storage and analysis of the blood variables and parameters. Typical blood instrumentation system can be mechanical, automated or a hybrid. The principle of operations of blood instrumentation are unique in certain circumstances and in many instances relied on widely used physical measurements. The design or specification of blood or biomedical instrumentation systems take into consideration the range, sensitivity, linearity, hysteresis, frequency response and accuracy. Other factors worthy of note in the design of bioinstrumentation are simplicity, isolation and signal to noise ratio.

Components of Instrumentation for Blood and Body Fluids

The Instrumentation system comprised of:

i. **Source of Experimentation**
The human body or animal serve as source of energy for experimentation (*in vivo, in vitro and ex vivo*)
ii. **Sensors**
These sensors detect physiological signals such as haemoglobin content, blood volume, size of blood, nuclea content, nuclea lobulation, cell width etc.
Transducer

It converts biologic responses to electrical signal

iii. **Signal modification**

The electrical output generated by the transducer is modified or amplified in this section to prepare signals suitable for operation of the instrumentation system.

iv. **Display output**

The instrumentation system communicate with humans through visual or audible display such as graph, chart, sound, images, digital number or a combination of the above.

Haematological Parameters

S/No	**Variable**	**Abbreviation**	Unit	Symbol
1	Red blood cell count	RBC	number × 10^{12}l	
2	White blood cell count	WBC	number × 10^{9}l	
3	Haemoglobin concentration	HB	Grams/l or grams/deciliter or mmoles/l	g/l
4	Haematocrit	Hct	litre/litre	l/l
5	Packed cell volume	PCV	litre/litre	l/l
6	Mean cell volume	MCV	femtolitre	Fl
7	Mean cell haemoglobin	MCH	Pictograms OR femtomoles	Pg or fm
8	Mean cell haemoglobin concentration	MCHC	grams/litre OR grams/deciliter or millimoles per litre	g/l or g/dl or mmol/l
9	Platelet count	Plt l	number × 10^{9}l	
11	Mean platelet volume	MPV	Femtolitre	Fl
12	Plateletcrit	Pct	litre/litre	l/l
13	Reticulocyte count	Retic	number × 10^{9}l	
14	Erythrocyte sedimentation rate Westergren	ESR	millimitres mm	**mm/hr**

Table 12.1: Haematological parameters

The Principle of Operation of the Blood Analyzers

The automated blood counters largely operates on the following principle or in combination to accurately evaluate the different blood cells.

1. **Electrical Impedance (Coulter)**

The electrical impedance technique size and count blood cells suspended in an appropriate diluent. It works on the assumption that the blood cells are poor conductors of electricity when compared to the diluting fluid. As the diluted blood pass through a very narrow aperture of known size with electrodes on either side, they temporarily block the path of the electrical current and cause a drop in electrical conductance (resistance) which is proportional to the size of the particle.

The automated counter approximate the haemoglobin content by optical density at 525 nm after a reaction time of 20–25 seconds. The MCH is derived from the Heamoglobin and the Red Blood Cells. The Mean cell haemoglobin concentration MCHC is derived from the Hb, RBC and MCV. The variation in size of red cells is indicated by the red cell distribution width (RDW), which is the SD of individual measurements of red cell volume. The equivalent platelet variable is the platelet distribution width (PDW).

Packed cell volume/haematocrit is computed from the number and size of electrical impulses generated by red cells passing through a sensor in automated blood analyser.

The electrical Impedance technology does not allow for differentiation of granulocytes subtypes but can deliver a three-part WBC differential, where cells are grouped into three sizes: lymphocytes, mid-range cells and granulocytes

2. **Radio frequency conductivity**

High radio frequency signals are allowed to penetrate the cell of interest usually the white blood cells. The variation in internal structures, cytoplasmic density and the nuclear content of the different white cells are monitored and evaluated. This allows the machine to discriminate and count the five different white cells. It has an advantage over the electrical impedance principle that categorize leucocytes into three forms.

3. **Optical Flow Cytometry**

The light scatter cytometry is an optical to electronic coupling system that helps in recording how a cell scatters incident light and emits fluorescence. A beam of laser light is allowed to pass through a stream of diluted blood which cause scattering of the focused light into different directions. The scattered light are detected by photodetectors which convert the signal into an electric pulse and transmit it to a computer for analysis and storage. The signals generated will be used for evaluation of cell size, internal complexity, nuclear lobularity/ segmentation and cytoplasmic granularity to identify cell types. Cells with similar light scatter properties form a cluster in the scattergram, and can be separated from other cell clusters using advanced software algorithms. Some analyzers only use two angles of light, whereas others use multi-angle optical scatter analysis.

4. Cytochemistry and
5. Fluorescence

Flow cytometry is an optical to electronic coupling system device that helps in recording how a cell scatters incident light and emits fluorescence. It's a technique used to measure and detect physical and chemical characteristics of a population of cells or particles which is suspended in a fluid and injected in the flow cytometer instrument.

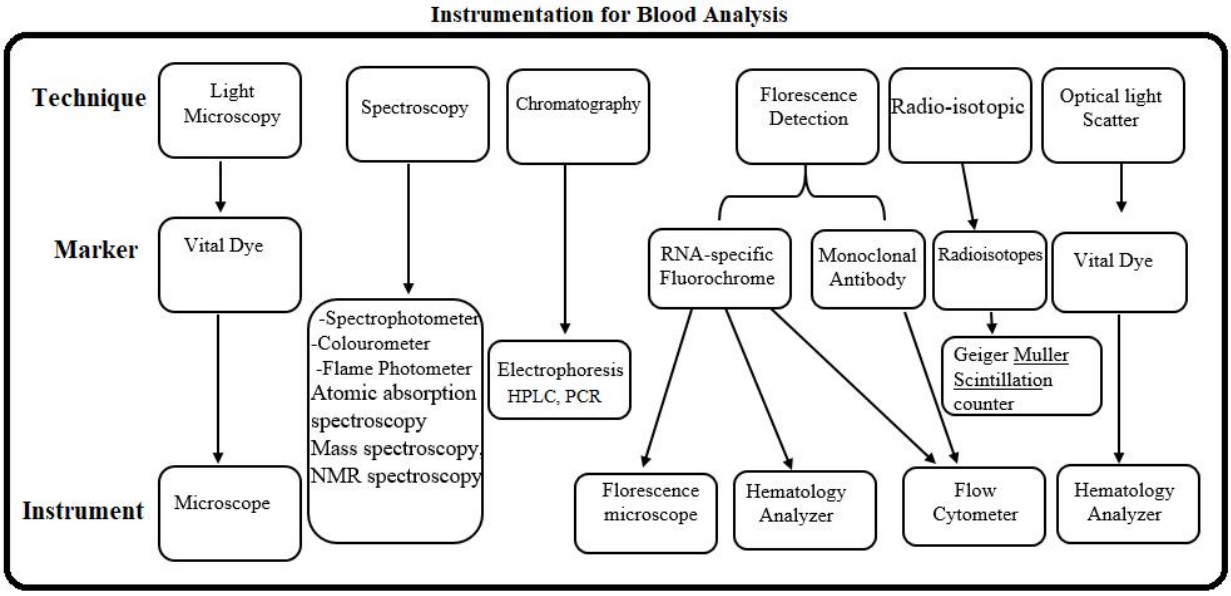

Figure 12.1: Instrumentation for blood analysis.

Biosafety Techniques

The purpose is to provide standard safety guide for efficient learning and effective working condition to limit health risk, prevent infection and adequately respond to incidents associated with handling of human samples. It involves the use of standard laboratory practices and procedures, safety equipment and laboratory facilities.

Biohazards in the laboratory emanate from infectious organisms (bacteria, viruses-HIV/AIDS, hepatitis-B and C, fungi, parasites, blood, cells, body fluid, saliva, sweat, tears, milk, cerebrospinal fluid, synovial fluid, pericardial fluid, amniotic fluid, peritoneal fluid, semen, vaginal secretions and tissues), urine, toxins, synthetic nucleic acid, recombinant and genetically modified organisms.

Biosafety Practices and Procedures in the Laboratory

The most common protocol to ensure biosafety and biosecurity in the laboratory is to eliminate routes of entry of contaminants through personal protective equipment of the face, eyes, body, hands and respiration.

Hand wash

Thorough hand washing protects self and others against contamination and minimize spread of infectious agents in the laboratory.

Always wash hand:

i. after removal of hand gloves

ii. before exit from the laboratory
iii. contact with contaminated or infection-risk agent

Procedure for hand washing

i. use soap and cold or warm water
ii. rub to foam lather for 15-30 seconds
iii. scrub the finger webs, cuticle beds, back of hands, wrist and palm
iv. rinse and dry the hand .
v. close water faucet with paper towel

Make sure that the hand sanitizer contain at least 60% alcohol (Isopropanol or ethanol). Use sufficient quantity as recommended by manufacturer. Continuously rub until dry completely. Once is water is available, wash with soap and water.

Hand Sanitizers

Absence of water and soap may warrant the use of waterless hand sanitizers as a temporary measure to reduce contamination.

NOTE: Hand sanitizers are NOT efficient replacement for hand washing with soap.

Eye Washes

Functional facilities for eye washes must be maintained for emergency eye washes. A good eye wash should spray stream of warm and clear water at reasonable pressure sufficient to reach the eye and flush the eye for at least 15 minutes.

Laboratory Coats

Properly worn white laboratory coat reduces the route of entry of contaminants and improve safety in the laboratory. It covers the exposed skin. Cover shoe should be used and not sandals or open toed shoe.

Hand gloves

Disposable hand gloves must be worn before handling contaminating or infectious materials. The glove should be resistant to fluid, powder free, right size, free of breaks or tears.

Always remove hand glove before you leave the laboratory. Do not touch door knobs, phones, keys etc.

Eye Protection

Safety glasses must be worn in areas with risk of aerosols, hazardous liquid, splashes, and sprays from infectious agents.

Face Protection

Face mask must be worn in the event of UV exposure or protection against splashes, and sprays from infectious agents.

Universal Precaution

Treat human blood or body fluids as potential infectious agents.

Do not mouth pipette.

Do not use sharp objects except where too necessary. Use needle, syringes and other sharps carefully to avoid self-inoculation

Do not recap syringes and needle

Dispose used lancet, scalpel blades, syringe and needle in leak and puncture resistant containers
Label samples in appropriate container. Adhere strictly to standard color coding for each sample.
Decontaminate and clean spills up immediately with disinfectant
Disinfect/clean work surfaces after each experiment
Do not eat, drink or apply cosmetics or smoke in the laboratory except when directed
Do not wear laboratory coat outside the laboratory
Do not store food/drink where human samples are collected, stored, or manipulated
Maintain good hygiene by washing hand after handling human samples

BLOOD GLUCOSE DETERMINATION

1. Glucose Oxidase Method (GOD method)

Principle (Megazyme, 2018):

Glucose + H_2O + O_2 → Gluconic acid + H_2O_2

4 Amino Phenazone + Phenol + H_2O_2 → Quinonimine – Pink colour compound

- Intensity is determined at on 520 nm wavelength.

Specimen: Serum or plasma free of hemolysis. Sodium fluoride is preferred as an anticoagulant due to its antiglycolytic activity.

Reagents: Glucose standard (100 mg/dl), GOD-POD reagent: Enzyme reagent mixture containing glucose oxidase (GOD), peroxidase (POD), 4-aminoantipyrine, phenol, and phosphate buffer (pH≈7.0), some stabilizers and activators.

Instruments: Test tubes, pipettes, disposable tips, rack, water bath, spectrophotometer.

Procedure

1. Label three clean, dry test tubes as Test (T), Standard (S), and Blank (B).

2. Pipette as follows:

	TEST	STANDARD	BLANK
Glucose reagent (ml)	1.0	1.0	1.0
Serum (ml)	0.01	-	-
Glucose standard (ml)	-	0.01	-
Distilled water (ml)	-	-	0.01

3. Mix and keep it for incubation at 37oC for 15 min or at room temperature for 30 min.

4. Measure the intensity of colour at 520 nm wavelength.

Calculation:

Concentration of glucose = O.D. of Test - O.D. x Concentration of Std

O.D. of Std. - O.D.

General Parameter:

- Reaction type: End point
- Standard Concentration: 100 mg/dl
- Linearity is up to 500 mg/dl
- If sample value is 500mg/dl, dilute the sample 1:2 with distilled water and repeat assay.

Advantages:

- It is specific for glucose estimation.
- This method is sensitive, simple.
- It is cheap method.

Disadvantage:

- This method shows linearity only up to 500 mg/dl of glucose concentration.

2. GLUCOMETER

Principle:

- The principle behind blood glucose meter is based on reactions that are analyzed by electrochemical sensor.
- The glucose in the blood sample reacts with the glucose oxidase to form glucuronic acid which then reacts with ferricyanide to form ferrocyanide.
- The electrode oxidizes the ferrocyanide, and this generates a current directly proportional to the glucose concentration.
- Glucometer is only type of dry chemistry.
- Currently many types of glucometers available give results as

- plasma equivalent
- whole blood glucose

- Glucose level in plasma is generally 10- 15% higher than whole blood.
- So it is important for patients to know whether it give result in “whole blood equivalent ” or “plasma equivalent ”.

Procedure

- Blood is placed onto a test strip and insert into the glucometer to measure blood sugar level.
- On each strip, there are about 10 layers, including a stiff plastic base plate and other layers containing chemicals or acting as spacer.
- For instance, there is a layer containing two electrodes (silver and other similar metals).

- There also is a layer of an immobilized enzyme, glucose oxidase and another layer containing microcrystalline potassium ferricyanide.
- The reaction interest between glucose and enzyme.

Advantages:

- Can do from capillary blood collection method.

Disadvantages:

- It is costly.
- It gave slightly higher result than actual.

GLUCOSE TOLERANCE TEST (GTT)

- A glucose tolerance test is the administration of glucose in a controlled and defined environment to determine how quickly it is cleared from the blood. The test is usually used to test for diabetes, insulin resistance and sometimes reactive hypoglycemia. The glucose is most often given orally.
- Glucose tolerance means ability of the body to utilize (tolerate) glucose in blood circulation.
- It is indicated by the nature of blood glucose curve following the administration of glucose.
- Temporary rise of blood sugar after food intake for few hours.
- Extent and duration of rise depends on type of food (Glycemic index).
- Glucose level returns to normal within 2 hrs.
- If it take >2 hours = Decrease glucose tolerance.

Types of GTT

1. Oral GTT (OGTT)
2. Intravenous GTT (IVGTT)

- OGTT is mostly preferred
- IVGTT is used for patients who are unable to absorb an oral dose of glucose (malabsorption syndrome).

Indications for GTT

- Having symptoms like diabetes mellitus, but fasting blood sugar value is inconclusive (between 100-126mg/dl)
- During pregnancy and past history of miscarriage.
- To rule out benign renal glucosuria.

Contra-indication

- Person with confirmed Diabetic patients.
- Mal-absorption disease (OGTT).
- Test should not be done in acutely ill patients.

Precaution

- Normal diet intake in last 3 days.
- Avoid heavy exercise.
- Report to lab after fasting for 8-12 hrs.
- Avoid drug that change glucose level. E.g. steroid, Insulin, Oral Hypo Glycemic Drug.
- Addiction: Alcohol and smoking.

Procedure

- Collection of fasting urine and blood (in fluoride) sample.
- Give 75gm of glucose dissolved in 300ml lemon water to the patient.
- Note the time of oral glucose administration.
- In pediatric patient 1.5 - 1.75 gm/kg glucose/dextrose powder.

- Collect five samples of venous blood at half hourly intervals.
- Determine blood glucose by the specific method. E.g. GOD-POD method.
- Prepare a glucose tolerance curve (plasma glucose level - time).

Advantages
- It is useful in recognizing of border line cases of diabetes.
- GTT is useful in early diagnosis diabetes melitus.
- It is useful in diagnosis of gestational diabetes.

Disadvantages
- GTT is not necessary in known cases of hyperglycemic patient.
- Oral GTT is also not necessary in known cases of mal -absorption.

Pregnancy Tests

Pregnancy test is used to determine if a woman is pregnant or not. Two methods are ordinarily used.

a. Testing for human pregnancy hormone, human chorionic gonadotropin (hCG) in the urine or in the blood

b. Obstetric ultrasonography – for the detection of gestation sac. [This is outside the scope of this chapter]

Human Chorionic Gonadotropin (hCG)

hCG Pregnancy Rapid Test Strip

The hCG Pregnancy Rapid Test Strip is a rapid chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin in urine or serum or plasma to aid in the early detection of pregnancy.

Principle

The hCG Pregnancy Rapid Test Strip is a rapid chromatographic immunoassay for the qualitative detection of human chorionic gonadotropin in urine or serum or plasma to aid in the early detection of pregnancy. The test uses two lines to indicate results. The test utilizes a combination of antibodies, including a monoclonal hCG antibody to selectively detect elevated levels of hCG. The control line is composed of goat polyclonal antibodies and colloidal gold particles. The assay is conducted by immersing the test strip in a urine or serum or plasma specimen and observing the formation of colored lines. The specimen migrates via capillary action along the membrane to react with the colored conjugate. Positive specimens react with the specific antibody-hCG-colored conjugate to form a colored line at the test line region of the membrane. Absence of this colored line suggests a negative result. To serve as a procedural control, a colored line will always appear in the control line region indicating that proper volume of specimen has been added and membrane wicking has occurred.

PROCEDURE

1. Bring the pouch or canister to room temperature before opening it. Remove the test strip from the sealed pouch or closed canister.
2. With arrows pointing toward the urine or serum or plasma specimen, immerse the test strip vertically in the urine or serum or plasma specimen for at least 15 seconds. Do not pass the maximum line (MAX) on the test strip when immersing the strip. See illustration below.

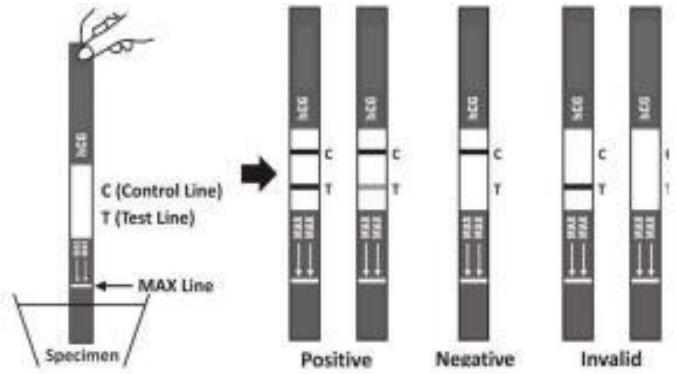

Figure 12.2: Title??

3. Place the test strip on a non-absorbent flat surface, start the timer and wait for the colored line(s) to appear. Read the result at 5 minutes when testing a urine specimen, or at 3 minutes when testing a serum or plasma specimen.

POSITIVE: Two distinct colored lines appear. One line should be in the control line region (C) and another line should be in the test line region (T). One line may be lighter than the other; they do not have to match.

NEGATIVE: One colored line appears in the control line region (C). No line appears in the test line region (T).

INVALID The result is invalid if no colored line appears in the control line region (C), even if a line appears in the test line region (T). You should repeat the test with a new strip.

Note: A low hCG concentration might result in a weak line appearing in the test line region (T) after an extended period. Do not interpret the result after time specified by the manufacturer.

GASTRIC ACID SECRETIONS ANALYSIS.

Gastric juice contains water, hydrochloric acid, pepsin, intrinsic factor, mucus and electrolytes. Of these, hydrochloric acid has been studied most extensively because of the development of peptic ulceration. Gastric acid secretion has a complex pathophysiological role being an important protective mechanism against ingested pathogens. The measurement of acid secretion is useful in the diagnosis of increased gastric acidity and patients with Zollinger-Ellison syndrome and in low or even absent acid secretion such as can be seen in patients with pernicious anemia and atrophic gastritis.

Methods for the measure of gastric acid secretion include invasive and non-invasive tests. The gold standard for measuring gastric acid secretion remains the invasive method that is aspiration test (26), involving placing a tube (endoscopic or nasogastric tube) in the lower part of the stomach.

The gold standard for measuring gastric acid secretion remains the invasive method that is aspiration test involving placing a tube (endoscopic or nasogastric tube) in the lower part of the stomach. The right position of the tube is usually determined with recovery test, which is performed administering 100 mL of water aspirated through the gastric tube. After that, the basal acid output (B.A.O.) is measured using a pump with continuous suction at a subatmospheric pressure of 30 to 50 mmHg or manually by a syringe in 15 minutes periods. Pentagastrin, histamine or tetragastrin are used as stimulation to collect maximal acid output (M.A.O.), which is aspirated for four 15-minute intervals for a total of one hour. After collecting the samples, the volume and titratable acid are measured using alkaline solution and chemical indicators and the amount of acid in each specimen is calculated.

Details of the steps are as shown below;

i. Make drinking water available to the animal, but solid food be withheld overnight before each experiment, for at least 3 days before the experiment.
ii. Histamine acid phosphate will be used and all doses are expressed as histamine base.
iii. Synthetic gastrin-like pentapeptide will be distributed into ampoules, freeze dried (25,g/ampoule) and reconstituted with saline before use.
iv. Animals would be anaesthetized with an intraperitoneal injection of urethane solution (25%, w/v), 5-7ml./kg, and all experiments performed at a rat rectal temperature of 30-31° C with the animal placed on its back.
v. Cannulate the trachea and insert a soft polyethylene tubethrough the oesophagus until the tip was close to the stomach. The oesophageal tube should be ligated in the oesophagus in the neck.
vi. The left jugular vein should then be cannulated for the injection of drugs.
vii. Make a mid line abdominal incision and insert a cannula into the stomach through the incision made, close to the pyloric sphincter and tied. Take care to prevent excessive blood loss.
viii. The pyloric cannula was exteriorized through the ventral surface and the abdomen closed.
ix. Washed the stomach free of debris with 5ml. volumes of glucose solution (5.15 %, w/v).
x. To measure gastric acid secretion the rat was incorporated into a circuit in which a roller pump was used to pass glucose solution (5.15 %, w/v) through the stomach.
xi. A nasogastric tube is inserted and the gastric contents are aspirated and discarded.
xii. Continuously titrate the acid secreted by the gastric mucosa. Alkali should be introduced into the tube draining the stomach in order to maintain the gastric per-fusate at pH 4, a pH .
xiii. The glucose solution should be pumped from the titration vessel, passed over a thermometer and returned to the rat stomach via the oesophageal tube at a temperature of 30-31° C.
xiv. Note the volumes of fresh glucose solution (adjusted to pH 4 with HCl) introduced into the perfusion circuit which should have been drained via the glass vessel at 15 min intervals.
xv. A chart recorder will used to detect the onset of acid secretion in a number of experiments. (note the experiments in which single intravenous injections of histamine or pentapeptide were used separately or in combination).
xvi. Note the various groupings of the animals: (e.g., the first group may have doses of up to 0.4ug of pentapeptide or histamine respectively; the second group, pentapeptide 0.8, 1.6 and 3.2 ug/kg or histamine, 0.8, 1.6 and 3.2 mg/kg; while the third group be given pentapeptide and histamine treatments in excess of 3.2 mg/kg respectively. The animals in each group also received histamine and pentapeptide simultaneously at selected dose levels.

xvii. After surgery no drug was given for 45 min after which time the rats were studied for 6-8 hr. The response to each dose of stimulant was calculated by subtracting the estimated basal level of acid secretion from the actual amount of acid secreted.

xviii. The basal rate of secretion can be calculated from the mean of the rates of secretion prior to and after recovery from a particular secretary stimulus.

xix. The acidity in each sample is estimated by titration with 0.1 N NaOH using two indicators - Topfer's dimethylaminoazobenzene for 'free', and phenolphthalein for 'total' acid.

Non invasive tests

A nasogastric tube is inserted and the gastric contents are aspirated and discarded. Current interest lies in finding a rapid, reliable and inexpensive non-invasive test. The determination of serum pepsinogen I is regarded as reliable gastric secretory parameter. Pepsinogens are aspartic proteinases from which derivate the active enzyme pepsin after exposure to hydrochloric acid, and they are responsible of initial protein digestion functioning between a pH of 1.5 and 5.0. Pepsinogens can be divided in two groups according to biochemical and immunological differences: pepsinogen I, and pepsinogen II is a product of the chief cells and the mucus neck cells in the fundus area and reflects the structural and functional status of the stomach. PGI is stable in the individual but show differences based on some individual factors such as age, weight, gender, ethnicity, diet, and circadian rhythm. PGI-II levels may change during different pathological conditions involving gastric mucosa and this reflects both functional and morphological status of stomach. If PGI/PGII ratio decreases, it might be an indication for precancerous disease such as atrophic gastritis. The plasma levels of fasting gastrin-17 are also able to give indirectly information of gastric acidity.

Gastric juice is then collected for 1 hour, divided into four 15-minute samples. These samples represent basal acid output. Gastric analysis can also be done during catheter-based esophageal pH-monitoring.

$Ac\ Vc = AB\ VB$,
$AC = AB\ VB/Vc$
Where;
Ac is the concentration of the acid
Vc is the volume of the acid used
AB concentration of the base
VB is the volume of the base used.

MEASUREMENTS OF ENVIRONMENTAL TEMPERATURE, HUMIDITY, AIR MOVEMENT AND RADIANT HEAT.

Optimal environmental conditions are essential for surface preparation, application, and curing of coatings and linings to maximize successful performance. A variety of instruments are available to measure the five conditions that should be observed and tracked:

i. Air temperature
ii. Surface temperature
iii. Relative humidity (RH)
iv. Dew point temperature
v. The difference between the surface and dew point temperatures

Atmospheric conditions are always changing: therefore measurements and calculations should be made frequently. Four hours is a typical minimum period. It is recommended that different locations be measured and conditions recorded before, during and after every task. Some meters calculate dew point temperature only, but the more practical instruments have an attached surface temperature probe. A probe allows a meter to calculate and display the important delta value; the difference between the surface and dew-point temperatures.

The first parameters necessary to assess the risk of moisture formation on a substrate are the temperature of the surface to be prepared or coated and the temperature of the air near that surface. At night, steel work usually radiates heat and is cooled below air temperature. During the day, it absorbs heat and is usually warmer than the air temperature. Since surface temperature is often different from air temperature especially for work performed outside, both temperatures should be measured to avoid application problems should air or steel temperatures become too hot or too cold for satisfactory film formation.

The dew-point temperature is the temperature at which moisture will begin to form on a steel surface. It is the temperature to which a volume of air must be cooled in order to reach saturation. It is a function of air temperature and the RH.

The final parameter to note is the amount of separation between the surface temperature and the dew-point temperature. Moisture will likely form if they are the same. Even if they are close, the risk of moisture forming may be unacceptably high. Documents such as ASTM D3276 and the international standard ISO 8502-42 state that the surface temperature must be a minimum of 5ºF (3ºC) above the dew-point temperature during the critical 3 phases of coating: preparation, application and cure. This minimum separation also helps allow for surface temperature reduction as solvents evaporate or when cold coating materials are applied.

The air temperature, dew-point temperature and the RH can be determined with a sling or battery-operated psychrometer. These instruments are equipped with two thermometers. The first thermometer, called a “dry bulb”, measures the ambient air temperature. The second thermometer is wrapped in a muslin sock or wick which is wetted prior to use -- hence the name “wet bulb”. This “wet-bulb temperature” represents the heat loss from the evaporation of water in the sock. Low RH will cause a faster rate of evaporation and a lower wet-bulb temperature than high humidity.

The sling psychrometer is twirled through the air to obtain the two temperature values. The electric psychrometer remains stationary as a motor driven fan draws air across the thermometers. Students are advised to note the following:

vi. Read the instrument directions carefully.

vii. The instrument should be inspected and prepared properly before each and every test.

viii. Inspect the damp covering regularly and kept in good condition. (The evaporation of the water from the muslin always leaves a small quantity of solid material. It is therefore desirable to use as pure water as possible and also to renew the muslin from time to time).

The physical location of the test and the amount of time spent whirling or blowing air over the wet bulb are factors which directly affect the accuracy of the test result.

ix. The thermometers should be whirled rapidly for 15 or 20 seconds (stopped and quickly read; the wet bulb first because it will begin to change when the air movement stops).

x. The test should be repeated until two or more wet-bulb readings equal the lowest reading obtained.

For best accuracy, the psychrometer should be whirled in the shade. The observer should face the wind and step back and forth a few steps to prevent their body from adversely affecting observations.

Be aware that when the temperature is near or below the freezing point, the psychrometer is not a very reliable instrument with which to measure humidity. A psychrometer does not directly measure RH and dew-point temperature.

xi. These values are calculated using a formula into which the dry and web bulb temperatures are inserted.

xii. Graphs and psychrometric slide-rule calculators are available for this.

xiii. Select the table corresponding to the local atmospheric pressure for that day (this value can be obtained from the nearest airport weather office. Generally, 30 inches (76 cm) of mercury is used and corresponds to sea level).

xiv. At higher elevations, 74 to 58 cm is used.

Read the thermometers carefully because there are many opportunities for interpolation errors. Slight differences in the values obtained from temperature scales and humidity lookup tables can cause considerably different results.

xv. (Although both thermometer values are within tolerance, the resultant humidity formula calculation differs by 8.8 percentage points. If a lookup table is used instead of a formula calculation, the difference might be even greater. This error budget is greatest in the wet/dry-bulb calculations at very low and very high RH).

The RH can also be read directly from a hygrometer or continuously recorded with a hydrograph.

xvi. Thermometers should remain in place for a sufficient period of time for the temperature to stabilize (typically 2 or 3 minutes).

xvii. Tap the dial lightly before taking a final reading and take care to read straight-on.

xviii. Avoid direct sunlight, wind, thermal radiation, heating or ventilation ducts, or other such conditions.

xix. Obtain data for hot and cold areas as well as for average areas.

Digital, noncontact infrared thermometers can also be used to measure surface temperature. The further away from the surface the device is held, the larger the area of measurement is; causing potential error.

xx. Continuous measurement is one reason why digital, all-in-one instruments are quickly becoming popular.

xxi. Some digital instruments continuously and simultaneously display all five environmental parameters on the liquid crystal display . Not only are the values displayed, but these values can be stored in the gage's memory at the press of a button along with the date and time.

All-in-one instruments usually provide high accuracy, greater simplicity, and faster response than mechanical methods.

Another advantage that digital instruments provide is that they take much of the guesswork out of measuring. Many models have alarms that automatically alert the user when the surface temperature is too close to the dew-point temperature; this feature signals the high risk of moisture formation. Most display the readings in Celsius.

Some record the surface temperature value only after that value has stabilized. In other words, touch a cold or hot surface and the instrument will measure the temperature reading as it drops or rises to the actual surface temperature.

In a few seconds, once the gage determines that the reading has stabilized, the gage beeps and freezes the display. This is particularly handy when measuring remote areas where the display is difficult or impossible to view.

The Simple Muscle Twitch experiment by

Definition and aim: The aim of the experiment is to investigate the time relations of a single maximal contraction of an isolated muscle and determine the effect of temperature, multiple stimuli and continued stimulation on muscle contraction.

Introduction

Gastrocnemius Muscle-Sciatic nerve preparation

Properties of skeletal muscle

When the muscle is activated it either shortens or, if it is attach to a rigid skeleton, develops tension. Its properties can be investigated by attaching it to a movable lever that write in a revolving drum (kymograph). The muscle can be activated by stimulating it, its nerve, with brief electric shocks. A preparation commonly used in this kind of works is the calf (Gastrocnemius) muscle of the frog. The muscle is stimulated with single or repetitive shocks; either direct or through its nerve and the resulting contractions is recorded on the drum.

The voluntary (skeletal) muscles are in a state of asynchronous contraction resulting from activity in its motor unit. Each motor unit in a muscle may contract to a different degree and some may be at rest, while others are working. In an isolated tissue, as in this experiment, an experimentally useful application may be achieved by strong enough artificial (electrical) shock to all its motor nerve fibres, and therefore, all the muscle fibres may be excited at the same time (synchronously). The muscle thus, behaves as a single motor unit and the effect of different frequencies of stimulation of the production of work or tension development by the muscle fibres may be readily studied.

Apparatus and materials

- Toads, frog boards,
- Dissecting instrument (students should come with their own instruments)
- Fitting needle
- Kymograph/ Stimulator
- Tuning fork
- Electronic time marker
- Toad's (frog's) Ringer's solution
- Hot plate
- Thermometer

Methods

The Dissection

Pith the frog and remove the skin from the legs by making an incision through the skin and around the entire lower abdomen. Cut the connections between the skin and the body. Use stout forceps to pull the skin off the frog in one piece (like a pair of pants).

Use forceps to separate the muscles of the thigh (the leg not covered with the paper towel). The muscles are surrounded by connective tissue called fascia, and the large medial and lateral muscles on the dorsal side of the

upper leg are joined to each other by a fusion of their fascia along a thin "white line". Grab the muscle groups on either side of the "white line" with forceps, and firmly pull the muscle groups apart. The fascia will tear.

Pin the muscles apart so that more underlying muscle is visible. This should also expose the cream-colored Sciatic Nerve lying deeply between the muscles. Use forceps or tweezers to slide one end of the suture thread under the nerve. Move the thread as close to the knee joint as possible. Ligate (tie off) the nerve TIGHTLY using a DOUBLE KNOT.

Free the nerve from the surrounding tissue by lifting the nerve gently by the suture thread and undercutting any muscle or connective tissue attaching the nerve to the body. Once you reach the pelvis, place the nerve down and rinse with Ringers solution.

Carefully separate the muscles of the pelvis to expose the Sciatic nerve. Remember to rinse any blood away with Ringer's solution. The Sciatic nerve enters the abdomen of the frog through an opening at the end of the urostyle, a bone that forms part of the pelvis.

Carefully expose the remainder of the nerve through an opening along the lateral side of the urostyle. To avoid cutting the nerve: lift the end of the urostyle with forceps and cut the muscle away (SHALLOW CUT!) with blunt scissors. Cut along the urostyle from its tip to the vertebral column.

Deflect the muscle away from the urostyle to expose the Sciatic nerve. Slide one end of a suture thread under the proximal end of the nerve. Move the thread as high as possible to obtain as large a section as possible. Ligate (tie off) the nerve TIGHTLY using a double knot; the leg may jump again as the knot is tied.

Cut the nerve between the knot and the vertebral column. Keep moist at all times.

Some hints:

1. Do not touch the nerve or muscle with instruments.
2. Avoid excessive stretch on nerve and muscle.
3. Handle the tissue gently. Make sure they are kept moist with toad's (frog's) Ringer's solution.
4. Do not leave toad around. It is toxic to the tissue you want reaction from.
5. Ensure that your apparatus is working before dissection.

Connecting the Electrodes:

Connect the stimulating electrode leads (+ and --) to pins IN CONTACT with the nerve near its proximal end. Place the negative and positive leads on opposite sides of the bath, spaced apart by one pin. Note: the leads should NOT be connected to the SAME pin!

Connect the leads of the recording electrode to pins in contact with the distal end of the nerve. Place the negative and positive leads on opposite sides of the bath, spaced apart by one pin. Note: the leads should NOT be connected to the SAME pin!

Connect ground (green) to a pin near the middle of the nerve, between the stimulating and recording leads.

The Compound Action Potential

Goal: To apply a brief stimulus at the proximal end of the nerve and record a compound action potential from the distal end.

Procedure

The stimulator panel allows you to manipulate the stimulus intensity (i.e. amplitude in Volts), the duration of the stimulus (in mm/sec) and the rate at which a stimulus is applied (Hz).

Remove the Ringer's solution from the nerve chamber to ensure that the nerve no longer in contact with the solution. If necessary, remove any large drops of saline from the electrode pins (metal pins within the nerve chamber) and the nerve with the tip of a pipette.

Stimulate and record from the nerve (note: the default value for the stimulus is 25 Volts). Look for a stimulus artifact on your trace. The artifact usually appears as a small, sharp deflection in the trace and precedes the response. The compound action potential (response) usually reaches its peak value a few milliseconds after the artifact.

After observing a response, refill the nerve chamber with fresh frog Ringers solution to keep the nerve from desiccating.

Stimulus and Response Procedure

Drain the Ringer's solution from the nerve chamber, and carefully remove any large drops of saline from the electrode pins and the nerve using a pipette.

Set the stimulus to 0.00V, hit the Apply 1 button and then select Start. Stop the recording after a few seconds (no response should be observed).

Continue to increase the stimulus in increments by clicking the up arrow in the stimulator panel. Continue until there is no further increase in response amplitude (the maximum response). As you record data, be sure to use the Apply1 button to change voltages and record marks in the same manner as before.

If less than 5 measurements are made before reaching the maximum amplitude response, select appropriate increments to obtain at least 5 data points between the first response and maximum response.

Fill the nerve chamber with fresh Ringer's solution to prevent desiccation of the nerve.

Conduction Velocity

Goal: To measure the velocity of action potential conduction

Procedure

Fill the nerve chamber with Ringer's solution to keep the nerve wet.

Bi-directionality Procedure

Reverse the position of the electrodes attached to the pins on the nerve bath.

Place the stimulating electrodes on the distal end of the nerve, where the recording electrodes used to be, and vice versa.

Drain the Ringer's solution from the nerve chamber, and carefully remove any large drops of saline from the electrode pins and the nerve with a pipette.

Stimulate the nerve with the same amplitude used in the last exercise.

Measure the conduction velocity of the nerve.

Calculate the conduction velocity as done in the previous exercise and record this value in your lab notebook.'

Fill the nerve bath chamber with ice cold Ringers Solution. Allow the nerve to remain in the cold saline for at least one minute.

Conduction Velocity and Temperature

Procedure

Drain the chilled Ringer's solution from the nerve chamber and measure the conduction velocity of the nerve as done in the previous exercise.

Procedure for Kymograph use

1. Time Relations of Single Maximal Twitch
   Round by hand so that contact is just made and then, move the eye with the finger so as to mark the drum.
   Put a time trace on the record and varnish the paper.
   Three measurements should be made:
   i. Time from stimulation to beginning of contraction
   ii. Duration of contraction phase
   iii. Duration of relaxation phase

Sciatic-gastrocnemius preparation set up in chamber. A pin through the knee joint, but not through the nerve fixes the preparation to the cord disc. Most of the muscle is covered with Ringer’s solution. The nerve is laid over the electrodes, which remains in the air.

2. Effect of temperature

Measure the temperature of the fluid in the bath with the thermometer provided. Then repeat the experiment at temperatures below and above this value.

What conclusions do you draw as to the effect of temperature on the twitch?

3. Effect of 2 stimuli in close succession

Two stimuli can be given by separating the two arms of the contact maker, and the interval varied by altering amount of separation. Keeping the lower arm fixed, and moving the upper arm stepwise, in an anticlockwise direction, make a series of records showing the effects of 2 stimuli sent at different intervals.

Can you measure the strength of the refractory period, i.e., the interval after the application of the stimulus during which a second stimulus has no effect?

4. Genesis of tetanus

When a muscle responds to a series of rapidly repeated individual stimuli, by one sustained contraction, which the effects of individual stimuli can no longer be recognised, the result is called a complete tetanus. By stimulating the nerve at various lower frequencies, many different stages of incomplete tetanus (clonus) between complete tetanus and twitch responses can be obtained.

Use a slowly moving drum. Record the effect of stimulation for 3-5 seconds at frequencies ranging from the lowest available to about 50 seconds, leaving a few minutes rest between stimulation periods. What is the lowest frequency, which gives a complete tetanus? Why is the muscle response larger in tetanus than in twitch?

5. Fatigue Curve

Isolated muscle fatigues more readily than muscle in vivo and recovery is less complete. Using the drum spindle contact-maker, takes a series of records of a single twitch on a fast drum allowing the drum to revolve several times. As fatigue sets in, the height of contraction will decrease and the duration will increase. Evaluate the effect on the latent period, the phase of contraction and the phase of relaxation.

6. Effect of fatigue on the tetanus fusion frequency of striated muscle

Dissect out a new sciatic-gastrocnemius muscle preparation from the other limb of the frog. Using a slow moving drum, which should not be included in the circuit, determine the least frequency at which the nerve needs to be stimulated to give fused tetanus (tetanic fusion frequency). Then stimulate the nerve with single supre-maximal shocks until the muscle is fatigued. Re-determine the tetanic fusion frequency immediately after.

CLINICAL EXAMINATION OF THE MOTOR AND SENSORY SYSTEM

Learning Objectives

By the end of this section, students will be able to:

- Describe the arrangement of sensory and motor regions in the spinal cord
- Relate damage in the spinal cord to sensory or motor deficits
- Differentiate between upper motor neuron and lower motor neuron diseases
- Describe the clinical indications of common reflexes

Sensory exam Introduction and informed consent, adequate exposure, inspect for SWIFT (Scars, Wasting, Involuntary movements, Fasciculations and Tremor), pain, light touch, temperature, vibration sense, proprioception, graphesthesia and stereognosis, Romberg's test

Sensory examination

Apparatus: cotton wool, divider, turning fork (128Hz), pin, hot and cold water in test tubes, and rubber (knee) hammer.

Variations of sensation

Allodynia - Painful response to a non-painful stimulus

Analgesia - Numbness, loss of sensation

Dysaesthesia - Painful or unpleasant pins and needles

Hyperaesthesia - Increased sensation in response to stimuli

Hyperalgesia - Increased detection of painful stimulus

Hypoaesthesia - Decreased detection of normal stimulus

Paraesthesia - Pins and needles; Not Painful or unpleasant

Tactile sensation

Fine/light touch is tested with a wisp of cotton wool. Show the patient the item that will be used to conduct the test to help relieve any anxiety they may be experiencing. The cotton wool should be placed on the skin gently without disturbing the hair. Ask the patient to close their eyes as the stimulus is being applied. This eliminates the possibility that the patient will see when the stimulus is being applied and assume that it is felt. Apply the stimulus to the dermatomal areas and ask the patient whether or not they felt the stimulus.
Crude touch is tested with the tip of the index finger.

Ability to distinguish between two points (two-point discrimination) is detected with the help of a divider.

Pain sensation

Superficial pain is tested with a pin but distinction should be made between pain sensation and fine touch. Pressure pain is tested by pressing hard or squeezing muscles. Do not use hypodermic needles for this test; and be sure to use a fresh pin with each patient and discard them after use.
Alternatively, break a tongue depressor (orange stick) in half to create a pointy end and a dull end.

Temperature sensation

Temperature sense is tested with test tubes containing hot and cold waters or tuning fork.

Adaptation of these receptors can be demonstrated by feeling water at room temperature after keeping the finger in hot or cold water for two minutes.

Vibration sense

Vibration is the impression given off by a rapidly alternating object. The ability to detect this stimulus – known as vibration sense – can be assessed with the aid of a 128 Hz tuning fork.

To initiate the test, strike the prongs of the tuning fork against the thenar eminence of the hand to initiate vibration. Be careful to hold the tuning fork at the stem, and not by the vibrating prongs as the latter will reduce the vibration. Ask the patient to close their eyes, then place the foot piece of the vibrating tuning fork on the most distal bony prominence on the foot (i.e. the distal interphalangeal joint of the great toe), or at the distal interphalangeal joint of the index finger (forefinger). Repeat the process on the contralateral side.

Proprioception (Position sense)
The ability to recognize the location of a body part with respect to the environment and the rest of the body is known as proprioception. This sensory modality is assessed by testing the joint position sense of the patient. Position sense is tested in all joints. The patient closes eyes or looks away. The joint to be tested is stabilized by one hand holding it by the thumb and other fingers across the axis of movement to be tested.

The distal part is flexed or extended by the other hand, holding on the sides, across the axis of movement to avoid the force used for movement giving any clue. The patient should respond when the position is changed by saying – up or – down. The dynamic appreciation of movement is tested by asking the patient to say –now as soon as he/she feels the movement. Normally movement is felt within an angle of 10o.

Stereognosis
Stereognosis is the ability to identify a three-dimensional object by touching it and without visual support. It is tested by asking the patient to close their eyes, and placing a relatively common object like a pen, coin or a key in their palm. With stereognosis intact, the patient should be able to identify the object without trouble. Be sure to test both sides during this procedure as well.

Graphaesthesia
Graphaesthesia refers to the ability to detect the tracing of letters or numbers on the skin just by feeling it (i.e. without visual input). Graphaesthesia is assessed by using a blunt object to make tracings of letters or numbers in the palms of the patient while their eyes are closed. The patient should be able to tell the examiner what letter or number was outlined if this modality is intact.

Romberg's test (Gait)
If proprioception is impaired, then voluntary movements – including gait – will also be significantly affected. However, this is also a problem if there is a lesion (vascular or space-occupying) in the cerebellum; which is responsible for balance, movement, and motor coordination. The former disorder is referred to as sensory ataxia, while the latter is called cerebellar ataxia.

The Romberg's test was designed to differentiate the two abnormalities. The test requires that the patient stands with a narrow stance base and close their eyes. The physician should be close by to catch the patient should they topple over. Ask the patient to close their eyes and attempt to walk; provide reassurance that someone is close by to prevent them from falling. If the patient has a sensory ataxia, then the examiner will note that the patient's gait is relatively normal as long as their eyes are open. However, once their eyes are closed, their stance and gait becomes uncertain, insecure, and teetering. This is because having visual input compensates for not being able to determine the position of the body parts with respect to the environment. However, in cerebellar ataxia, there is no change with the removal of visual input as the problem is at the source of proprioceptive integration.

Exercise: Describe the changes in sensation in various conditions- sensory nerve lesions, peripheral neuropathy, spinal cord lesions.

Motor system examination

Muscle Strength and Voluntary Movement

The skeletomotor system is largely based on the simple, two-cell projection from the precentral gyrus of the frontal lobe to the skeletal muscles. The corticospinal tract represents the neurons that send output from the primary motor cortex. These fibers travel through the deep white matter of the cerebrum, then through the midbrain and pons, into the medulla where most of them decussate, and finally through the spinal cord white matter in the lateral (crossed fibers) or anterior (uncrossed fibers) columns. These fibers synapse on motor neurons in the ventral horn. The ventral horn motor neurons then project to skeletal muscle and cause contraction. These two cells are termed the upper motor neuron (UMN) and the lower motor neuron (LMN). Voluntary movements require these two cells to be active.

The motor exam tests the function of these neurons and the muscles they control.

First, the muscles are inspected and palpated for signs of structural irregularities.

Movement disorders may be the result of changes to the muscle tissue, such as scarring, and these possibilities need to be ruled out before testing function.

Muscle tone is assessed by moving the muscles through a passive range of motion. The arm is moved at the elbow and wrist, and the leg is moved at the knee and ankle. Skeletal muscle should have a resting tension representing a slight contraction of the fibers. The lack of muscle tone, known as hypotonia or flaccidity, may indicate that the LMN is not conducting action potentials that will keep a basal level of acetylcholine in the neuromuscular junction.

If muscle tone is present, muscle strength is tested by having the patient contract muscles against resistance. The examiner will ask the patient to lift the arm, for example, while the examiner is pushing down on it. This is done for both limbs, including shrugging the shoulders. Lateral differences in strength—being able to push against resistance with the right arm but not the left—would indicate a deficit in one corticospinal tract versus the other. An overall loss of strength, without laterality, could indicate a global problem with the motor system.

Diseases that result in UMN lesions include cerebral palsy or MS, or it may be the result of a stroke.

A sign of UMN lesion is a negative result in the subtest for pronator drift. The patient is asked to extend both arms in front of the body with the palms facing up. While keeping the eyes closed, if the patient unconsciously allows one or the other arm to slowly relax, toward the pronated position, this could indicate a failure of the motor system to maintain the supinated position.

Bulk of muscles

Observe the muscle bellies and compare with opposite side, look for atrophy, hypertrophy, tremors and fasciculation.

Tone of the muscles

When the patient is completely relaxed move the limbs gently and feel the resistance to movement. Look for hypertonia or hypotonia.

Strength of muscles

Ask the patient to force his limbs against resistance offered by you. Test the strength of each muscle separately and compare with the opposite side.

Coordination of movement

Upper limb

Ask the patient to touch the tip of his/her nose and then your finger. Then ask the patient to repeat it with eyes closed. Look for past pointing and shaky movement. Ask the patient to tap on the table rapidly. Look for inability to perform rapid repeated movements (dysdiadochokinesia).

Lower limb

Ask the patient to walk on a straight line. Get the patient to a bed and ask to raise one leg in air, place the heel on the knee of the other leg and slide towards the ankle.

Exercise: Describe the changes expected in upper motor and lower motor lesions, cerebella lesions and basal ganglia lesions.

Reflexes

Reflexes combine the spinal sensory and motor components with a sensory input that directly generates a motor response. The reflexes that are tested in the neurological exam are classified into two groups.

A superficial reflex is elicited through gentle stimulation of the skin and causes contraction of the associated muscles.

A deep tendon reflex is commonly known as a stretch reflex, and is elicited by a strong tap to a tendon, such as in the knee-jerk reflex.

For the arm, the common reflexes tested are of the biceps, brachioradialis, triceps, and flexors for the digits.

For the leg, the knee-jerk reflex of the quadriceps is common, as is the ankle reflex for the gastrocnemius and soleus.

The most common superficial reflex in the neurological exam is the plantar reflex that tests for the Babinski sign on the basis of the extension or flexion of the toes at the plantar surface of the foot.

Comparison of Upper and Lower Motor Neuron Damage

Many of the tests of motor function can indicate differences that will address whether damage to the motor system is in the upper or lower motor neurons.

Signs that suggest a UMN lesion include muscle weakness, strong deep tendon reflexes, decreased control of movement or slowness, pronator drift, a positive Babinski sign, spasticity, and the clasp-knife response.

Spasticity is an excessive contraction in resistance to stretch. It can result in hyperreflexia, which is when joints are overly flexed.

The clasp-knife response occurs when the patient initially resists movement, but then releases, and the joint will quickly flex like a pocket knife closing.

A lesion on the LMN would result in paralysis, or at least partial loss of voluntary muscle control, which is known as paresis. The paralysis observed in LMN diseases is referred to as flaccid paralysis, referring to a complete or partial loss of muscle tone, in contrast to the loss of control in UMN lesions in which tone is retained and spasticity is exhibited.

Other signs of an LMN lesion are fibrillation, fasciculation, and compromised or lost reflexes resulting from the denervation of the muscle fibers.

The plantar reflexes

Get the patient relaxed on a bed and stroke the outer edge of the sole of the foot, from heel towards the little toe, with blunt instrument such as a key. In normal person planter flexion of the toes is seen (contraction of tensor fascia lata). Stronger stimulus produces dorsiflexion at the ankle and even withdrawn of the limb.

In pyramidal tract lesions the toes fan out and dorsiflex. This is positive Babinski response. The response with dorsiflexion of the ankle and flexion of the knees resembles withdrawal reflex to noxious stimulation.

Exercise: What changes occur in the lesions

Abdominal reflex

The patient lays in a supine position on the bed, with the abdomen uncovered. Gentle stroke of the abdominal skin towards the midline causes contraction of the underlying muscles and manifests by pulling the umbilicus towards the stimulated area. This reflex is absent in upper motor neuron lesions.

Exercise: What changes occur in the lesions?

Tendon (deep) reflexes

Tendon reflexes are monosynaptic reflexes where sudden stretch of the muscle spindles results in brief contraction of the muscle. This shows the integrity of the reflex pathway and excitability of the anterior horn cells. In order to reduce sudden stretch, the patient should be completely relaxed; the muscle should be slightly stretched by passive movement of the limb and a single sharp blow is given with a soft rubber hammer. The response is assessed by observing the sudden slight movement of the distal part, or preferably observing the muscle belly contracting. Always compare the response with the opposite side.

Exercise: What are the changes that occur in reflex responses in upper motor, lower motor, cerebellar and basal ganglia lesions?

Knee jerk

Get the patient in a bed, completely relaxed. Pass one hand under the knee and lift the joint a little. Strike the patellar tendon at the middle. This reflex can also be tested while the patient is seated up, longs dangling freely over the edge of the bed. List the muscles and the spinal segments involved.

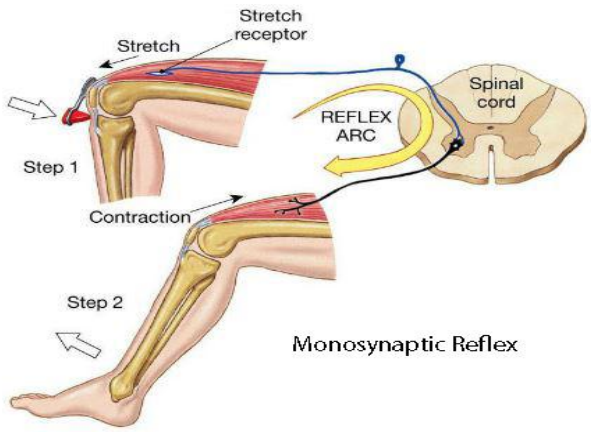

Figure 12.3: The knee jerk

Ankle reflex

Bend the knee slightly and place the leg on the opposite leg. Hold the foot and dorsiflex the ankle slightly. Strike the tendon at the posterior surface and look for the response or preferably feel the force by the hand holding the foot. List the muscles and the spinal segments involved.

Figure 12.4: Ankle reflex

Biceps jerk

Flex the elbow to a right angle and keep the forearm in a semi-prone position. Place your thumb or index finger of one hand on the biceps tendon and strike over your finger.

Exercise: Explain why biceps tendon was not stretched by extension of the elbow). List the muscles and the spinal segments involved

Triceps jerk

Flex the elbow and allow the forearm to rest on the chest of the patient, Strike the triceps tendon just above the olecranon.

Exercise: List the muscles and the spinal segments involved

Supinator jerk

Allow the forearm to rest on the chest of the patient in semi-pronation. Strike the styloid process of the radius.

Exercise: List the muscles and the spinal segments involved.

Jaw jerk

Ask the patient to open the mouth slightly. Place your index finger firmly on the chin and tap on the finger as in percussion.

Exercise: List the muscles and the spinal segments involved.

Clonus

Clonus is regular oscillations of contraction and relaxation. It is generally elicited in the ankle and some times in the knee. Sustained clonus occurs in upper motor neuron lesions. Unsustained clonus may occur in healthy persons who are tense or anxious.

Flex the ankle and support the leg with one hand. Dorsiflex the foot suddenly with the other hand and hold it dorsiflexed.

Exercise: List the muscles and the spinal segments involved

VISUAL ACUITY

Overview

The eye is a special sense organ that functions in the perception of light, image formation and transmission of impulses. The function is further carried out in the occipital cortex, association areas and finally in the Wernicke's area. These functions are facilitated by the eye muscles supplied by somatic nerves and cornea and ciliary body supplied by autonomic nerves. Complete examination of the eye, therefore, comprises several different procedures.

Visual illusions

Several pictures are displayed for observation. Observe each picture from a distance and then read the notes given about the picture. This will help you to understand that vision is not just image formation but also interpretation in the cortex.

Field of Vision

Gross abnormalities of the field of vision can be detected by clinical examination. Perimeter is used to map the field of vision accurately.

Clinical Examination for Field of Vision is based on comparing the field of vision of the examiner with that of the subject, one eye at a time. The subject is seated in front of the examiner at about two feet, eyes of both at the same level. The subject covers that left eye and the examiner covers the right eye. Both fix the gaze of the uncovered eye on the other's eye.

The subject is instructed to keep the eye fixed on the examiner's eye and to indicate when the moving finger of the examiner comes into view. The examiner moves the finger in the plane between the two. First the finger is raised up above the visual area and lowered slowly: when the subject reports of seeing the finger, the examiner will be able to judge the subjects upper quarter of the visual field by comparing with the personal perception. Similarly the finger is moved from nasal, inferior and temporal areas and the field of vision is tested. The procedure is repeated with the other eye.

Perimetry

Apparatus and materials: Perimeter

Procedure

Take the perimeter chart and fix it on to its holder, so that the marks on the holder correspond to the marks on the chart. Move the pointer to the mark (bring the pin to the centre) and press the paper against the pin to make sure that the centre of the chart corresponds to the centre of the holder.

Seat the subject comfortably and cover one eye. Position the chin on its stand so that the eye to be examined is against the central mark on the perimeter. Instruct the subject to fix the gaze on the mark and indicate when the pointer comes into view. Take the pointer to the outer most point by rotating the wheel and move it slowly towards the centre. As soon as the subject gives the signal, stop the wheel and press the paper holder against the pin to get the position entered in the chart. Rotate the arc by 30° and repeat the procedure. Record the field of vision until the circle is completed.

Remove the chart and fit it again to test the other eye and carry out the procedure for the other eye.

Remove the paper and join the points made by the pin to obtain the field of vision. Paste a copy of the Perimeter chart. Give examples of change in visual field.

Visual acuity

The degree to which the details and contours of objects are perceived is the visual acuity. It is usually defined by the minimum separable distance between two lines. It is the shortest distance between two lines which can be identified as two lines. Defects in visual acuity may occur due to neural or refractive errors.

Snellen’s chart

The Snellen’s chart is commonly used to test visual acuity. The letters on it are prepared so that the width of the lines in the letter subtend 1 minute arc and the minimum distance between the lines is also 1 minute and the width of the whole letter subtends 5 minute arc from the distances marked below them. An individual with normal

visual acuity could read the first row of letters from a distance of 60 meters (200 feet). Similarly, the row of letters marked 6 meters (20 feet) could be read from that distance.

Procedure:

The Snellen chart is placed at the eye level and illuminated well. The subject is placed 6 meters (20 feet) from the chart. One eye is blind folded. The subject is asked to read from top. The last line that is clearly read is noted. The procedure is repeated for the other eye.

The visual acuity is determined by dividing the distance from which the chart is read by the distance from which a normal person can read the last row read by the subject. If the subject has read the row marked 6 meters, his visual acuity is 6/6 (or 20/20). If the subject read up to the row marked 18 meters, the acuity is 6/18- less than normal. If the subject goes on to read the row marked 5 meters, then the acuity is 6/5 which is better than normal.

If the visual acuity of the subject is reduced, the test is repeated allowing the subject to read through a pin hole. The pin hole eliminates the function of the refractive mechanisms and the performance improves if the subject had refractive error. If the reduction of visual acuity was due to neural problems, pin hole does not improve the acuity.

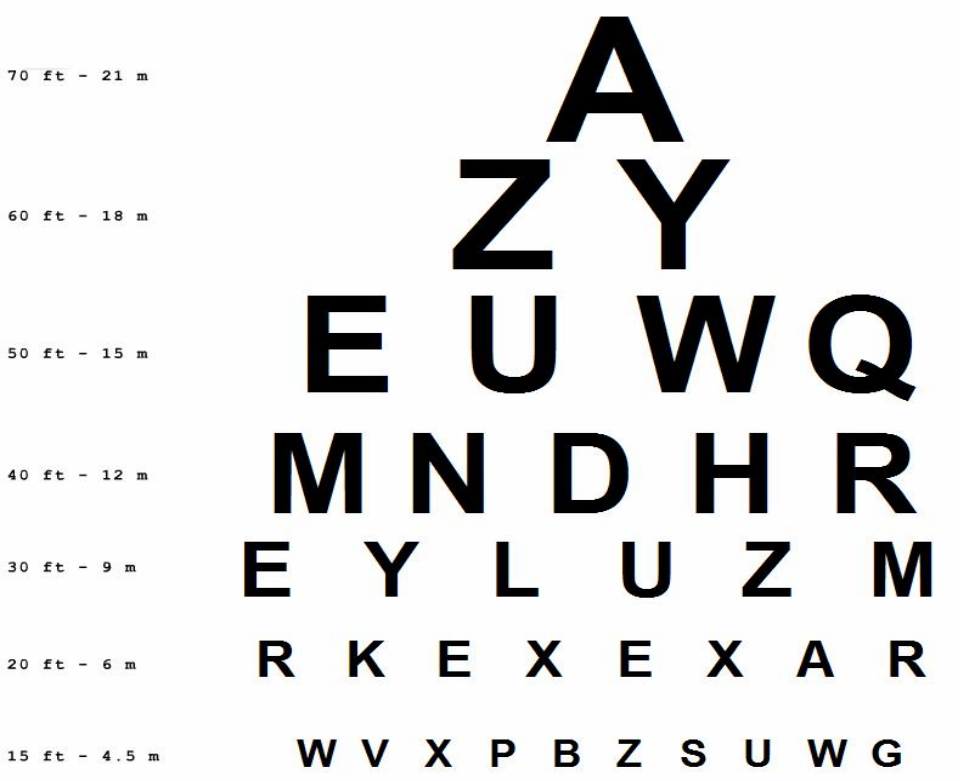

Figure 12.5: Snellen's Chart

Test for near vision

Jaeger's chart or Rayner test types chart is used. These are made of letters of different sizes. The subject starts at the smallest and goes on trying to read bigger letters. The chart should be kept at about 35cm from the eye.

Test for astigmatism

The chart with parallel lines radiating from a central point is observed by the subject. All lines will be alike if no astigmatism and certain lines will be blurred while others remain clear if the defect is present.

Exercise: List the visual defects and the lenses used to correct them.

Colour Vision

Colour vision is a complex function which involves retinal and cortical functions. Presence of three types of cones which respond maximally to blue, green and red (yellow) and the fact that these colours could be mixed to produce any colour sensation forms the basis for the three primary colours. Even though the three types of cones respond maximally to specific colours, they respond at various levels to all light rays in the visual range of wave length. The final perception of colour, therefore, appears to be the integration of the impulses from all cones by the cortical areas.

Demonstration of complementary colour Place a rectangular sheet of any colour in well illuminated white background. Fix the gaze on the sheet for two minutes without moving the eyes. Remove the sheet of paper suddenly (preferably by another person). For a few seconds a different colour comes into view and fades off. This colour is the complementary colour for the colour of the sheet. Repeat the test with different colours and determine the complimentary colour for all colours.

Test for colour blindness

The cone pigments are essential for the perception of light by the cones. The gene for the blue sensitive cone pigment is on chromosome 7 and the genes for green and red sensitive pigments are on X chromosome. Because the red-green colour blindness is sex-linked recessive characteristics, females are generally carriers and males are the sufferers.

Detection of colour blindness is not easy because those who are deficient in colour vision has been also perceiving the rays and they were trained to call whatever the sensation they got as the colour. Various tests have been developed to identify colour blindness.

Yarn-matching test

This is a simple test. The subject is presented with a skein of yarn and asked to pick out the one which matches the colour from a pile of various coloured skeins.

Ishihara charts

These are series of charts produced by tricky colour dots. The subject is asked to read the number or trace the pattern in each chart and the interpretation of the response is given in a booklet.

Eye Reflexes

The activities of the eye are effected by skeletal and smooth muscles which are supplied by somatic and autonomic nerves. Also several portions of the eye are rich in sensory nerves and several reflexes can be demonstrated.

Protective reflex

Ask the subject to look at a distance object. Bring an object (may be your hand) rapidly towards the ubjects eye. Observe the blinking of both eyes. Ask the subject to look ahead.

Corneal reflex

Ask the subject to look ahead. Take a wisp of cotton wool and touch the cornea gently by the side without bringing the wool in to sight. Observe blinking of both eyes. Repeat the test by touching the conjunctiva and eyelashes.

Exercise: Trace the pathway and describe the findings in possible lesions.

Light reflex

Ask the subject to fix the gaze on a distant object. Inspect the iris and identify the pupil of both eyes. Take a touch and shine it into one eye from one side, avoiding the visual attention on the torch. Observe constriction of the pupils of both eyes. Repeat the test with the other eye. As an alternative, observe the size of the pupil of one eye and then cover the other eye suddenly and observe the change in the size of the pupil.

Exercise: Trace the pathway and describe the findings in possible lesions:

Near Response

The subject fist fixes the gaze on a far object while the examiner holds an illuminated object in front of the subject about 50 cm. away. The subject is then asked to look at the near object. Three important changes occur: convergence, pupillary constriction and accommodation. Convergence and pupillary constriction are easy to observe. Accommodation is difficult to observe. The images formed by reflection on the different surfaces are used to indicate accommodation.

When the subject is looking into distance and the object is held in front of the subject 3 reflections are seen: a clear, small upright image reflected from the cornea; a larger fainter upright image reflected from the anterior surface of the lens; and a small inverted image reflected from the posterior surface of the lens. Identify these images before asking the subject to look at the object and keep on observing the images while the subject does so. The first image does not change. The second image becomes smaller and moves towards the third image. The third image change very little.

Eye Muscles

The muscles of the eye keep both eyes focused on the same object at all times. This is shown by the position of the cornea. If the eyes are not parallel, it indicates presence of squint as a result of weakness or paralysis of one or more of the eye muscles. This is further tested by moving a finger in front of the patient towards up, down, right, and left. Defects in the movement of any eye indicate paralysis or paresis of the muscle.

AUDIOMETRY

Overview

Hearing includes perception of sound waves in terms of pitch, amplitude and amber, higher functions such as recognizing and understanding the meaning of the words and the source of sound. This practical demonstrates the tests for perception of sounds only. The receptors are in the internal ear and different areas in the basilar membrane respond to different frequencies. When sound waves reach the ear, they vibrate the tympanic membrane, which is amplified by the ossicles and transmitted to the fluid in the inner ear where appropriate receptors are stimulated: air conduction. Any vibration that travels through the bones of the skull will also be transmitted to the bony covering of the inner ear and to the fluid in it and stimulate the receptors: bone conduction. When there is defect in the external or middle ear, the air conduction is defective but hearing is possible through bone conduction. In defects of inner ear, hearings by both conductions fail.

Tuning fork test

Tuning forks of different frequencies are used to test the whole hearing range of frequencies. Two different types of tests are available to test for hearing loss and to differentiate the conduction deafness from nerve deafness.

Rinne's test

Strike a tuning fork and place its base on the mastoid process and ask the patient whether the sound is heard. If it is not heard, strike hard and repeat it. If it is not heard the subject is likely to have nerve deafness for that frequency. If it is heard hold it until the sound disappears. As soon as the subject indicates the disappearance of the sound hold the top of the tuning fork near the external auditory meatus. If the subject hears the sound, the car is probably normal and if not the subject probably has conduction deafness. Repeat the test for that ear with tuning forks of varying frequencies to cover the audible range. Then test the other ear

Weber's Test

Strike a tuning fork and place its base on the vertex or at the centre of the forehead. Ask the subject whether the sound is heard in both ears equally or which ear is louder. If both ears are similar the hearing is normal. If one ear is louder than the other, the louder ear may have conduction deafness or the other ear may have partial or complete nervous deafness.

The effect of blocking the external auditory meatus

Block one auditory meatus with a piece of cotton wool and repeat the tests, auditory acuity, Weber and Rinne’s tests. To show that the latter two tests depend on the masking effect of room noise, remove the cotton wool, place the fork on the mastoid process and at the moment when it becomes inaudible, insert in the ear, where upon the sound will once be heard for a few seconds.

Localization of sound

The subject closes his eyes. The observer makes clicking noises with the forceps behind the subject and asks him to locate the direction/position of sound. Record the result in a tabular form.

Masking of sound

Ask the subject to read from a book. After a few sentences, make a rattling noise, use a tin box with some stones etc. near his ear. The intensity of the voice will be raised. This does not occur in deaf persons.

Interpretation of hearing test results

Hearing condition	Webers test	Rinnes test
Normal	Midline	AC>B for both ears
Conduction loss	Lateralization to the affected ear	BC>AC for affected ear
Nerve Deafness	Lateralization to the normal ear	AC>BC for both ears

Audiometry

Principle: Audiometer is an instrument which has several facilities for objective assessment of hearing ability. It has two types of graded out-puts. One out-put goes to earphones for testing air conduction. The other output goes to a vibrator which can be fitted over the mastoid process for assessment of bone conduction. The instrument can generate pure tones at selected frequencies which covers the hearing range. Complicated inputs from tape recorders or conversation are also possible: this facility is not used for routine testing.

Procedure: Seat the subject comfortably and switch on the audiometer. Turn the amplitude knob to the maximum. Initiate the sounds of pure tones and let the subject to familiarize with sounds of various frequencies. Then explain to the subject that during testing, the subject will have to indicate as the sound is recognized through the hearing aid.

Reduce the amplitude to the lowest level and fit the earphones. Select the output to one ear and select the lowest frequency. Switch on the sound generating mechanism and go on increasing the amplitude slowly. As the subject signals of hearing the sound, note the amplitude and enter it on the record sheet against that frequency. Repeat the procedure with the next frequency until all are tested.

Then perform the test for the other ear and follow it with test for bone conduction on both sides. At the end a record of minimum amplitude of the sound heard by the subject at each frequency by each ear through air and bone conduction is made out.

Exercise: Describe the findings in possible lesions:

VESTIBULAR FUNCTION TESTS

Overview

Each inner ear balance organ has five end organs: the three semicircular canals (anterior, posterior and horizontal canals) which sense rotation or “angular acceleration” and two gravity sensors (utricle and saccule) that sense “linear acceleration” including gravity. Tests for vestibular function are done to assess if one or both inner ears are functional. First, examination of the eye movement is made to rule out nystagmus.

Caloric Test

Lying semi recumbent on a bed, dark goggles will be placed on your eyes and a small infrared camera records your eye movements. Each ear is irrigated (flushed out) with warm and cool water alternately for 30 to 40 seconds. A sensation of dizziness and/nausea lasting for 5 minutes may be experienced. The caloric test determines the difference between the function of the left and right inner ears.

Video-Nystagmography (VNG)

This test examines the eye movements using video recording or electrodes (the VNG machine). The test is carried out with the subject seated comfortably in a chair in dark and light rooms.

Rotational chair test

The rotational chair test is used along with the VNG to confirm the diagnosis and assess compensation of the vestibular system. This test measures responses of head movements that are similar to daily activities. During this test, the subject sits in a chair that moves to the right and left at various speeds and eye movements are recorded. Subject is also asked to look at a black and white striped curtain which moves around the room.

Subjective Visual Vertical/Horizontal (SVV/SVH)

The subjective visual vertical (SVV) test evaluates the utricle, which is sensitive to changes in gravity. Subject will be tasked to set the vertical and horizontal positions of a light bar by using a controller. In a dark room, the subject is asked to click on a mouse when he/she observes a vertical movement of a projected image (particularly, a line). Typically, subject is made to complete ten trials of this test. When you have damage of the inner ear or in the brainstem on one side, you lines will be tilted.

Vestibular Evoked Myogenic Potential (VEMP)

The purpose of this test is to determine the functionality of the otolith in the saccule and the vestibular nerve. Three electrodes are attached to the neck, the forehead and the clavicle. Repetitive loud clicks or sounds are presented to each ear and the electrical response of the muscle is recorded.

Video Head Impulse Test (VHIT)

The Video Head Impulse test uses cameras and sensors (mounted in goggles) to observe the eye movements during quick head movements. This test is used to assess the function of the six semicircular canals. The VHIT tests the ability to match rapid head movements with equal and opposite eye movements.

Summary: at the end of the course, the student is expected to know the normal Physiologic values and if there deviation in the normal, the student can make simple diagnosis arising from the abnormality.

Exercise

1. Draw a table and plot a graph of glucose concentration against time to show fasting glucose concentration, the peak of glucose concentration within the 2hours as well as the time it takes for glucose level to fall back to normal (fasting).
2. What is meant by normal real threshold for glucose
3. Using the time trace calculate the following
    a. Latent period (mm/sec) (what causes this?)

b. contraction period (mm/sec)
4. measure the height of contraction
5. Discuss your results and explain the various path ways involved. On what part of the nervous path way would you expect to find an interruption of?
   a. A tendon reflex was absent and
   b. A tendon reflex was exaggerated?
   c. Explain the physiological principle involved.

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Chapter 13

PHS 309 NEUROENDOCRINOLOGY

Victor D. Dapper, Samuel O. Odeh, Alhassan Abdulwahab, Adesoji A. Fasanmade

Overview

Neuroendocrinology is the study of the interactions between the endocrine and the nervous system. Neuroendocrinology basically describes how the nervous system controls the endocrine system. Neuroendocrine studies have paved the way for understanding a number of human disease condition particularly brain disorders of neurobiological origin. Neuroendocrine systems have also enhanced our understanding of neuroscience and physiology. Historically neuroendocrinology as a field of study developed rapidly over the past 50years. The hypothalamus and the pituitary gland are intimately and intricately linked. This linkage extends embryologically and morphologically resulting in a hypothalamo-hypophysial system that is of immense endocrine importance. This linkage results in the hypothalamus regulating the pituitary gland. Hypothalamic regulation of the anterior pituitary gland is via the release of specific hormones called either inhibitory or releasing factors that control the secretion of specific anterior pituitary hormones. Hypothalamic regulation of the posterior pituitary on the other hand involves the synthesis and transport of specific hormones that are subsequently stored and released from the posterior pituitary gland. These hormones are released in response to nerve stimuli originating from the hypothalamus. The pituitary gland has been described as the 'master' endocrine gland because it initiates a cascade of events that results in the control of almost all endocrine organs of the body. The role of hormones in ensuring homeostasis cannot therefore be overemphasized. The hypothalamus by controlling the anterior pituitary gland via the hypothalamo-hypophysial system therefore plays an essential role in homeostasis. The roles of the hypothalamus and the pituitary gland in the orchestration of the activities of endocrine glands can not be overemphasized, as the functions of most of other endocrine glands are dependent directly or indirectly on the hormonal activity of the Hypothalamo-hypophyseal axis. The hypothalamus is below the thalamus and the pituitary gland is anatomically and physiologically connected to the hypothalamus. Both of them are situated within the intracranial cavity Hypothalamus in an essential part of the brain and is often considered the "control center" for most hormones. Neurosecretion is defined as the synthesis and storage of neuropeptides in brain neurons and their release from axonal terminals into the circulation. Hypothalamus is considered as neurosecretory organ that produces the neurosecretions due to the presence of several groups of cells that are defined as hypothalamic neurosecretory cells.

Objectives

At the end of this chapter, the student should be able to:

1. Define and explain the term neuroendocrinology
2. Differentiate between Endocrine hormones and neuroendocrine hormones
3. Describe the neuroendocrine functions of the hypothalamus and other associated organs
4. Provide a brief history of the development of neuroendocrinology as a field under physiology

5. Explain the pituitary gland and define its relationship to the hypothalamus
6. Identify the hormones of the anterior and posterior pituitary and describe their general functions
7. Understand the basic anatomy, histology, and embryology of the pituitary gland
8. Identify the various stimulatory and inhibitory factors or hormones released by the hypothalamus and describe their specific functions.
9. Understand the role of the hypothalamo-hypophysial system in ensuring homeostasis
10. Identify the hormones secreted by the hypothalamus
11. Describe the physiology of the control systems involving the hypothalamus and the pituitary gland
12. Describe the connection of hypothalamus to the pituitary gland
13. Describe the tropic hormones of the anterior pituitary gland and their functions
14. Describe the hormones of the posterior pituitary gland, their source and their functions
15. Describe the self-regulatory mechanism between the hypothalamus, the pituitary and other endocrine organs

Historical origins of a Neuro-endocrine connection

Introduction

Neuroendocrinology is the study of the interactions between the endocrine and the nervous system. Neuroendocrinology basically describes how the nervous system controls the endocrine system. Specifically, it explores the role of the hypothalamus in regulating the functions of the pituitary and other endocrine glands thereby ensuring homeostasis.

Endocrine hormones and neuroendocrine hormones: The endocrine system refers to the several endocrine glands in the body that produce chemical substances called hormones. Endocrine hormones are secreted by specialized endocrine organs or cells released into the circulatory system and affect the functions of cells distant from their site of release. Endocrine hormones present with three different types of chemical structures viz:

1. Proteins or polypeptide hormones

Most endocrine hormones are either proteins or polypeptides. By definition polypeptide hormones have less than 100 amino acid residues while protein hormones have more. It includes hormones of the anterior and posterior pituitary, pancreatic hormones and hormones of the parathyroid gland amongst others. These hormones are water soluble.

2. Steroid hormones

These are hormones derived from cholesterol or its derivatives. It includes all hormones of the adrenal cortex, hormones of the gonads including the testes and the ovaries and placental hormones. These hormones are lipid soluble.

3. Derivatives of the amino acid tyrosine

These hormones are derived from the amino acid tyrosine. They include just two types of hormones; these are the Thyroid metabolic hormones called thyroxine and triiodothyronine and the hormones of the adrenal medulla called the catecholamines.

Neuroendocrine hormones are hormones secreted by neurons into the circulating blood and influence the function of cells distant from their site of secretion. An important neuroendocrine axis is the posterior and the anterior pituitary. Their specific mechanism would be described in details in **the following chapter.**

A BRIEF HISTORY OF NEUROENDOCRINE DEVELOPMENT

For their study of neuropeptides in 1945, Ernst and Berta Scharrer are regarded as co-founders of the subject of neuroendocrinology. Neuropeptides are messenger molecules usually released in association with neurotransmitters at nerve endings. They can act to modulate the activity of the released neurotransmitter by increasing or decreasing synaptic transmission. Neuropeptides are small proteinaceous substances produced and released by neurons through the regulated secretory route and acting on neural substrates. Neuropeptides can function or be regarded as peptide hormones as they can modulate most body functions. The description of the hypothalamic control of anterior pituitary functions via hypothalamic neuronal secreting cells into the hypothalamic-hypophysial portal system by Geofrey Harris earned him the father of neuroendocrinology status. The neural control of immune functions was demonstrated in 1952 by Andor Szentivanyi.

Following these early discoveries, a more neuroendocrine axes have been described. For instance, neuroendocrine neurons controlling the gonads and thus influencing the human brain are known. Neuroendocrine axes exist in the peripheral nervous system modulating the absorption and digestion of ingested food. The cells of the adrenal medulla that release noradrenaline and adrenaline in response to nerve stimulation are neuroendocrine in nature. Indeed, the discovery that the adrenal cortex could be modified by nerve stimulation under the influence of makes the adrenal cortex a possible neuroendocrine axis.

A REVIEW OF THE PHYSIOLOGIC ANATOMY OF HYPOTHALAMO-PITUITARY LINK

General introduction

The hypothalamo-hypophyseal system is an intricate system that refers to the hypothalamus and the pituitary gland. This system includes parts of the hypothalamus and essentially the whole of the pituitary gland. Through an intricate anatomical network, the hypothalamus controls both the anterior and the posterior parts of the pituitary gland. Hypothalamic control of the anterior pituitary gland is via the release of certain inhibitory and stimulatory factors that either stimulate or cause the inhibition of certain appropriate hormones or factors from the anterior pituitary gland. The control of the posterior pituitary on the other hand is via direct nervous stimulation.

The Pituitary Gland

The pituitary gland otherwise also called the hypophysis is a small gland that is situated in the Sella turcica. Physiologically the pituitary gland is divided into two distinct portions: anterior pituitary and posterior pituitary; both are separated by an avascular third portion called the pars intermedia. The pars intermedia is poorly

developed in humans. The anterior pituitary is called the adenohypophysis while the posterior pituitary is called the neurohypophysis.

Embryologically, both the anterior and posterior pituitary arise from ectodermal; however, they arise from different sources. For instance, the anterior pituitary arises from an upward growth of a portion of the roof of the pharyngeal epithelium called the Rathke's pouch. Therefore, the cell types of the anterior pituitary are essentially of epithelioid nature. The posterior pituitary on the other hand, it arises from a downward growth of neural tissue (the diencephalon) making its major cells components to be neural. Though physically separate and distinct the pituitary gland is connected to the hypothalamus is via a stalk called the pituitary stalk.

Histologically, the anterior pituitary is composed of five cellular types. These cell types are somatotropes, corticotropes, thyrotropes, gonadotropes and lactotropes. The posterior pituitary on the other hand is composed of pituicytes which are glial cells, they function mainly as a site of storage and release of hormones of the posterior pituitary.

Vascular supply of the pituitary gland is from the internal carotid arteries via the hypophysial arteries. These form the hypothalamo-hypophyseal portal system that supplies the hypothalamus and the pituitary gland allowing rapid and easy exchange of materials between them. It is this system that transports all the hormones of the hypothalamus to the anterior pituitary and transports the hormones of the anterior and posterior pituitary into the systemic circulation. This vascular system does not include the posterior pituitary gland.

Nerve supply of the pituitary gland is exclusively from the hypothalamus via neurosecretory cells. The anterior pituitary essentially has no important nerve supply.

The Hypothalamus

The hypothalamus lies immediately below the thalamus and above the pituitary gland and the brain stem. It is part of the limbic system. Physiologically the hypothalamus is a major controlling centre of body function as it receives impulses from almost all parts of the human body. It therefore plays critical role in ensuring homeostasis by integrating these impulses and directly influencing either the autonomic nervous system or by managing hormones secreted by the pituitary gland. The hypothalamus links the nervous system to the endocrine system through the posterior pituitary gland and is critical to the vegetative functions of the human body including temperature regulation, regulation of autonomic functions and the control of appetite.

The hypothalamo-hypophysial system:

This is an intricate system that anatomically connects the hypothalamus and the pituitary gland. The figure below shows the intricate connections between the hypothalamus and the pituitary gland. Of note is the hypothalamo-hypophysial portal system. This is a portal vascular system that connects the hypothalamus with the highly vascularised anterior pituitary gland through the pituitary stalk. Each of the pituitary inhibitory or stimulating factors is transported from the hypothalamus where they are synthesized to the anterior pituitary gland through the hypothalamo-hypophysial portal system. These hypothalamic factors are secreted by specific centers in the hypothalamus via special hypothalamic nerve cells. It is these factors that enables the hypothalamus to control the functions of the anterior pituitary gland.

Endocrine functions of the Hypothalamus: The hypothalamus is involved in hormone secretion essentially via regulation of the secretions of the hormones of the anterior pituitary gland and synthesis and transport of specific hormones that are subsequently stored and released from the posterior pituitary gland.

Hypothalamic regulation of anterior pituitary secretion: The releases specific hormones into the hypothalamo-hypophysial portal system. These hormones are subsequently transferred to the anterior pituitary gland. These hormones include:

1. Corticotropin-releasing hormone (CRH). This hormone stimulates the anterior pituitary gland to cause release of ACTH which helps to stimulate the secretion of hormones of the adrenal cortex.

2. Gonadotropin-releasing hormone (GnRH). This hormone causes the release of the gonadotrophic hormones from the anterior pituitary gland. The gonadotrophes are Follicle stimulating hormone (FSH) and luteinizing hormone (LH). These hormones ensure normal functioning of the gonads: ovaries and testes.

3. Growth hormone-releasing hormone (GHRH). This hormone causes the release of Growth hormone from the anterior pituitary gland.

4. Growth hormone-inhibiting hormone (GHIH). This hormone is also called Somatostatin. It has an effect opposite to Growth hormone-releasing hormone and acts to inhibit the release of Growth hormone.

5. Prolactin-releasing hormone (PRH). This hormone causes the release of Prolactin from the anterior pituitary gland thereby enhancing the production of milk.

6. Prolactin-inhibiting hormone (PIH). This hormone is also known as Dopamine inhibits prolactin secretion and the production of milk.

7. Thyrotropin releasing hormone (TRH). This hormone causes the release of Thyroid stimulating hormones from the anterior pituitary and eventually stimulates release of thyroid hormones from the Thyroid gland.

Hypothalamic regulation of posterior pituitary secretion: The hormones of the posterior pituitary are Oxytocin also called arginine vasopressin and Antidiuretic hormone (ADH). Both hormones are actually synthesised in the hypothalamus but released from the posterior pituitary gland. They are synthesized in both the supra-optic nuclei and the paraventricular nuclei and then transported along the axonal nerve fibres of nerve cells whose cell bodies are in these nuclei and then stored in secretory vesicles on nerve endings located in the posterior pituitary gland. The cells that secrete these hormones have their cell bodies at either of the two hypothalamic nuclei and nerve endings in the posterior pituitary gland.

Hormones of the anterior pituitary gland

The anterior pituitary secretes six essential hormones that encourage growth and regulate metabolic activities in the human body, induce follicular development and ovulation and regulate fluid balance. These hormones include:

Growth hormone (GH)

Prolactin (PRL)

Thyroid stimulating hormone (TSH)

Follicle stimulating hormone (FSH)

Luteinizing hormone (LH)

Adrenocorticotropic hormone (ACTH)

Growth hormone also called Somatotrophin is secreted by sommatotropes of the anterior pituitary gland. It promotes body growth by causing protein deposition and affects both lipid and carbohydrate metabolism.

Prolactin (PRL) also called Lactotropin is a polypeptide hormone secreted by lactotrophs that targets ovaries, the mammary glands, testes and prostate. It promotes the secretion of estrogens, progesterone and induces lactation and spermatogenesis.

Thyroid stimulating hormone (TSH) is also called Thyrotropin is a glycoprotein hormone secreted by Thyrotrophs. It acts almost exclusively on the thyroid gland to stimulate the secretion of the Thyroid metabolic hormones.

Follicle stimulating hormone (FSH) is a glycoprotein hormone secreted by gonadotrophs and acts on the gonads in both males and females to cause reproductive growth and development. It acts to cause follicular growth and development critical for female reproduction.

Luteinizing hormone (LH) also called Lutropin is a glycoprotein hormone secreted by gonadotrophs and acts on the gonads in both males and females to cause reproductive growth and development via stimulating sex hormone secretion. Along with FSH, it is also responsible for ovulation.

Adrenocorticotropic hormone (ACTH) also called corticotropin is a peptide hormone secreted by corticotrophs and acts almost exclusively on the adrenal glands to cause the secretion of mineralocorticoids, glucocorticoids and the adrenal androgens.

Hormones of the posterior pituitary gland

The posterior pituitary secretes two hormones that play vital roles water homeostasis, milk expression during breast feeding and perhaps facilitates the process of labour. These hormones are:

Oxytocin

Antidiuretic hormone (ADH)

Oxytocin is a polypeptide hormone secreted by the supraoptic and paraventricular nucleus of the hypothalamus. Its target organs are mainly the uterus where it stimulates uterine contractions and in the mammary glands where it causes lactation and induces the milk-let down reflex.

Antidiuretic hormone (ADH) is also called arginine vasopressin. Its target are the kidneys and arterioles. As its the name implies, in the kidneys it causes retention of water (anti diuresis) and causes arteriolar contraction thereby increasing in blood pressure via a pressor effect.

THE “MASTER GLAND” OF THE ENDOCRINE SYSTEM. PITUITARY SECRETIONS AND THEIR CURRENT CONCEPTS OF THE SERVOMECHANISMS BETWEEN THE HYPOTHALAMUS, THE PITUITARY AND OTHER ENDOCRINE ORGANS.

The hypothalamus and pituitary gland complex has long been termed the 'master gland' due to the roles played by the secretions of these endocrine glands on the activities of other endocrine glands in the body. Some people refer to the hypothalamus as the conductor of the endocrine orchestra. This is borne out of the controlling effects of the endocrine part of the hypothalamus on the anterior pituitary, which also plays a role on most of the endocrine glands.

The hypothalamus is a small part of the diencephalon, just below the thalamus. It is made up of several nuclei grouped into four main regions:

- Mammillary: in the posterior hypothalamus. The mammillary bodies serve as relay station for reflexes along with the posterior hypothalamic nucleus.
- infundibulum connects the hypothalamus with the pituitary gland. The median eminence encircles the infundibulum.
- Supraoptic: lies above the optic chiasma. It contains the supraoptic, paraventricular, anterior hypothalamic and suprachiasmatic nuclei.The posterior pituitary glans is connected with the supraoptic and paraventricular nuclei through the infundibulum.
- Preoptic: contains the lateral and medial preoptic nuclei, which participate in autonomic activities.

The hypothalamus is the major regulator of homeostasis through its hormones as well as the control of other hormonal functions in the body. It is important for autonomic activities as well as regulation of temperature.

The hypothalamus has two major connections to the pituitary, and secretes hormones that control the hormones of the anterior pituitary and hormones that are stored in the posterior pituitary for later release when required.

The hypothalamo-adenohypophyseal tract is made up of blood vessels (portal veins) that connect the hypothalamus with the anterior pituitary. Hormones that are transported through this tract are the releasing hormones (growth hormone releasing hormone, gonadotropin releasing hormone, thyrotropin releasing hormone, corticotropin releasing hormone and prolactin releasing hormone) and inhibiting hormones (Growth hormone inhibiting hormone and prolactin inhibiting hormone, also known as dopamine).

The hypothalamo-nuerohypophyseal tract is a network of nerves connecting the hypothalamus with the posterior pituitary. Hormones secreted by the supraoptic nucleus (vasopressin – antidiuretic hormone) and paraventricular nucleus (oxytocin) are transported by axonic transport to the posterior pituitary for storage. When required, the posterior pituitary stores release the hormones.

Other functions of the hypothalamus include:

- Maintenance of daily physiologic cycles
- Control of appetite
- Control of sexual behaviour
- Regulation of emotional responses
- Maintenance of body temperature

- Blood pressure maintenance

Endocrine function of the adenohypophysis includes secretion of hormones from the endocrine cells (corticotropes, thyrotropes, gonadotropes, somatotropes and lactotropes). The secretion of these hormones is controlled by the corresponding stimulating or inhibiting hormones produced in the hypothalamus. The hormones also stimulate their corresponding peripheral hormones through a negative feed back mechanism.

The negative feed back mechanism is represented by loops that control the hormonal action of the major hormones of the thyroid gland, adrenal cortex and the gonads. The loops are the long, short and ultrashort loops.

The long loop is the inhibiting effect of the peripheral hormone (e.g. glucocorticoid from the adrenal cortex) on the hypothalamus to inhibit the secretion of the releasing hormone (e.g. corticotropin releasing hormone).

The short loop is the inhibiting effect of the peripheral hormone (e.g. glucocorticoid from the adrenal cortex) on the anterior pituitary to inhibit the secretion of the tropic hormone (e.g. adrenocorticotropic hormone – ACTH).

The ultrashort loop is the inhibiting effect of the tropic hormone (e.g. adrenocorticotropic hormone – ACTH) on the hypothalamus to inhibit the secretion of the releasing hormone (e.g. corticotropin releasing hormone).

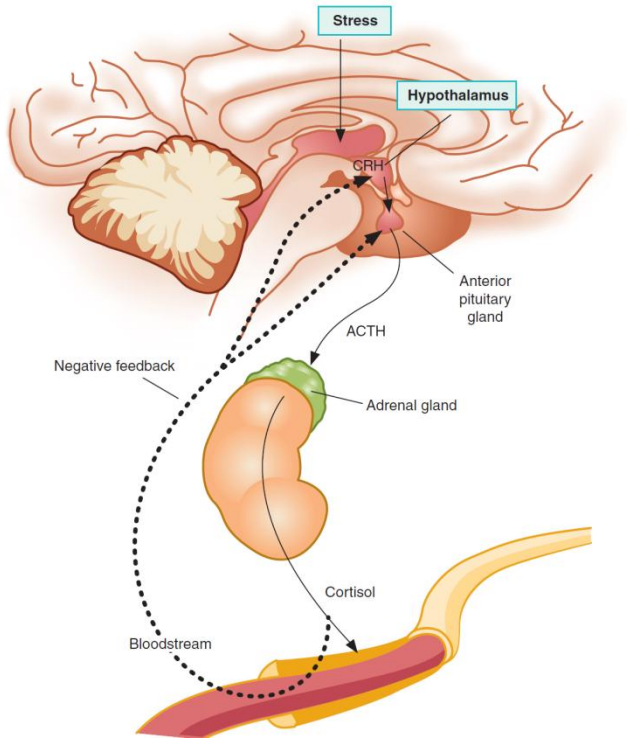

Figure 13.1: Hypothalamic-pituitary-adrenal axis

The hormones of the posterior pituitary are the neuropeptides produced by the magnocellular neurons of the hypothalamus (supraoptic and paraventricular nuclei). The hormones are subsequently released by the posterior pituitary, where they are stored. The hormones are vasopressin (antidiuretic hormone) and oxytocin.

Vasopressin release is triggered by stimulation of the osmoreceptors of the pituitary when the plasma osmolarity is high. Low plasma volume can also stimulate the receptors. Vasopressin acts on the distal convoluted tubes and the collecting ducts of the kidney to increase water reabsorption from the renal tubules, producing concentrated urine.

Oxytocin is produced in response to stimuli from the uterine cervix during parturition and the myoepithelial cells of the lactating breast. Pressure on the cervix from the presenting part of the baby, during parturition, sends signals to the hypothalamus, with the release of oxytocin. Oxytocin causes dilatation of the cervix in a characteristic positive feedback mechanism. The more the pressure on the cervix, the more is the uterine contraction and cervical dilatation, for the expulsion of the baby. Oxytocin effect on the myoepithelial cells of the breast is similarly by a positive feedback mechanism, for milk ejection.

HYPOTHALAMIC NEUROSECRETIONS: THE 'MASTER GLAND' OF THE ENDOCRINE SYSTEM

The Hypothalamus

The hypothalamus is located at the base of the brain just below the thalamus. Hypothalamus is a key centre regulating numerous and diverse physiological functions, including growth, metabolism, stress responses, reproduction, osmoregulation, and circadian rhythms

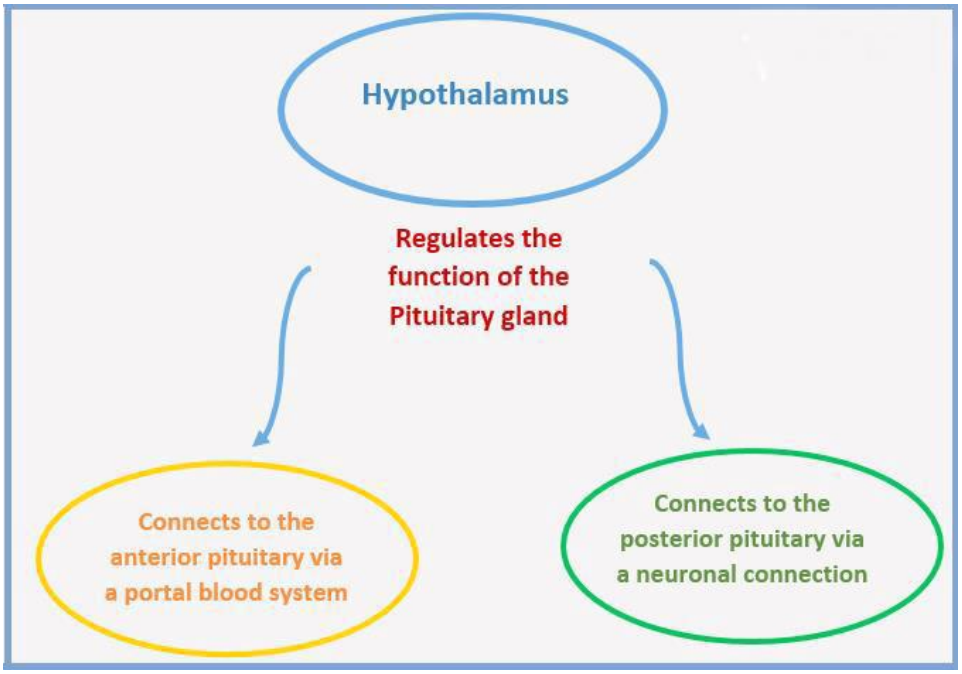

Figure 13.2: Relationship between hypothalamus and pituitary gland.

Hypothalamic neurosecretory cells

Neurosecretory cells are modified nerve cells which, rather than secreting a neurotransmitter, release a hormone into the circulation for neuroendocrine communication. There are two groups of hypothalamic neurosecretory cells: the magnocellular and parvicellular systems

The magnocellular system

The large magnocellular neurosecretory cells are located in the paraventricular (PVN) and supraoptic nuclei (SON). The paraventricular nucleus consists of two cell types, one produces the hormone oxytocin and the other vasopressin (antidiuretic hormone).Similarly, the supraoptic nucleus (SON) produces both oxytocin and vasopressin. These hormones are released from the nerve terminals of the axons of the magnocellular neurosecretory cells in the pars nervosa (neurohypophysis).

The parvicellular system

The smaller parvicellular neurosecretory cells are found in the preoptic area, VMN, and arcuate nucleus, as well as various other hypothalamic areas and project to the median eminence. The parvicellular neurosecretory cells terminating at the median eminence release their hypothalamic hormones into the primary plexus, from which they enter the hypophyseal portal veins. These hormones modulate the release of adenohypophyseal hormones and are thus referred to as the 'hypophysiotropic hormones'.

Hypothalamic nuclei

The hypothalamus contains discrete, organised clusters of neurons (group of nerve cell bodies) called the hypothalamic nuclei, which synthesis the hypothalamic releasing and inhibiting hormones that regulate the activity of the anterior pituitary as well as the neurohormones which are released by posterior pituitary. These nuclei include arcuate nucleus, periventricular nucleus, and supraoptic nucleus. The medial basal hypothalamus, comprising the ventromedial nuclei (VMN), arcuate nuclei and the median eminence, it’s often referred to as the endocrine hypothalamus because of its neuroendocrine functions.

Hypothalamic–pituitary neurosecretory systems

Is a system that is responsible for controlling endocrine activities through actions initiated by the hypothalamus and are mediated through hormonal secretions produced by the pituitary gland beneath it. The system comprises of hypothalamic neurosecretory cell, a corresponding pituitary hormone, and a target organ and/or hormone.

Hypothalamic–adenohypophyseal system

The hypothalamic–adenohypophyseal system, comprise neurosecretory neurons in the hypothalamus, which synthesizes adenohypophyseal hormone releasing factors and secretes them into the hypophyseal portal vein to control the secretion of adenohypophyseal hormones.

The hypothalamic–neurohypophysial system

The activity of the posterior pituitary gland is through a neural connection between the hypothalamus and the posterior lobe of the pituitary gland. The hormones of the posterior pituitary gland are synthesized in the cell

bodies of the magnocellular neurons in the supraoptic and paraventricular nuclei and transported down the axons of these neurons to their endings in the posterior lobe of hypothalamus.

Hypothalamic-Pituitary-GH Axis

GH secretion is regulated by two hormones produced by the hypothalamus:

- Growth hormone-releasing hormone (GHRH) stimulates the release of GH
- Growth hormone-inhibiting hormone (GHIH) also known as somatostatin acts antagonistically to inhibit the release of GH.

Hypothalamus-Pituitary-Adrenal Axis

Hypothalamic-pituitary-adrenal axis describes the interactions between the hypothalamus, anterior pituitary, and the adrenal cortex, involving stimulatory effects of hypothalamus on corticotrophs of the anterior pituitary and anterior pituitary on adrenal cortex as well as negative feedback actions of the end product hormone on the hypothalamus or anterior pituitary.

Hypothalamic-Pituitary-Thyroid Axis

The thyrotropin-releasing hormone (TRH) is a tripeptide that stimulates the release of thyroid-stimulating hormone (TSH) and prolactin from the anterior pituitary gland.

Hypothalamic-Pituitary-Gonadal Axis

The main gonadrotrophins are FSH and LH; the release of both is regulated by gonadotropin-releasing hormone (GnRH), which is produced by the hypothalamus.

Hypothalamic-Pituitary-Lactotroph Axis

Prolactin is the hormone which initiates and maintains lactation. The physiological control of prolactin levels is coordinated by the hypothalamic pituitary lactotroph axis.

Summary

Neuroendocrinology is the study of the interactions between the endocrine and the nervous system. Neuroendocrinology basically describes how the nervous system controls the endocrine system. For their study of neuropeptides in 1945, Ernst and Berta Scharrer are regarded as co-founders of the subject of neuroendocrinology. Neuropeptides are messenger molecules usually released in association with neurotransmitters at nerve endings. The hypothalamo-hypophysial system plays an important role in hormonal regulation of homeostasis. The hypothalamus and the pituitary gland are closely related functionally although they differ morphologically and are embryologically distinct. The hypothalamus regulates anterior pituitary function via the release of either stimulatory or inhibitory factors while the hypothalamus regulates posterior pituitary function via a direct effect of nerve stimulation for the release of posterior pituitary hormones. The hormones of the posterior pituitary are synthesized in the hypothalamus but transported to the posterior pituitary for storage and subsequent release. The hypothalamus has two major connections to the pituitary, and secretes

hormones that control the hormones of the anterior pituitary and hormones that are stored in the posterior pituitary for later release when required. It is connected to the anterior pituitary through portal veins, by which the releasing and inhibiting hormones affect the activities of the anterior pituitary. The connection with the posterior pituitary is by neurons through which neuropeptide hormones produced in the hypothalamus travel to the posterior pituitary for storage until needed in the body. Hypothalamus in an essential part of the brain and is often considered the "control center" for most hormones as well as a key centre regulating numerous and diverse physiological functions which is exemplified by the hypothalamic-pituitary-GH axis, hypothalamus-pituitary-adrenal axis, hypothalamic-pituitary-thyroid axis, hypothalamic-pituitary-gonadal axis and hypothalamic-pituitary-lactotroph axis.

Exercises

1. What is neuroendocrinology?
2. Explain the differences between endocrine and neuroendocrine hormones
3. What are the important historical developments in neuroendocrinology that are relevant to physiology
4. Describe the pituitary gland and define its relationship to the hypothalamus
5. Identify the various hormones secreted by the anterior gland. Briefly outline their specific functions
6. Identify the various hormones of the posterior pituitary. Are these hormones similar? Describe their general functions
7. Identify the various stimulatory and inhibitory factors or hormones released by the hypothalamus. Briefly outline their specific functions.
8. Describe the role of the hypothalamus in ensuring homeostasis
9. Why is the pituitary gland described as the 'master' endocrine organ and not the hypothalamus?
10. Discus the hypothalamic neurosecretions
11. Write short notes on the following:
    a. Hypothalamic-pituitary-GH axis
    b. Hypothalamus-pituitary-adrenal axis
12. Describe the role of the hypothalamus in the control of endocrine organ function in the body
13. Describe the anatomical connections between the hypothalamus and the pituitary gland
14. Differentiate the negative and positive feedback mechanisms

Describe the functions of the posterior pituitary hormones.

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Chapter 14

PHS 311 PATHOPHYSIOLOGY II

Samuel O. Odeh, Walter C. Nwafia, Aliyu Mohammed , Adesoji A. Fasanmade, Maisaratu A. Tukur, A. Ibrahim Salisu , Fortune S. Amah-Tariah, Victor D. Dapper, Jude N. Egwurugwu, Eze K. Nwangwa

OVERVIEW

Pathophysiology enables the student to understand how diseases changes normal function of a cell, tissue or organ from normal to disease condition. This condition changes the normal well being of an individual and causes symptoms related to the abnormality. The disorders of gastrointestinal system leads to the inappropriate digestion and absorption of food substances leading to deficiency of certain food substances and can lead to symptoms like diarrhoea, constipation or due to abnormal secretion of hydrochloric acid that lead to peptic ulcer disease. Tremor is defined as rapid alternate rhythmic and involuntary movement of flexing and extension in the joint of fingers. Tremor is the most commonly encountered movement disorder. It is symptomatic of an underlying disorder however; some tremors are without underlying disorder. A wide range of pathologies may manifest with tremor either as a presenting or predominant symptom. Speech disturbances occur as result damage to the central speech apparatus consists of higher centers, i.e. the cortical and subcortical centers. Peripheral speech apparatus includes larynx or sound box, pharynx, mouth, nasal cavities, tongue and lips. Human gait depends on a complex interplay of major parts of the nervous, musculoskeletal and cardio-respiratory systems. The individual gait pattern is influenced by age, personality, mood and socio-cultural factors. Safe walking requires intact cognition and executive control. Gait disorders lead to a loss of personal freedom, falls and injuries and result in a marked reduction in the quality of life. Memory disturbances occur as a result to the neuroanatomical structures that hinders the storage, retention and recollection of memories. Memory disorders can be progressive, including Alzheimer's disease, or they can be immediate including disorder resulting from head injury. Parkinsonism is a motor disorder characterized by rigidity, tremors and bradykinesia. A typical example of Parkinsonism is Parkinson's disease (PD). Parkinson disease (PD) is one of the disorders of the basal ganglia which form part of the extrapyramidal system, which is concern with integration and regulation of motor activities. It occurs in elderly people due to a steady loss of dopamine and dopamine receptors with age. Ataxia refers to incoordination of voluntary movement which occurs due to loss of kinesthetic sensation. Ataxia is a neurological sign that manifests in a lack of coordination in the movement of different muscles in the body. It is a clinical finding and not a disease, which mainly presents abnormalities in gait, changes in speech such as scanning speech, and abnormal eye movements such as nystagmus. Trunk ataxia often indicates cerebellar vermis lesions and limb ataxia often indicates cerebellar hemisphere lesions. Growth hormone is produced from the somatotrophs of the anterior pituitary with a releasing hormone from the hypothalamus and an inhibiting hormone, also from the hypothalamus, controlling the activity of growth hormone. Growth hormone stimulates somatic growth and regulates metabolism. Excessive production of growth hormone may have consequences of abnormal growth, with differences in presentation when it occurs in children and adults. In pathology of the anterior pituitary, defects in the secretory pattern of hormones of the anterior pituitary may be apparent. Infertility is the inability of a couple to achieve pregnancy after one year of regular unprotected sexual intercourse. . It also includes the inability to carry a pregnancy to the delivery of a live baby. Male infertility is established when the female partner is known to be fertile, but the male could not impregnate the female. Male factor infertility is responsible for 40–

50% of all infertility in Nigeria although it varies from one region to another, and the causes also vary from place to place. This section deals with pathophysiology of errors of refraction, myopia, and hypermetropia, pathophysiology of visual pathway disturbance and disturbances colour vision. It also gives the highlight of deafness and pathophysiology of hearing disturbance. The pathophysiology of sensory disturbances and the pathophysiology of syringomyelia and peripheral neuropathies, neurosyphilis, thalamic syndrome, herpes simplex is examined in this chapter. Although these are of varied aetiology, they are considered together here for convenience. Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It serves a protective function to avoid further damage of tissues. The current chapter examines the pathophysiology of pain, types of pain including hyperalgesia, algesia, and allodynia. Headache is a common neurologic disorder that affects more than 90% of the population at some time in their life. It is usually a benign symptom, though can be associated with serious diseases such as brain tumor, meningitis and cerebrovascular diseases. The basal ganglia are deep symmetrical structures of the gray matter. There are five nuclear masses in the basal ganglia: caudate nucleus, putamen, globus pallidus, substantia nigra and subthalamic nucleus. Cerebral palsy(CP) is a heterogenous group of neurodevelopmental disorder of movement, muscle tone, or posture caused by nonprogressive injury or abnormal development in the immature brain, before, during or after birth up to 1 year of age. There are two main types of cerebral palsy, spastic/pyramidal cerebral palsy and nonspastic/extrapyramidal cerebral palsy. The deep tendon reflexes, also called muscle stretch reflexes or myotatic reflexes are used to examine and diagnose neurologic diseases affecting afferent nerves, spinal cord synaptic connections, motor nerves, and descending pathways. They are essentially used to assess the upper and lower motor neuron lesions in clinical practice. The primary deep tendon reflexes are biceps, brachioradialis, triceps, patellar, and ankle. Equilibrium is the state of the body where neither the internal energy nor the motion of the body changes with respect to time. Therefore, different forces act on the body in diverse directions with no change in state of rest or motion.

The human ear is anatomically and functionally designed with a lot of sensory apparatus essential for the coordination of the head and movement of the eyes. The vestibular system located in the inner ear helps in the maintenance of postural equilibrium.

The vestibular apparatus consist of the semi-circular canal (which is loop-shaped canal containing fluid and fine, hair-like sensors), utricle and saccules (each containing a patch of sensory hair cells). Within each cells are tiny particles (otoconia) which help in monitoring the position of the head in relation to gravity and linear acceleration

The cerebellum which sits at the back of the brain is also very important in the control of sense of balance. There is also presence of vestibular nuclei in the brain stem which mediates balance.

The basal ganglia are concerned with the integration and regulation of motor activities and and non-motor functions, including higher order cognition, social interactions, speech and repetitive behaviors.

OBJECTIVES

The objectives of this section are to:

1. Differentiate between coarse and fine tremor
2. Mention the causes/pathophysiology of fine tremor

3. Mention the causes/pathophysiology of coarse tremor
4. Understand the pathophysiology of speech disturbances.
5. Briefly explain the physiology of gait
6. Mention the pathophysiology of musculoskeletal gait changes
7. Mention the pathophysiology of neuromuscular gait changes
8. Understand the pathophysiology of memory disturbances
9. Understand what Parkinsonism is.
10. Know pathophysiology of Parkinson's disease.
11. Know the signs and symptoms of Parkinson's disease
12. Mention the meaning of ataxia.
13. Explain the pathophysiology of ataxia.
14. Describe the pathophysiology of
    a. Gigantism and acromegaly
    b. Dwarfism
    c. Infantilism
    d. Simmond's disease
15. Have a basic understand the pathophysiology of the following conditions:
    a. Sensory disturbances and peripheral neuropathies
    b. Syringomyelia
    c. Neurosyphilis
    d. Thalamic syndrome
    e. Herpes simplex
16. Define and understand the terms associate with the physiology of pain
17. What are the types and classification of pain?
18. Outline the pathway for pain perception and transmission
19. Understand the theories of pain

20. Appreciate analgesia system of the nervous system
21. Define headache
22. Types of headache
23. Trigger factors of headache
24. Pathophysiology of headache
25. Outline the five nuclear masses seen in basal ganglia.
26. Mention the triad of Parkinson Disease
27. State the three possible pathophysiological mechanisms associated with Parkinson diseases.
28. State three genes associated with Parkinson Disease.
29. Explain the possible pathophysiological mechanisms that lead to chorea, athetosis and hemiballismus.
30. Describe the features of chorea, athetosis and hemiballismus.
31. Mention the nuclear masses involved in the various conditions
32. Describe cerebral palsy
33. State the the types of cerebral palsy
34. Explain the basic pathophysiological mechanisms of cerebral palsy
35. Mention aetiologic/risk factors
36. Mention the deep tendon reflexes
37. Clinical importance of the reflexes
38. Know the segmental innervations involved
39. Grade the lesions involving the deep tendon reflexes
40. Understand the the functional anatomy of the ear;
41. Highlight the structures that are found in the different parts of the ear;
42. Describe the light microscopic structure of the auricle, ear drum and membrane lining the tympanic cavity;
43. Explain the components of the vestibular apparatus
44. Explain the light microscopic picture of the membranous labyrinth of the inner ear including the maculae, cristae and organ or Corti;
45. Understand the spinal cord as a part of the CNS;

46. Explain the challenges of complete and incomplete section of the spinal cord;
47. Highlight the causes of aphasia;
48. Physiological bases of corneal opacity and cataract; and
49. Highlight the consequences of glaucoma.

PATHOPHYSIOLOGY OF STOMATITIS

Stomatitis is the inflammation and redness of the oral mucosa. It is usually characterized by intense pain, and difficulty in eating and sleeping. The condition most commonly affects the inner cheek, gums, inner lips and the tongue. A type of stomatitis is Canker ulcer (aphthous ulcer) which is a single pale or yellow ulcer with a red outer ring, or as a cluster of ulcers in the mouth. Another is cold sores (fever blisters), a fluid filled sore on the lips, and burning in nature.. The sores usually form crusts with outer scabs.

The symptoms of stomatitis may result from biting the tongue, wearing dental braces, chewing tobacco, burns from hot food, mouth infection like gingivitis, or from autoimmune challenges. Some drugs used in cancer treatment, and radiotherapy may also result in stomatitis. The treatment for stomatitis may be withdrawal of causative agents, pain relief, and anitimicrobials.

XEROSTOMIA

Dry mouth, or xerostomia, is the sensation of not having enough saliva in the mouth. Saliva is important for mouth health. A lack of saliva can lead to tooth decay. Saliva is the fluid produced by the salivary glands in your mouth. Dry mouth occurs as a result of inadequate production of saliva. The most common causes of dry mouth are medications and irradiation. Most often, it happens as side effects of medications, such as antihistamines or decongestants taken for allergies conditions.

Xerostomia is a symptom of a condition, not a condition itself. Dry mouth is common, especially among older adults. Other causes include:

i. Dehydration, when the body lacks enough fluids
ii. Mouth-breathing
iii. Medical conditions like diabetes mellitus and menopause

Lack of saliva can cause problems including:

i. Bad breath, also known as halitosis.
ii. Oral cavities, tooth decay and other mouth diseases.
iii. Disturbance of speech and swallowing.

The goal of dry mouth treatment is to:

i. Manage any underlying condition causing dry mouth.

ii. Prevent tooth decay.

iii. Increase saliva flow.

DYSPHAGIA,

Dysphagia is the medical name for difficulty swallowing. Swallowing difficulty is the inability to swallow foods or liquids with ease. Difficulty swallowing doesn't always indicate a medical condition. It may be transient.

Some conditions related to difficulty swallowing include:

i. Acid reflux and gastrooesophageal reflux disease (GOERD).

ii. Heartburn

iii. Goiter.

iv. Inflammation of the oesophagus.

v. oesophageal tumours

vi. Other medical conditions that may produce swallowing problems as a result of either the condition or its treatment include

Signs and symptoms of dysphagia include painful swallowing, feeling like something is obstructing the throat, regurgitation and weight loss. Some swallowing difficulties can't be prevented, and dysphagia treatment is necessary. Management approaches include dietary changes and oropharyngeal swallowing exercises to strengthen muscles. However, treatments may be prescribed depending on the medical condition causing swallowing difficulty.

ACHALASIA

This is a disorder characterized with difficulty in swallowing food, and even liquids at times. It results from damage of nerves supplying the oesophagus. Peristalsis is thus impaired as the lower oesophageal sphincter fails to relax appropriately. Three types of achalasia are known: type 1 which is the classic, type 2 in which there occurs some pressure build up and compression within the oesophagus, and type 3 often referred to as spastic achalasia due to the abnormal contractions that take place in the lower end of the oesophagus.

The causes of achalasia are not clear, but herpes virus has been implicated. It has been suggested that it may be an autoimmune disorder. Achalsia can occur at any age but appears most frequent in people between ages 30 to 60 years. Symptoms of this condition include dysphagia, heartburn, impaired appetite, regurgitation, an occasionally chest pain. The management is to relax the muscles involved by myotomy or dilation, to enable

easier passage of food into the stomach. Injection of butolinum toxin into the gastro-oesophageal sphincter may be useful. Drugs containing nitrates or calcium channel blockers can help in a temporary relief of the symptoms.

UPPER OESOPHAGEAL REGURGITATION

Upper oesophageal regurgitation, also known as gastro - oesophageal reflux disease is a syndrome in which food substances being swallowed, get thrown out and out through the mouth. When substances move into the stomach from the oesophagus, it is intended that it should move caudally. However, there may be the backflow (reflux) of substances from the stomach into the oesophagus. Remembering that the stomach is an environment of high acidity, the refluxed substances bring an increased acidity to the oesphageal lumen. In occasional (ie non frequent) re-fluxes, there would be no damage to the oesophageal mucosa. However, with repeated, frequent gastro-oesophageal reflux, the mucosal irritation leads to an increase in blood flow to the area (a stage in the inflammatory process). Following the erythema of the oesophageal mucosa, an erosion occurs with progressive epithelial damage. Without an intervention, the erythema progesses to frank oesophagitis. The body attempts a healing process, and this is usually by fibrosis. It thus results in the development of strictures in the oesphagus or of gastric type epithelium in the oesophagus (Barrett's oesophagus).

Aetiology:- Gastrooesphageal reflux disease usually follows heavy smoking habits, ingestion of large meals, fatty foods and obesity. These are behaviours with chemically and mechanically negative effects on the mucosal surface, in the oesophagus and stomach areas.

Symptoms The symptoms of the disorder can be classified into local and systemic. The influence of the gastric acid on the oesophageal mucosa leads to the feeling of heartburn. This is also frequently accompanied by regurgitation. When the disorder has progressed to a stage in which there are mechanical affectations on the oesophageal mucosa, the individual would experience difficulty in swallowing frequently painful, and a chest pain of non-cardiac origin.

The systemic manifestations of the gastroesophageal reflux disease include cough, pneumonia and .induction of asthmatic attack in predisposed subjects. These symptoms follow aspiration in. cases associated with regurgitation. Dental erosions are not uncommon, an vocal cord polyps have also been described.

Management: An understanding of the pathophysiology predicts the course for management. For example, if the disorder is related to harmful habits, a change of habit is required. Because of the effect of H^+ on the mucosa, stimulating the production of mucus by prostaglandins, or surface coating with antacids would relive the discomfort. Antihistamines (H2 antagonists) and proton pump inhibitors would inhibit gastric acid secretion, and provide relief to the subject. Other possible physiologic approaches include the augmentation of .the lower oesophageal sphincteric tone to prevent a reflux, or to enhance, gastric, emptying by the use of parasympathomimetics (antagonists of dopamine; cholinergic agonists, agonists of 5' hydroxytryptamine, motilin agonists)

Pathophysiology of Peptic Ulcer

Peptic ulcer disease (PUD) is characterized by discontinuation in the inner lining of the gastrointestinal tract (GIT) because of acid secretion or pepsin. It extends into the muscularis propria layer of the gastric epithelium. It usually occurs in the stomach and proximal duodenum. It may involve the lower oesophagus, distal duodenum,

or jejunum. Epigastric pain usually occurs within 15- 30 minutes following a meal in patients with gastric ulcer; on the other hand, the pain with duodenal ulcer tends to occur 2-3 hours after a meal.

The PUD mechanism results from an imbalance between gastric mucosal protective and destructive factors. The risk factors predisposing to the development of PUD:

a) *Helicobacter (H.) pylori infection*

b) Non steroidal anti inflammatory disease NSAID

c) First- degree relative with PUD

d) Emigration from a developed nation

e) African American/ Hispanic ethnicity.

With peptic ulcers, there is usually a defect in the mucosa that extends to the muscularis mucosa. Once the protective superficial mucosal layer is damaged, the inner layers are susceptible to acidity. Further, the ability of the mucosal cells to secrete bicarbonate is compromised.

H. pylori are known to colonize the gastric mucosa and causes inflammation. The H.pylori also impairs the secretion of bicarbonate, promoting the development of acidity and gastric metaplasia.

The Pathophysiology of gastric ulcer development depends on the insult. About 80- 90% result from either *Helicobacter pylori* and/ or NSAID use. The *H.pylori* colonize about 45- 50% of the stomach mucosa worldwide. People are usually inoculated with it at an early age, especially in developing countries. It induces an inflammatory response in the host that leads to an epithelial response, degeneration, and injury, known as gastritis leading to the development of pan- gastritis. This leads to the damage of the antral somatostatin release, leading to an increase in gastrin secretion that stimulates increased acid production. Patients that develop gastric ulcers are those in whom the bacteria have remained in the antrum. However, not all patients with this infection are symptomatic; it depends on the bacteria virulence and other host risk factors.

NSAID users have a high risk of development of gastric ulcer. They go through multiple mechanisms; most significant is a decrease in prostaglandin synthesis and loss of its protective ability of the gastric mucosa. It use allow the gastric mucosa to become more vulnerable to gastric acid and pepsin damage. The most significant effect of NSAID use is physiological damage resulting from the decrease in gastric blood flow and the mild ischaemia it causes in the gastric mucosa. Overall, the Pathophysiology of gastric ulcer development depends on the aetiology, but they all lead to the loss or damage of the gastric mucosal integrity.

Although the pathophysiology of gastric and duodenal ulcer is similar, there are clearly differences between the two. Duodenal ulcer is typified by *H. pylori* infection and duodenitis and in many cases impaired duodenal bicarbonate secretion in the face of moderate increases in acid and peptic activity.

PATHOPHYSIOLOGY AND CAUSES OF VOMITING

Pathophysiology of Vomiting

Vomiting also called emesis is the forceful ejection of stomach contents from the mouth. It can be caused by; motion sickness, use of certain drugs, intestinal obstruction, disease or disorder of the inner ear, injury to the

head, and appendicitis. It may even occur without nausea, such as after extreme physical exertion. The development of vomiting involves multiple factors which include: psychological states, the central nervous system, the autonomic nervous system, gastric dysrhythmias, and the endocrine system. The threshold for nausea varies minute by minute in individuals. It depends at any given moment on the interaction of certain inherent factors of individual with the more changeable psychological states of anxiety, anticipation, expectation, and adaptation.

Vomiting originates as stimuli from visceral, vestibular and chemoreceptor trigger zone inputs which are mediated by serotonin/ dopamine, histamine/ acetylcholine and serotonin/ dopamine, respectively. It is controlled by two distinct brain centers; the vomiting center and the chemoreceptive trigger zone, both located in the medulla oblongata. The vomiting center responds directly to stimuli from various parts of the body that may be stressed or diseased. However the chemoreceptive trigger zone in contrast is stimulated by many toxins and drugs.

Vomiting can be caused by the following; gastroenteritis, pregnancy, migraines, labyrinthitis, motion sickness, appendicitis, certain medicines e.g. antibiotics, excessive alcohol ingestion, kidney infections/ stones, intestinal obstruction, chemotherapy or radiotherapy, and acute cholecystitis.

ACUTE PANCREATITIS

This is a condition where the pancreas becomes inflamed (swollen) over a short period of time. Symptoms includes: sudden severe pain in the center of the stomach, feeling of being sick, a high temperature -38^{o}C or more. Causes include: excessive alcohol, gallstones or unknown aetiology.

The pathophysiology is based on the premature activation of the enzymes zymogen and trypsin, resulting in local pancreatic destruction and activation of the inflammatory cascade which causes the systemic inflammatory response syndrome (SIRS) and edema often associated with acute pancreatitis. According to severity, it is classified as mild, moderate, severe and critical by the absence or presence of organ failure and local or systemic complications.

PATHOPHYSIOLOGY OF PARALYTIC ILEUS

Paralytic Ileus

Paralytic ileus occurs when the muscle contractions that move food through your intestines are temporarily paralyzed. It's a functional problem of the muscles and nerves that mimics an intestinal obstruction even when nothing is obstructing them. Paralytic ileus is a disease with transport disturbance of intestinal contents due to decreased smooth muscle activity in the small intestine or colon. Paralytic ileus is one of the causes of gastrointestinal disease, but may also be one of the symptoms of other diseases, including postoperative peritonitis, sepsis, electrolyte disturbance, hormonal disturbances or gastrointestinal ischemia. Paralytic ileus should be distinguished from ileus obstruction or known as intestinal obstruction. Ileus obstruction is caused by a blockage, resulting in food transport interruption in the gastrointestinal tract. However, the interruption found in paralytic ileus might be the result of continuous obstruction, leading to decreased intestinal peristalsis to stimulate food movement.

Pathogenesis
This problem occurs due to impaired intestinal peristaltic movement controlled by the autonomic nervous system. One of the causes of paralytic ileus is the postoperative state involving intestine,

inflammatory process or infections, electrolyte disturbances, hormonal disorders or certain drug consumption capable of inhibiting intestine motility such as narcotics.

Postoperative ileus is a paralytic ileus that appears after surgery involving the intestine. Postoperative ileus is divided into two:

a. immediate postoperative ileus after surgery and diminishing with flatus and bowel, and

b. prolonged postoperative ileus.

Some of the factors associated with paralytic ileus include :

i. Inflammation resulting in paralytic ileus may be due to inflammatory bowel disease or infection, such as pneumonia or sepsis. Inflammatory intestine results in inflammatory mediators' release such as nitric oxide, Vasoactive Intestinal Peptide (VIP), substance P, and prostaglandins, causing interference with intestinal motility that subsequently results in paralytic ileus. In addition, inflammation also causes leukocyte infiltration that will further aggravate ileus.

ii. Electrolyte disorders may result in paralytic ileus. These are generally due to impaired potassium, particularly hypokalemia. This is because potassium is responsible for depolarization in nerve cells that innervate muscle. If it occurs in smooth muscle cells in the intestine, it will slow smooth muscle contraction in the intestine that subsequently results in paralytic ileus. In addition to hypokalemia, hypocalcemia conditions can cause paralytic ileus. This is because calcium is associated with smooth muscle contractility, and therefore, lower calcium levels may cause paralytic ileus

iii. Paralytic ileus can also be caused by metabolic disorders such as hypothyroid conditions. The mechanism of paralytic ileus in hypothyroid remains unclear, but the possibility of abnormalities in the autonomic nervous system that conserve the nervous system in the colon results in decreased intestine motility that subsequently causes paralytic ileus. Another possibility is material deposition in the intestine that blocks the relationship between muscle fiber in the intestine and autonomic ganglion. In addition, renal impairment, particularly uremic conditions, can cause paralytic ileus. Uremic gastropathy and diabetes mellitus can also cause paralytic ileus. Another cause of impaired intestinal motility is systemic lupus erythomaosus (SLE). SLE causes ulcers in intestinal mucosa and edema, resulting in intestinal dilatation and impaired intestinal motility which may lead to the emergence of paralytic ileus. In addition, hypoparathyroidism can also cause paralytic ileus. This is due to hypocalcemia occurring in hypoparathyroidism leading to muscle motility disorders that subsequently result in paralytic ileus.

iv. Drug, particularly opioids which can decrease intestine movement, can increase paralytic ileus incidence.

Symptoms

Paralytic ileus causes symptoms that can make patients feel very uncomfortable with their stomach condition. Symptoms associated with paralytic ileus include mild to moderate abdominal pain, appetite loss, abdominal fullness, abdominal distension, bowel movement difficulty, breathing difficulty, nausea and vomiting. There may also be signs of paralytic ileus causes, for instance a burning sensation may be found if inflammation causes the ileus. The physical examination of paralytic ileus patients shows decreased

bowel sounds with a distended stomach. This gastrointestinal symptom is the main symptom occurring in paralytic ileus patients. Paralytic ileus commonly has intestinal dilation and gas accumulation in the stomach, intestine and colon.

CAUSES OF DIARRHOEA AND CONSTIPATION

Gastroenteritis

Gastroenteritis is an intestinal infection that can occur due to viruses, bacteria, or parasites. Some people also get gastroenteritis while traveling, which people call traveler's diarrhea. Viral gastroenteritis is highly contagious and spreads easily from person to person. The most common cause of gastroenteritis is norovirus which takes about 48 hours to incubate. The symptoms of gastroenteritis include:

a. abdominal pain with cramps

b. watery diarrhoea

c. nausea or vomiting

d. occasionally, fever

Most people recover from viral gastroenteritis in just a few days. However, some viruses can last for weeks. These include adenovirus and rotavirus, which most often affect young children.

Food poisoning

Food poisoning occurs when someone eats or drinks contaminated food or water. Like gastroenteritis, viruses, bacteria, or parasites can cause food poisoning. However, food poisoning is not contagious. Food poisoning often occurs suddenly. Depending on the type of virus or bacteria a person ingests, it may develop not long after eating the contaminated food. The most common symptoms include:

- stomach cramps
- nausea and vomiting
- diarrhea
- fever

Most people with food poisoning get better without treatment. However, the older adults, children under 5, and people who are pregnant, or have weaker immune systems, are more likely to develop complications.

Medications

Some medications can also cause vomiting and diarrhea as a side effect. These include antimicrobials and antacids. Long-term antibiotic use can change the gut flora in the large intestine and cause chronic digestive problems. It can also increase the likelihood of a *Clostridium* infection.

Other causes

These are many other causes .of diarrhea and vomiting. Below is a list of causes and their symptoms.

Cause	Symptoms
Anxiety	rapid heartbeat, shortness of breath, sweating, feelings of stress or panic, vomiting, diarrhea
Food allergies	nausea, abdominal pain, vomiting, diarrhea, nasal congestion, itching, swelling of the lips
Respiratory tract infections	fever or chills, fatigue, cough, sore throat, body aches, headaches, vomiting and diarrhea
Appendicitis	severe abdominal pain, nausea, vomiting, diarrhea, fever, loss of appetite
Allergy	swollen throat or tongue, hives, difficulty breathing, dizziness or fainting, vomiting, and diarrhea
Abdominal malignancies	abdominal pain, yellowing of the skin and eyes, loss of appetite, nausea, vomiting, diarrhea, greasy stools, weakness, weight loss

Treatment

i. For temporary cases of vomiting and diarrhea, a person may not need any medical treatment. Symptoms caused by a hangover, anxiety, gastroenteritis, or food poisoning can resolve on their own.

ii. Gradually replacing lost fluids and electrolytes can be of immense help.

iii. Once vomiting subsides, a person can start drinking sips of clear liquids, such as broth, diluted apple juice, herbal tea, or oral rehydration solutions.

iv. After a person can tolerate liquids again, they can slowly introduce bland foods, such as crackers, and plain rice.

v. Antidiarrhoeal medications may be used, but with great caution, as they can be dangerous for children. Also, people with blood in their stool should not take them.

IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome (IBS) is a common condition that affects the digestive system. It causes symptoms like stomach cramps, bloating, diarrhoea and constipation. These tend to come and go over time, and can last for days, weeks or months at a time. It's usually a lifelong problem. Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain and altered bowel habit in the absence of a specific and unique organic pathology. The syndrome has also been referred to by other terms, such as spastic colon, irritable colon, and nervous colon. No specific motility or structural correlates have been consistently demonstrated in the disorder.

Pathophysiology

The pathophysiology of irritable bowel syndrome (IBS) may be visualized as a three-part complex of altered gastrointestinal (GI) motility, visceral hyperalgesia, and psychopathology. Components of the gut microbiota potentially influence brain morphology and function, behavior, and cognition, which explains the psychological component

Altered GI motility: Altered GI motility includes distinct aberrations in the small and large bowel motility. The myoelectric activity of the colon is composed of background slow waves with superimposed spike potentials. Colonic dysmotility in irritable bowel syndrome manifests as variations in slow-wave frequency and a blunted, late-peaking, postprandial response of spike potentials. Small bowel dysmotility manifests in delayed meal transit in patients prone to constipation and in accelerated meal transit in patients prone to diarrhea. It is held that these widespread motility aberrations and a generalized smooth muscle hyperresponsiveness is implication in the disorder.

Visceral hyperalgesia: Enhanced perception of normal motility and visceral pain characterizes irritable bowel syndrome. Notably, hypersensitivity appears with rapid but not with gradual distention.

Psychopathology: Psychopathology is the third aspect. Associations between psychiatric disturbances and irritable bowel syndrome pathogenesis are not clearly defined. Clinical alertness to depression and hopelessness is mandatory. A higher prevalence of physical and sexual abuse has been demonstrated in patients with irritable bowel syndrome. Whether psychopathology incites the development of irritable bowel syndrome or vice versa remains unclear.

Both colonic inflammation and small bowel inflammation have been discovered in a subset of patients with irritable bowel syndrome after an episode of infectious enteritis.

ULCERATIVE COLITIS

Ulcerative colitis is a chronic inflammatory bowel disease (IBD), in which abnormal reactions of the immune system cause inflammation and ulcers on the inner lining of the large intestine. Ulcerative colitis can develop at any age, but the disease is more likely to develop in people between the ages of 15 and 30.

The exact cause of ulcerative colitis remains unknown. Previously, diet and stress were suspected. However, researchers now know that these factors may aggravate but don't cause ulcerative colitis. One possible cause is an immune system malfunction. When the immune system tries to fight off an invading virus or bacterium, an irregular immune response causes the immune system to attack the cells in the digestive tract, too.

Heredity also seems to play a role in that ulcerative colitis is more common in people who have family members with the disease. However, most people with ulcerative colitis don't have this family history. Most people with ulcerative colitis have mild to moderate symptoms. The course of ulcerative colitis may vary, with some people having long periods when it goes away. This is called remission. Health care providers often classify ulcerative colitis according to its location. Symptoms of each type often overlap. Types of ulcerative colitis include:

- Ulcerative proctitis. Inflammation is confined to the area closest to the rectum. Rectal bleeding may be the only sign of the disease.
- Proctosigmoiditis. Inflammation involves the rectum and sigmoid colon. Symptoms include bloody diarrhea, abdominal cramps and pain, and an inability to move the bowels despite the urge to do so. This is called tenesmus.
- Left-sided colitis. Inflammation extends from the rectum up through the sigmoid and descending portions of the colon. Symptoms include bloody diarrhoea, abdominal cramping and pain on the left side, and urgency to defecate.
- Pancolitis. This type often affects the entire colon and causes bouts of bloody diarrhea that may be severe, abdominal cramps and pain, fatigue, and significant weight loss.

Other presentations

Physical findings are typically normal in mild disease, except for mild tenderness in the lower left abdominal quadrant. The tenderness or cramps are generally present in moderate to severe disease. Patients with UC predominantly complain of the following; rectal bleeding, frequent stools, mucous discharge from the rectum, tenesmus, lower abdominal pain, and severe dehydration from purulent rectal discharge. In severe disease, the following may be observed:

a. Fever
b. Tachycardia
c. Significant abdominal tenderness
d. Weight loss

The severity of UC can be graded as follows:

i. Mild: Bleeding per rectum, fewer than four bowel motions per day
ii. Moderate: Bleeding per rectum, more than four bowel motions per day
iii. Severe: Bleeding per rectum, more than four bowel motions per day, and a systemic illness with hypoalbuminemia (< 30 g/L)

Ulcerative colitis may also be associated with various extracolonic manifestations, such as follows:

- Uveitis
- Pyoderma gangrenosum
- Pleuritis
- Erythema nodosum
- Spondyloarthropathies

Risk factors may include:

- Sex .Ulcerative colitis affects about the same number of women and men.
- Age. Ulcerative colitis usually begins before the age of 30, but it can occur at any age. Some people may not develop the disease until after age 60.
- Race or ethnicity. It can occur in any race.
- Family history. Risk is higher if one has a close relative, such as a parent, sibling or child, with the disease.

PATHOPHYSIOLOGY OF JAUNDICE

Jaundice is a symptom of an underlying condition, and not necessarily a disease condition in itself. It usually features in entities that impair the excretion of bilirubin from the body. It is a yellowing of the skin, nail beds and whites of the eyes that is caused by a build-up of bilirubin in the body's tissues. Jaundice clinically, is when there is an increase in the amount of bilirubin in the serum rising above 85mmol/l (5mg/dl).

When the red blood cells become damaged, the cell membrane becomes weak and susceptible to rupture. With the damage, the cells circulate through the reticuloendothelial system, and the contents of the cell are expelled into the bloodstream. Haemoglobin is released from the RBCs, and is ingested by macrophages. This phagocytosis splits the haemoglobin into the haeme and globin portions. The haeme undergoes an oxidation reaction catalyzed by the enzyme oxygenase, to give biliverdin, iron and carbon monoxide. The biliverdin, a green-colored pigment, then undergoes a reduction reaction to yield a yellow pigment called bilirubin. This reaction is catalyzed by the cytosolic enzyme biliverdin reductase.

The insoluble bilirubin is referred to as "free," "indirect" or "unconjugated" bilirubin and it is transported to the liver bound to albumin through the bloodstream. In the liver, the bilirubin is conjugated with glucuronic acid (catalyzed by UDP-glucuronyl transferase) to give bilirubin diglucuronide or "conjugated" bilirubin, which is water soluble. In this form, bilirubin can be excreted. This conjugated bilirubin leaves the liver and enters the biliary system as part of bile. Bacteria in the intestine convert the bilirubin into urobilinogen. Urobilinogen is either converted into stercobilinogen and excreted in the feces, or it is reabsorbed by the intestinal cells and taken to the kidneys via the blood to be excreted in the urine. When in utero, unconjugated bilirubin is cleared in the placenta to produce cord serum bilirubin of approximately 35mmol/L (2mg/dl). After birth, jaundice is a reflection of the bilirubin present in the liver, the rate of hepatic excretion and the ability to bind to serum proteins to retain the bilirubin present in the plasma.

Jaundice is divided into three forms, depending on what has caused the bilirubin to accumulate. The different types of jaundice are;

i. Pre-hepatic jaundice due to obstruction in transportation of blood to the liver. This is the type found in hemolytic anemia and in sickle cell disease.

ii. Hepatocellular jaundice caused by disease in the liver such as liver cirrhosis and Gilbert's syndrome.

iii. Post-hepatic jaundice or obstructive jaundice, due to obstruction of bile from draining into the digestive system from the gallbladder. Tumours and gallstones can cause this type of jaundice..

Patients with jaundice may not experience any symptoms, although some present with a life-threatening condition. Patients who present with acute illness, which is usually due to infection, may present with fever, chills, abdominal pain, and flu-like symptoms. In these patients, skin discoloration may not be their chief complaint. Patients with non-infectious jaundice may complain of weight loss or pruritus.

HEPATITIS

Hepatitis is a general term used to describe inflammation of the liver. hepatitis may be caused by viruses (viral hepatitis), chemicals, drugs, alcohol (alcoholic hepatitis), certain genetic disorders or by an autoimmune process. Hepatitis can be acute, in which case it comes up rather suddenly and then resolves. It may also be chronic, producing more subtle symptoms over a longer period of time, and progressive liver damage.

Types of Hepatitis There are five viruses that cause the different forms of viral hepatitis. These are. hepatitis A, B, C, D and E. Hepatitis A is transmitted mostly as a water/food-borne illness. It is the easiest to transmit, but is also the least likely to damage the liver, being completely resolved usually within six months. Hepatitis B is transmitted through exposure to contaminated blood, needles, syringes or bodily fluids and from mother to baby. It is a chronic disorder and in some cases may lead to long-term liver damage, cirrhosis, and liver cancer of the liver. Hepatitis C is transmitted only through infected blood or from mother to newborn during childbirth. It too can lead to liver cirrhosis and cancer over time. Hepatitis D is only found in people who are also infected with hepatitis B. Hepatitis E is usually drug induced. Some drugs when taken over a long period of time can become toxic to the liver following their accumulation in the system, and cause hepatitis (drug-induced hepatitis). These include acetaminophen, (paracetamol) and even vitamin A.

Symptoms Symptoms of hepatitis include a feeling of general weakness of the body, right sided abdominal pain, jaundice, and abdominal swelling due to fluid retention (ascites), especially in the terminal stage. On a physical examination, the liver is usually enlarged being palpable below the costal margin. Investigations required to confirm diagnosis of hepatitis include; blood tests for liver enzymes and proteins which are elevated when the liver is damaged or infected, ultrasound scan of the liver and on rare occasions, a biopsy.

Treatment There is no cure for hepatitis once it occurs. To prevent infection, individuals should be vaccinated against hepatitis B and hepatitis A. There are no vaccines yet against hepatitis types C, D and E. Treatment focuses on preventing further damage to the liver, reversing existing damage if possible and symptomatic relief. Most cases of acute hepatitis will resolve over time. In autoimmune hepatitis, immunosuppressant drugs may be used to help attacks on the liver.

CHOLECYSTITIS

The gallbladder is a pear-shaped organ connected to the liver. It stores bile and releases it into the small intestine for the digestion of fat. The bile travels out of the gallbladder through the cystic duct that leads to the common bile duct, and ultimately, into the small intestine. Cholecystitis is an inflammation of the gallbladder. It can occur when a gallstone gets stuck at the opening of the gallbladder. The main cause of cholecystitis is gallstones being trapped at the gallbladder's opening. Risk factors developing cholecystitis include;

i. Diabetes mellitus

ii. prolonged fasting

iii. shock

iv. obesity

v. immune deficiency

vi. older age

vii. pregnancy

Without treatment, cholecystitis can result in perforation of the gallbladder, tissue death, bacterial infections, and the shrinking of the gallbladder. The signs and symptoms of cholecystitis include right upper quadrant pain and low grade fever,. Pain generally occurs around the gallbladder, in the right upper quadrant of the abdomen.

Acute cholecystitis In cases of acute cholecystitis, the pain starts suddenly. It does not go away, and it is intense. Without treatment, it will usually get worse, and breathing in deeply will make it feel more intense. The pain may radiate from the abdomen to the right shoulder or back.Other symptoms may include: abdominal bloating, tenderness in the upper-right part of the abdomen, depressed appetite, nausea and vomiting. A slight fever and chills may be present with acute cholecystitis. After a meal, especially one that is high in fat, the symptoms will worsen. A blood test may reveal a high white blood cell count.

Chronic cholecystitis People with chronic cholecystitis have pain similar to the acute variant, but it tends to occur primarily in the evenings or at night. The symptoms usually appear gradually over the course of weeks or months, and people do not typically experience fever or chills. The pain may worsen over time, and the condition can progress to the acute version.

Complications: Untreated cholecystitis can lead to:

i. Fistula which occurs when a large stone erodes the wall of the gallbladder.

ii. Gallbladder distension because of bile accumulation

iii. The bile duct becoming blocked, and bile is unable to flow.

iv. Pancreatitis occurs when gallstones pass from the gallbladder into the biliary tract, leading to an obstruction of the pancreatic duct.

Management Treatment of cholecystitis usually takes place in the hospital. Treatments may include:

- to rest the gallbladder (e.g.. by fasting)
- parenteral fluids to prevent dehydration.
- Pain medication.
- Antibiotics to treat infection.
- Removing the gallbladder by surgery.

GALLSTONES

Gallstones, which are created in the gallbladder, form when substances in the bile create hard, crystal-like particles. Cholesterol stones are made of cholesterol, bilirubin and calcium salts that are found in bile. About twenty percent of gallstones are pigment stones. Risk factors for pigment stones include; cirrhosis of the liver, biliary tract infections and hereditary blood cell disorders (such as sickle cell anemia). The gallbladder may develop many smaller stones, or a single, often large one. A stone may become lodged in the bile duct due to the size of the stone or the anatomy of the biliary tree. Thus, bile duct stones are gallbladder stones that have become lodged in the bile duct. When the bile contains much of cholesterol and not enough bile salts, cholesterol gallstones may develop. Aside from a high concentration of cholesterol, there are two other factors that seem to be of importance in causing gallstones.

i. Movement of the gallbladder. This small but muscular organ squeezes to force bile into the bile duct. If the gallbladder does not contract appropriately, the bile may become concentrated and forming small crystals.

ii. Gallstones may also be created by proteins in the liver and bile. These proteins may either promote cholesterol crystallization into gallstones.

Other factors are;

- Obesity
- Low calorie diets
- Prolonged fasting
- Increased levels of oestrogen
- Hormone replacement and contraceptive medications

Symptoms include;

- Acute pain, that occurs very suddenly.
- Pain is usually located behind your breastbone, but may occur in the upper right abdominal area
- Pain between your shoulder-blades
- Chills and fever

- Jaundice
- Nausea and vomiting

A common complication cause by gallstones is blockage of the cystic duct. An inflammation of the gallbladder (cholecystitis) can occur if the flow of bile in the cystic duct is severely impeded or blocked by any gallstones. A more serious complication occurs if the gallstones become lodged in the bile ducts between the liver and the small intestine. This condition, called cholangitis, can block bile flow from the gallbladder and liver, causing pain, jaundice and fever. Prolonged blockage of any of these ducts can cause severe damage to the gallbladder, liver, or pancreas, which can be fatal.

RISK FACTORS FOR HEPATIC CANCER

Hepatocellular carcinoma (HCC) is the most often primary cancer of the liver and is one of the leading causes of cancer-related death worldwide. Hepatocellular carcinoma has a poor prognosis. Risk factors include;

i. Chronic infection with HBV or HCV. Chronic infection with the hepatitis B virus (HBV) or hepatitis C virus (HCV) increases the risk of liver cancer.

ii. Chronic alcoholism and chronic hepatitis infections are common causes of cirrhosis. People with HCV-related cirrhosis have a higher risk of developing liver cancer than people with cirrhosis related to HBV or alcohol use.

iii. Heavy alcohol use can cause cirrhosis, which is a risk factor for liver cancer.

iv. Diabetes mellitus predisposes to non-alcoholic fatty liver disease, and is a risk factor for cancer of the liver. ...

v. Exposure to aflatoxins. Aflatoxin is a mycotoxin produced by Aspergillus flavus and related fungus that contaminates stored foods. Aflatoxin is highly associated with HCC due to the damage it does to the DNA of hepatic cells, and causing mutation of the p53 tumor suppressor gene.

vi. Cigarette smoking: HCC can develop due to smoking. DNA adducts of 4-aminobiphenyl and polycyclic aromatic hydrocarbons are human carcinogens derived from cigarette smoke that cause liver tumors.

Other, less common causes are Wilson's disease, hereditary hemochromatosis, alpha1-antitrypsin deficiency, primary biliary cirrhosis and autoimmune hepatitis. Any agent leading to chronic hepatic injury and eventually cirrhosis, has been associated with HCC.

RISK FACTORS FOR CANCER OF THE HEAD OF PANCREAS

A risk factor is anything that increases the chances of getting a disease such as cancer. Different cancers have different risk factors. However, having a risk factor does not mean that one will necessarily get the cancer. Indeed, some people who get cancers may have few or no known related risk factors. Risk factors known to increase the risk for pancreatic cancer include the following;

i. Smoking is one of the most important risk factors for pancreatic cancer. The risk of getting pancreatic cancer is about twice as high among people who smoke compared to those who have never smoked. Cigar smoking and the use of smokeless tobacco products also increase the risk.

ii. Obesity is a risk factor for pancreatic cancer. Obese people are about 20% more likely to develop pancreatic cancer. Gaining weight as an adult can also increase risk.

iii. Pancreatic cancer is more common in people with diabetes mellitus, especially in people with type 2 diabetes. Type 2 diabetes mellitus in adults is also often related to being overweight or obese. It's not clear if people with type 1 (juvenile) diabetes mellitus also have a higher risk.

iv. Chronic pancreatitis, a long-term inflammation of the pancreas, is linked with an increased risk of pancreatic cancer. Chronic pancreatitis is often seen with heavy alcohol use and smoking.

v. Heavy exposure at work to certain chemicals used in the dry cleaning and metal working industries may raise a person's risk of developing pancreatic cancer.

vi. The risk of developing pancreatic cancer goes up as people age.

vii. Men are slightly more likely to develop pancreatic cancer than women. This may be due, at least in part, to higher tobacco use in men, which raises pancreatic cancer risk.

viii. African Americans are slightly more likely to develop pancreatic cancer than whites. This may be due in part to having higher rates of some other risk factors for pancreatic cancer, such as diabetes, smoking, and being overweight.

ix. Pancreatic cancer seems to run in some families. Although family history is a risk factor, most people who get pancreatic cancer do not have a family history of it.

x. Inherited gene mutations can be passed from parent to child. Sometimes these changes result in syndromes that increase risks of other cancers such as; hereditary breast and ovarian cancer syndrome, familial pancreatitis, and hereditary non-polyposis colorectal cancer.

xi. Diets with red and processed meats and saturated fats, and sugary drinks, may increase the risk of pancreatic cancer. Heavy alcohol use can also lead to conditions such as chronic pancreatitis, which is known to increase pancreatic cancer risk.

Infection of the stomach with the ulcer-causing bacteria *Helicobacter pylori,* or infection with Hepatitis B may increase the risk of getting pancreatic cancer.

Gigantism and acromegaly

Gigantism and acromegaly are syndromes of excessive secretion of growth hormone (hypersomatotropism). Before closure of the epiphyses, it results in gigantism, and after the closure of the epiphyses, it results in acromegaly.

Pituitary gigantism is a condition that occurs if growth hormone hypersecretion occurs in childhood, before closure of the epiphyses. Skeletal growth velocity and ultimate stature are increased, with little or no bony deformity, as the increased growth is uniform.

In acromegaly, growth hormone hypersecretion starts after the closure of the epiphyses. Linear growth stops but the bones of the hands, feet, cheeks and jaw thicken with enlargement of the eyelids, lips, tongue and nose. The skin become coarse with development of furrows in the forehead and soles of the feet.

Associated with the growth abnormalities are metabolic consequences of excessive growth hormone secretion. These include diabetes mellitus and insipidus.

Abnormalities of other anterior pituitary hormones may co-exist with excessive growth hormone secretion.

Dwarfism

Dwarfism results from hypopituitarism occurring in children. It usually results in abnormally slow growth and short stature with normal proportion. A pituitary dwarf is childlike in many physical respects. Puberty may be delayed, but sexual activity is usually normal. Intellectual development is not affected.

Pituitary dwarfism is different from achondroplastic dwarfism in that the body proportion is maintained in pituitary dwarfism whereas the upper body is proportionally more than the lower body in achondroplasia, which is a genetic disease.

Infantilism

Sexual infantilism is permanent lack of sexual development in an individual. This becomes obvious at an age after puberty is expected. It is also called adiposogenital dystrophy, a condition that may be caused by tertiary hypogonadism originating from decreased levels of gonadotropin releasing hormone from the hypothalamus. It is characterized by growth delays and delayed sexual development, atrophy or hypoplasia of the gonads and altered secondary sexual charateristics. They may also present with polyuria and polydipsia. This disorder appears to be more common in male children.

Simmond's disease

Simmond's disease is caused by atrophy or destruction of the anterior lobe of the pituitary gland, resulting in hypopituitarism. This is a form of pituitary failure, with deficiency of the hormones produced from the anterior pituitary, particularly thyroid stimulating and adrenal cortical stimulating hormones. It is called Sheehan's syndrome the pituitary necrosis is caused by postpartum haemorrhage. Following postpartum necrosis of the pituitary gland, the woman will be unable to breastfeed her infant, due to inability of the pituitary to produce prolactin. Amenorrhea or oligomenorrhea may be present with secondary infertility. There is extreme weakness and hypotension with features of hypothyroidism and hypocortisolism. Hypoglycemia is a common feature of the syndrome The disease, in the acute form, can be fatal unless replacement therapy with cortisol and thyroxin is given for life.

PATHOPHYSIOLOGY OF CRETINISM, MYXEDEMA AND GRAVE'S DISEASE

CRETINISM

Cretinism is a condition of severely stunted physical and mental growth due to untreated congenital deficiency of thyroid hormones (congenital hypothyroidism). Congenital hypothyroidism can be endemic, genetic, or sporadic. Cretinism may be of two types:

i. Neurological, or

ii. myxedematatous.

The three characteristic features of neurological endemic cretinism are extremely severe mental deficiency, deaf mutism, and motor spasticity. They usually have a goiter. The neuropathological basis of the clinical picture includes under-development of the cochlea for deafness, mal-development of the cerebral neocortex for mental retardation, and mal-development of the substantia nigra for the motor disorder. The cerebellum, hypothalamus, visual system, and hippocampus are relatively spared. Neurological cretinism is predominantly caused by maternal hypothyroidism due to iodine deficiency. It may have an autosomal recessive predisposition also. The clinical features of people affected by neurological cretinism are completely different from those affected by congenital hypothyroidism.

Myxedematatous cretinism may present with severe growth retardation, incomplete maturation of the facial features, and much delayed sexual maturation. Goitre is usually absent and the thyroid is often not palpable, suggesting thyroid atrophy. The serum levels of T4 and T3 are extremely low, often undetectable, and TSH is dramatically high. This condition is irreversible, even after treatment with thyroid hormones or iodine soon after birth, but can be corrected if treatment with iodine starts prior to or early in gestation. There has been increasing evidence of the protective role of maternal thyroid hormones. Most of the effects of iodine deficiency during brain development are related to hypothyroxinemia of the mother.

The definition of cretinism involves three features:

(i) an association with endemic goitre

(ii) clinical symptoms which includes some form of mental deficiency and/or defects in hearing, speech, stance, gait, hypothyroidism, and stunted growth; and

(iii) when iodine deficiency is corrected in the area, cretinism is prevented.

Other factors such as the presence of goitrogens in the diet, thyroid immunity, and interactions with other trace elements such as selenium, also have a role in the development of cretinism.

Myxedematous and neurological cretinism, are the most severe consequences of lack of iodine. The absence of goitre in myxedematous cretins is caused by thyroid atrophy. Hypothyroidism is not frequent in neurological cretins and goitre is common. The thyroid atrophy of myxedematous cretins could result from the toxic effect of increased H_2O_2 generation by the thyrocytes due to chronic TSH stimulation induced by iodine deficiency. The decreased activity of enzymes, such as glutathione peroxidase, which normally protect thyrocytes and other cells from H_2O_2 toxicity would lead to thyroid necrosis.

Because selenium deficiency impairs the conversion of T4 to T3 in the periphery, preserving maternal levels of circulating T4, this mechanism was proposed to supply the necessary T3 to the fetal brain during the critical period when the maturation of the nervous system depends mainly on maternal T4.

MYXEDEMA

Myxedema is the extreme clinical condition in adults where no thyroid hormones are secreted. In these patients, swelling of the skin and subcutaneous tissues is caused by the extracellular accumulation of a high-protein fluid. The term myxedema refers to thickening of the skin and other organs due to the accumulation of

glycosaminoglycans associated with low serum thyroid hormone concentrations. Myxedema coma is characterized by nonresponsiveness, low body temperature (hypothermia), and respiratory depression. This condition is commonly precipitated by intake of sedating drugs, cold exposure, or infection and occurs most often in elderly women.

The changes come on gradually: enlarged tongue; thickened skin with underlying fluid causing puffiness, particularly in the face around the eyelids and in the hands; drowsiness; apathy; sensitivity to cold; failure to menstruate or excessive menstrual bleeding; cardiac enlargement; and lowering of the BMR (basal metabolic rate). In the male, sexual activity and sperm production decrease. Fertility is reduced in both sexes. Myxedema may also cause delayed sexual maturation, but sexual precocity can also occur. At times, the myxedema is accompanied by permanent primary hypofunction of the adrenal cortices.

Hypothyroidism usually results from a disorder of the thyroid gland, described as primary hypothyroidism. Congenital primary hypothyroidism is caused by lack of, or abnormal development of the thyroid in utero, and inherited defects in the synthesis of thyroid hormone. A major cause of acquired primary hypothyroidism is chronic autoimmune thyroiditis. This condition has two forms: Hashimoto thyroiditis, which is characterized by enlargement of the thyroid (goitre), and atrophic thyroiditis, which is characterized by shrinkage of the thyroid gland. There also exists a form of hypothyroidism known as central hypothyroidism in which there is a deficiency of thyroid-stimulating hormone (TSH). Central hypothyroidism may be caused by pituitary disorder, or deficiency of the hypothalamic hormone that maintains thyrotropin secretion.

Hypothyroidism also may be caused by hyperthyroidism treatments such as radioiodine therapy or surgery. Other causes include infiltrative diseases of the thyroid, severe iodine deficiency. Hypothyroidism is more common in women than men. The onset is usually gradual, taking several years for notable symptoms and signs to develop. However, it may be abrupt, taking only a few months to develop. Abrupt onset of hypothyroidism occurs most commonly after radioiodine treatment for hyperthyroidism. In some cases, hypothyroidism is very mild and is difficult to recognize because it causes few symptoms. In these patients, the condition may be attributed to age. In other cases, hypothyroidism can be very severe, especially if it is allowed to progress untreated for months or years.

The clinical manifestations of hypothyroidism are characterized by slowing of most body functions. Neuromuscular symptoms include slowing of thought, speech, and action. Lethargy, sleepiness, muscle aches and weakness, and slow reflexes may also be seen. Other common symptoms are dry skin and hair, puffy eyes, cold intolerance, deepening of the voice, but a tendency to gain weight. Irregular menstrual periods and increased menstrual blood flow in women are not infrequent. In later stages of thyroid deficiency, fluid may accumulate around the heart, causing a condition known as pericardial effusion. Hypothyroidism also raises serum cholesterol concentrations.

Hypothyroidism refers to any condition where levels of thyroid hormones are insufficient due to defects of primary (at the thyroid) or secondary (hypothalamus or pituitary) origin. It is especially serious in children because of marked effects on both general growth and neural development. The term juvenile hypothyroidism refers to cases of hypothyroidism in children that do not lead to severe retardation in somatic and intellectual development. However, if hypothyroidism in the neonate is detected at birth by using a simple thyroid test, it can be alleviated with thyroid hormone therapy so that growth and development from that time are normal. Generalized myxedema is a rare condition that results from chronic hypothyroidism, which causes the accumulation of mucin within the dermis.

Myxedema describes a specific form of cutaneous and dermal oedema secondary to increased deposition of connective tissue components. The connective fibres are separated by an increased amount of protein and mucopolysaccharides. Myxedema represents the leading symptom in hypothyroidism but also occurs in a localized form in autoimmune hyperthyroidism. Pretibial myxedema is an extrathyroidal manifestation of Graves' disease and is characterized by an infiltrative lesion of the derma and the subcutaneous tissue.

Myxedema ascites accounts for less than 1% of all causes of ascites. It usually is chronic. The ascitic fluid is protein-rich (>2.5 g/dl), has a moderate WBC count that is predominantly lymphocytic. There is complete resolution with thyroid hormone replacement. Myxedema coma is an endocrine emergency characterized by severe hypothyroidism, hypothermia, and altered mental status. There is usually a precipitating cause, such as an infection, myocardial infarction, stroke, or cold exposure. Several other factors, such as hypoglycemia, have been associated with myxedema coma. Most cases of myxedema coma are due to primary hypothyroidism, with less than 10% being related to central hypothyroidism.

Pathogenesis
Calorigenesis: The actions of thyroid hormone are mediated by nuclear receptors. A major effect is to stimulate the sodium pump via the cell membrane enzyme Na +, K +-ATPase. This process increases oxygen consumption and probably accounts for the characteristic increase in basal metabolic rate associated with thyroid hormone administration. Mitochondrial metabolism also is influenced by thyroid hormonel. The mechanism by which this occurs is not clearly understood. This action also appears to increase oxygen consumption.
Respiratory function: The most consistent pulmonary abnormalities seen in severely hypothyroid patients are diminished ventilatory drive to both hypoxia and hypercarpnia.

GRAVES DISEASE
Graves disease is an autoimmune disorder characterized by hyperthyroidism caused by circulating autoantibodies. Thyroid-stimulating immunoglobulins bind to, and activate thyroid-stimulating hormone (TSH) receptors, causing the thyroid gland to grow and the thyroid follicles to increase synthesis of thyroid hormone. In some patients, Graves disease represents a part of more extensive autoimmune processes leading to dysfunction of multiple organs.

Pathophysiology: In Graves disease, B and T lymphocyte-mediated autoimmunity are known to be directed at four thyroid antigens: thyroglobulin, thyroid peroxidase, sodium-iodide symporter and the TSH receptor. However, the TSH receptor itself is the primary autoantigen of Graves disease and is responsible for the manifestation of hyperthyroidism.

The thyroid gland is under continuous stimulation by circulating autoantibodies against the TSH receptor, and pituitary TSH secretion is suppressed because of the increased production of thyroid hormones. These thyroid-stimulating antibodies cause release of thyroid hormone and thyroglobulin that is mediated by 3,'5'-cyclic adenosine monophosphate (cyclic AMP), and they also stimulate iodine uptake, protein synthesis, and thyroid gland growth.

The anti-sodium-iodide symporter, antithyroglobulin, and antithyroid peroxidase antibodies appear to have little role in the etiology of hyperthyroidism in Graves disease. However, they are markers of autoimmune disease against the thyroid. Also, the thyroid cells express molecules that mediate T cell adhesion and complement regulation that participate and interact with the immune system. Viral infection is an environmental factor linked to Graves disease. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has also been linked

to the development of subacute thyroiditis and Graves disease. A genetic predisposition to thyroid autoimmunity may interact with environmental factors or events to precipitate the onset of Graves disease.

PATHOPHYSIOLOGY EXOPHTHALMOS, ADDISON'S DISEASE, CUSHINGS DISEASE, VIRILISM.

EXOPHTHALMOS

Exophthalmos is the protrusion of one or both eyes anteriorly out of the orbit due to an increase in orbital contents within the rigid bony orbit. It most commonly manifests in thyroid-associated eye disease such as Graves' disease ophthalmopathy.

Pathophysiology: The etiological basis of proptosis can include inflammatory, vascular, infectious, cystic, neoplastic (both benign and malignant, metastatic disease), and traumatic factors. Some other examples include infectious causations such as orbital cellulitis and subperiosteal abscesses. Traumatic causations could be orbital emphysema, retro-orbital hemorrhage, and carotid-cavernous fistula. Vascular causations not traumatically related would be orbital arteriovenous malformation (AVM) varices and aneurysms. Neoplastic causations include adenocarcinoma of the lacrimal gland, pleomorphic adenoma of the lacrimal gland, meningioma, lymphoma, and metastatic disease.

In children, unilateral proptosis is often due to an orbital cellulitis–type picture, and, in bilateral cases, neuroblastoma and leukemia are more likely. Thyroid orbitopathy, also referred to as thyroid ophthalmopathy, is categorized as an inflammatory process that is autoimmune-mediated. In adults, it is the most common cause of unilateral and bilateral exophthalmos.

The etiology of the thyroid-related orbitopathy is an autoimmune-mediated inflammatory process of the orbital tissues, predominantly affecting the fat and the extraocular muscles.

No matter what the etiology may be, globular protrusion is secondary to the increase in volume within the fixed bony orbital confines. Since the orbit is widest toward its anterior aspect, the orbital contents are displaced anteriorly, resulting in proptosis and exophthalmos.

ADDISON'S DISEASE

Addison's disease, also known as primary adrenal insufficiency or hypoadrenalism, is a rare disorder of the adrenal glands. Adrenal insufficiency, including Addison's disease, is a disorder that occurs when the adrenal glands don't make enough of certain hormones. These include cortisol, sometimes called the "stress hormone," which is essential for life.

The adrenal glands are 2 small glands that sit on top of the kidneys. They produce 2 essential hormones:

i. cortisol, and

ii. aldosterone.

The adrenal gland is damaged in Addison's disease, so it does not produce enough cortisol or aldosterone. It can affect people of any age, although it's most common between the ages of 30 and 50. It's also more common in women than men.

Symptoms: Early-stage symptoms of Addison's disease are similar to other more common health conditions, such as depression. Other symptoms include;

i. lack of energy or motivation

ii. muscle weakness

iii. loss of appetite and unintentional weight loss

iv. increased thirst

Over time, these problems may become more severe and one may experience further symptoms, such as dizziness, cramps and exhaustion. The individual may also develop small areas of darkened skin, or darkened lips or gums. Addison's disease is usually the result of a problem with the immune system, which causes it to attack the outer layer of the adrenal gland, disrupting the production of the steroid hormones aldosterone and cortisol.

Management: Addison's disease is treated with medicine to replace the missing hormones. With treatment, symptoms of Addison's disease can largely be controlled.

Adrenal crisis: Addison's disease stand the risk of a sudden worsening of symptoms, called an adrenal crisis.This can happen when the levels of cortisol in your body fall significantly.

CUSHINGS DISEASE

Cushing’s syndrome is a disorder that occurs when your body makes excess of cortisol over a long period of time. Cortisol is sometimes called the “stress hormone” because it helps your body respond to stress. Cortisol also helps to maintain and regulate blood glucose, reduce inflammation, and convert ingested food into energy.

Pseudo-cushing's syndrome

Hypercortisolism can occur in several disorders other than Cushing's syndrome. When such patients present with clinical features consistent with Cushing's syndrome, they may also be referred to as having physiologic hypercortisolism or pseudo-Cushing's syndrome. Clinically, patients with these physiologic forms of hypercortisolism seldom have the cutaneous or muscle signs of Cushing's syndrome.

ACTH-dependent Cushing's syndrome

The causes of ACTH-dependent Cushing's syndrome are associated with bilateral adrenocortical hyperplasia. Cushing syndrome can result from taking oral corticosteroid medication. Oral corticosteroids may be necessary to treat inflammatory diseases, such as rheumatoid arthritis, lupus and asthma. They may also be used to prevent your body from rejecting a transplanted organ, but may be the cause of certain cases of Cushing’s syndrome. Too much cortisol can cause some of the hallmark signs of Cushing syndrome i.e., a fatty hump between your shoulders, a rounded face, and pink or purple stretch marks on your skin. Cushing syndrome can also result in high blood pressure, bone loss and, on occasion, type 2 diabetes. Treatments for Cushing syndrome can return the body's cortisol levels to normal and improve symptoms. The earlier treatment begins, the better the chances for recovery.

Symptoms: The signs and symptoms of Cushing syndrome can vary depending on the levels of excess cortisol. Common signs and symptoms of Cushing syndrome include;

i. Weight gain and fatty tissue deposits, particularly around the midsection and upper back, in the face (moon face), and between the shoulders (buffalo hump)

ii. Pink or purple stretch marks (striae) on the skin of the abdomen, thighs, breasts and arms

iii. Thinning, fragile skin that bruises easily

iv. Slow healing of cuts, insect bites and infections

v. Acne

Women with Cushing syndrome may experience thicker or more visible body and facial hair (hirsutism), and Irregular or absent menstrual periods.

The role of corticosteroid medications (exogenous Cushing syndrome)

It's also possible to develop Cushing syndrome from injectable corticosteroids — for example,

In certain cases, Cushing syndrome may be related to:

i. A pituitary gland tumor (e.g., pituitary adenoma) that produces an excess amount of ACTH, which in turn stimulates the adrenal glands to make more cortisol. When this form of the syndrome develops, it's called Cushing disease. It occurs much more often in women and is the most common form of endogenous Cushing syndrome.

ii. An ACTH-secreting tumor that develops in an organ that normally doesn't produce ACTH will begin to secrete this hormone in excess. These tumors, which can be benign or malignant, are usually found in the lungs, pancreas, thyroid or thymus gland.

iii. A primary adrenal gland disease can cause them to produce too much cortisol. The most common is called an adrenal adenoma.

Pathophysiology: The pathophysiology of Cushing's syndrome is linked to excessive production of cortisol by the adrenal glands. The underlying mechanisms are usually genetic mutations or over-expression of proteins.

a. Excess ACTH secretion

The excess ACTH secretion can be due to the pituitary or non-pituitary secretion. ACTH stimulates the adrenal cortex to release cortisol and is not regulated by the feedback mechanism. The molecular defects leading to ectopic ACTH secretion from gastroenteropancreatic tumors are largely unknown. Ectopic secretion can be seen as a manifestation of the tumours of the bronchial and thymus.

b. Excess secretion of cortisol by adrenal gland. Excess secretion of the cortisol by the adrenal gland is due to the adrenal causes independent of ACTH secretion.

VIRILISM

Adrenal virilism is a syndrome in which excessive adrenal androgens cause virilization. It is dihydrotestosterone that mediates masculinization of the prostate and the external genitalia. Diagnosis is clinical and confirmed by elevated androgen levels with and without dexamethasone suppression. There may be functioning adrenal tumours resulting in masculinization of prepubertal children. In boys, it produces a pesudoprecocious puberty. Sexual hair develops and the penis is enlarged to adult size, with frequent erections.

Adrenal virilism is caused by

i. Androgen-secreting adrenal tumors

ii. Adrenal hyperplasia

Malignant adrenal tumors may secrete excess androgens, estrogens, cortisol, mineralocorticoids (or combinations of the four). Adrenal tumors that secrete androgens cause virilization. Adrenal hyperplasia is usually congenital; delayed virilizing adrenal hyperplasia is a variant of congenital adrenal hyperplasia. The defect is only partial in delayed virilizing adrenal hyperplasia, so clinical disease may not develop until adulthood.

Symptoms and Signs of Adrenal Virilism:

Effects depend on the patient's sex and age at onset and are more noticeable in women than in men.

i. Female infants may have fusion of the labioscrotal folds and clitoral hypertrophy resembling male external genitalia, thus presenting as a disorder of sexual differentiation.

ii. In prepubertal children, growth may accelerate. If untreated, premature epiphyseal closure and short stature in adulthood occur. Affected prepubertal males may experience premature sexual maturation.

iii. Adult females may have amenorrhea, atrophy of the uterus, clitoral hypertrophy, decreased breast size, acne, hirsutism, deepening of the voice, baldness, increased libido, and increased muscularity.

iv. In adult males, the excess adrenal androgens may suppress gonadal function and cause infertility. Ectopic adrenal tissue in the testes may enlarge and simulate tumors.

v. Adrenal virilism is suspected clinically, although mild hirsutism and virilization with hypomenorrhea and elevated plasma testosterone may also occur in polycystic ovarian syndrome (Stein-Leventhal syndrome). Adrenal virilism is confirmed by showing elevated levels of adrenal androgens.

Diagnosis of Adrenal Virilism:

a. Testosterone

b. Other adrenal androgens (dehydroepiandrosterone [DHEA] and its sulfate [DHEAS], androstenedione)

c. 17-hydroxyprogesterone

d. Dexamethasone suppression test

e. Sometimes adrenocorticotropic hormone (ACTH) stimulation test

f. Adrenal imaging

Treatment of Adrenal Virilism:

i. Oral glucocorticoids for hyperplasia. Although most symptoms and signs of virilism disappear with treatment, hirsutism and baldness disappear slowly, the voice may remain deep, and fertility may be impaired.

ii. Removal of tumors: Tumors require adrenalectomy. For patients with cortisol-secreting tumors, hydrocortisone should be given preoperatively and postoperatively because their nontumorous adrenal cortex will be atrophic and suppressed.

iii.

PATHOPHYSIOLOGY OF MALE INFERTILITY

Infertility is the inability of a couple to achieve pregnancy after one year of regular unprotected sexual intercourse. . It also includes the inability to carry a pregnancy to the delivery of a live baby. Male infertility is established when the female partner is known to be fertile, but the male could not impregnate the female. Male factor infertility is responsible for 40–50% of all infertility in Nigeria although it varies from one region to another, and the causes also vary from place to place.

Causes of male infertility

Male infertility has multifactorial causes. This could be genetic, physical abnormalities, injuries, drugs, infections of the genital tract, radiation, toxins or unexplained. The major causes of male factor infertility in Nigeria are infection and hormonal abnormalities.

AZOOSPERMIA

Azoospermia refers to the medical condition in which there are no sperm cells detected in at least 2 semen samples. It affects about 1% of male population and accounts for 20% of male infertility cases.

However, oligospermia is a marked reduction in the number of viable sperms cells present a male's ejaculate. The cut off value, according to WHO is 20 million cells per milliliter ($20x10^6$/ml). Therefore, any sperm count less than this value is referred to as oligospermia. It is the most common cause of infertility in men.

Whereas, teratospermia describes the presence of abnormal sperm morphology (normal morphology <4%), asthenozoospermia refers to the presence of immotile sperm cells (motility <32%), in any semen sample.

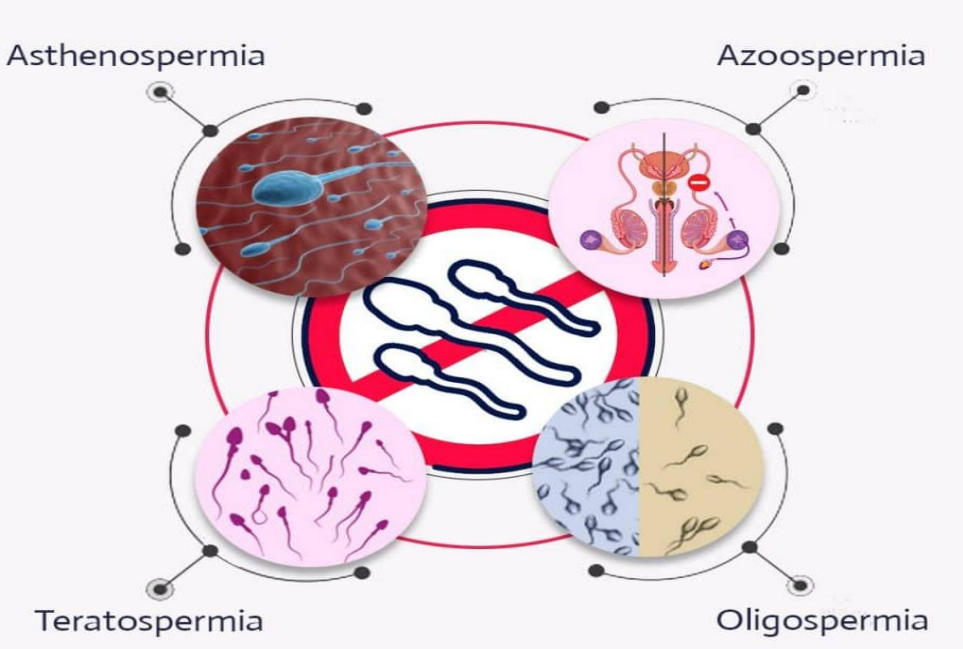

Figure 14.1: Forms of sperm abnormalities

All forms of sperm abnormalities can arise from a number of causative factors. These include:

- Hormonal imbalance
- Infections, sexually transmitted infections/diseases (STIs/STDs)
- Genetic conditions like Klinefelter's syndrome
- Varicocele
- Hydrocele
- Undescended testes
- Testicular inflammation or injury
- High testicular temperature
- Cancerous or non-cancerous tumours.
- Severe illness
- Anabolic steroid misuse or abuse,
- Opiate use and
- Other lifestyle factors such as alcohol and tobacco use
- Participations in high-intensity sports or activities that might expose the testicles to high temperatures (like saunas or occupational exposures).
- Obesity
- Some medications.

- Abnormalities that result in some parts of the male reproductive system not developing at all, such as in men with congenital bilateral absence of the vas deferens, can prevent the transport of sperm.
- Blockages in the reproductive tract due to scarring or accidental injury during surgery or for unknown reasons.
- Ejaculation problems and erectile dysfunction can be causes of male infertility.

Treatment of male infertility

Treatment is dependent on the cause.

Hormonal therapy for hormonal imbalance, modification of lifestyle, treatment of infection with the appropriate antibiotic, surgical intervention for structural defects, etc., are the mainstay of treatment.

If treatment of infertility is unsuccessful, assisted reproductive technologies (ART) may advised.

MALE CHROMOSOMAL ABNORMALITIES

Klinefelter's syndrome

This is the inheritance of one or more extra X chromosomes in a male, giving rise to XXY chromosome, or more rarely XXXY or XY/XXY mosaic.

The affected males usually exhibit relatively high-pitched voices, asexual to feminine body contours as well as breast enlargement, and comparatively little facial and body hair. They are sterile or nearly so, and their testes and prostate glands are small. As a result, they produce relatively small amounts of testosterone. The feminizing effects of this hormonal imbalance can be significantly diminished if Klinefelter's syndrome boys are regularly given testosterone from the age of puberty and onwards. Like triple-X females many Klinefelter's syndrome men are an inch or so above average height. They also are likely to be overweight. They usually have learning difficulties as children, especially with language and short-term memory. If not given extra help in early childhood, this often leads to poor school grades and a subsequent low self-esteem. However, most men who have Klinefelter's syndrome are sufficiently ordinary in appearance and mental ability to live in society without notice. They have a higher than average risk of developing osteoporosis, diabetes, and other autoimmune disorders that are more common in women. This may be connected to low testosterone production.

Those with mild symptoms may grow to adult stage without notice until an incidental test for infertility is carried out. They are usually capable of normal sexual function, including erection and ejaculation, but many, if not most, are unable to produce sufficient amounts of sperm for conception.

Klinefelter's syndrome males with more than two X chromosomes usually have extreme symptoms and are often slightly retarded mentally.

Men who are mosaic (XY/XXY) generally have the least medical complications. Subsequently, regular testosterone therapy is often prescribed.

The frequency of Klinefelter's syndrome has been reported to be between 1 in 500 and 1 in 1000 male births, making it one of the most common chromosomal abnormalities. Males with Down's syndrome sometimes also have Klinefelter's syndrome. Both syndromes are more likely to occur in babies of older mothers.

Jacobs's syndrome (XYY syndrome): This is a condition where males inherit an extra Y chromosome, giving rise to an XYY sex chromosome. As adults, these "super-males" are usually tall (above 6 feet) and generally appear and act normal. However, they produce high levels of testosterone. During adolescence, they often are slender, have severe facial acne, and are poorly coordinated. They are usually fertile and lead ordinary lives as adults. Many, if not most, are unaware that they have a chromosomal abnormality. The frequency of XYY syndrome is not certain due to statistical differences between different studies. It may be as common as 1 in 900 male births to as rare as 1 in 1500 or even 1 in 2,000.

IMPOTENCE

Impotence (also called erectile dysfunction – ED) is a term that describes the consistent inability to achieve or sustain penile erection of sufficient rigidity during sexual intercourse. It can be seen in varying degrees of severity. In Nigeria, the general prevalence of ED is 58.9% (47.2% mild, 11.3% moderate and 41.5% severe ED).

The causative or risk factors of impotence are increasing age, hypertension, use of anti-hypertensive drugs, diabetes mellitus and heart diseases etc. it was observed that ED occurs at an earlier age in people with diabetes than in the general population, and that there is an associated stigma with the condition posing difficulty in seeking medical help early enough.

The organic causes of ED include damage to or malfunction of the efferent nerves or descending pathways, endocrine disorders, various therapeutic and "recreational" drugs (e.g., alcohol), and certain diseases, particularly diabetes mellitus.

Erectile dysfunction can also be due to psychological factors (such as depression), which are mediated by the brain and the descending pathways.

Treatment includes the treatment of organic causes, lifestyle modifications , as well as use of some drugs e.g., cGMP-phosphodiesterase type 5 (PDE5) inhibitors including sildenafil (Viagra), vardenafil (Levitra), and tadalafil (Cialis) that can improve the ability to achieve and maintain an erection. The most important event leading to erection is the dilation of penile arteries by nitric oxide, released from autonomic neurons. Nitric oxide stimulates the enzyme guanylyl cyclase, which catalyzes the formation of cyclic GMP (cGMP). This second messenger then continues the signal transduction pathway leading to the relaxation of the arterial smooth muscle. The sequence of events is terminated by an enzyme-dependent breakdown of cGMP. PDE5 inhibitors block the action of this enzyme and thereby permit a higher concentration of cGMP to exist.

PUBERTY DISTURBANCES

Normal variants of puberty

The diagnostic evaluation of disorders of puberty necessarily involves the differentiation of pathological disorders from the normal variants of early or late puberty. Normal variants include constitutional delay or acceleration of growth and puberty (pubertas tarda, pubertas accelerata), early breast development (premature thelarche), early development of pubic hair (premature pubarche), and pubertal gynecomastia.

For example, in a girl with delayed puberty, breast development to Tanner stage B2 occurs when she is more than 13.3 years old; in a boy with pubertas tarda, a testicular volume of 3–4 mL is first reached when he is more than 13.7 years old.

The mirror image of constitutional delay of growth and puberty is constitutional acceleration of growth and puberty. The onset of puberty (breast development, testicular enlargement) occurs more than two standard deviations earlier than the normal mean age of onset. The hypothalamic-pituitary-gonadal axis is activated earlier than usual, but not before age 8 in girls (breast development) or before age 9 in boys (testicular enlargement)

In girls with premature thelarche, breast tissue develops early—sometimes in the first two years of life, sometimes later, and occasionally even in the neonatal period—and then persists until the true onset of puberty. Premature thelarche is an incomplete form of pubertal development without any other signs of early puberty, such as a pubertal growth spurt or marked acceleration of skeletal age. In rare cases, premature thelarche undergoes a transition to precocious puberty.

Premature pubarche is a further normal variant of pubertal development in which pubic and/or axillary hair develop in a girl before age 8 or in a boy before age 9. The serum levels of adrenal androgens are normal, and there is no androgen-induced growth spurt. The skeletal age corresponds to the chronological age or is only mildly accelerated. Premature pubarche is to be distinguished from premature adrenarche with elevated levels of adrenal androgens (adrenogenital syndrome), and an androgen-secreting tumor.

Some degree of pubertal gynecomastia can be observed in about 50% to 90% of boys. In most cases, breast tissue is palpable only as a small mass under the nipple that regresses spontaneously in 6 to 18 months. In rare cases, the gynecomastia is more pronounced and persists longer, so that severe psychosocial problems ensue that may necessitate medical treatment, e.g., with tamoxifen, or surgical intervention. Only in exceptional cases is pubertal gynecomastia due to increased estrogen production or other hormonal causes, chromosomal anomalies such as Klinefelter's syndrome (47, XXY), or medications such as spironolactone.

Psychosocial aspects of puberty: The mental and emotional changes of puberty include basic structuring of the personality (identity), separation of self from parents, and social orientation outside the family.

The pathology of early puberty

Pathological conditions in which puberty occurs early are divided into gonadotropin-dependent disorders (true precocious puberty) and gonadotropin-independent disorders (precocious pseudo-puberty). A further possibility to be considered is pathological adrenal dysfunction leading to the isolated, premature appearance of pubic hair (premature adrenarche).

Gonadotropin-dependent early puberty (true precocious puberty)

- True precocious puberty is initiated by premature activation of the hypothalamic-pituitary-gonadal axis.
- Its prevalence is estimated at 1:5000 to 1:10 000.

- It is five to ten times more common in girls than in boys.
- In girls, breast tissue develops under estrogenic influence.
- In boys, the testes enlarge first, and then the penis enlarges under the influence of testosterone.
- The clinical course resembles that of normal pubertal development.
- Pubic hair usually appears later, as a result of stimulation by androgens derived from the adrenal gland and from the testes or ovaries.
- An early pubertal growth spurt occurs at about the same time as the external signs of puberty appear.
- Because of the simultaneous acceleration of skeletal development, the individual's final height is often reduced, sometimes to the point of short stature.
- The diagnosis of true precocious puberty must be considered when the initial signs of puberty appear in a girl under age 8 or a boy under age 9.
- The diagnosis is then confirmed by the clinical findings, including
    - The Tanner stages and growth spurt,
    - Acceleration of skeletal growth,
    - The results of GnRH testing: the stimulated LH/FSH quotient at 30 minutes is greater than 1
    - Ultrasonography reveals a multicystic ovary with many follicles and increased uterine volume.
    - The estradiol level (in girls) or the testosterone level (in boys) is markedly elevated for chronological age, but corresponds to the current pubertal stage.

Causes of precocious puberty

- The cause of precocious puberty remains unidentified in 80% of girls and 40% of boys.
- Aside from these idiopathic cases, precocious puberty can also result from organic lesions in the hypothalamic and pituitary areas, primarily in boys.
    - Hypothalamic hamartoma, glioma, astrocytoma, and germinoma can cause precocious puberty
    - It can also occur in children with internal hydrocephalus or other lesions of the central nervous system, such as an earlier episode of meningitis or traumatic brain injury or prior radiotherapy to the head.

Magnetic resonance imaging of the brain should be performed in order to search for a possible organic cause.

Treatment

Treatment is indicated, often due to psychosocial stress on the affected child resulting from the very early appearance of signs of puberty, the frequent (and generally wrong) assumption by others that the child possesses a correspondingly early mental and emotional "maturity," and the risk of reduced adult height due to disproportionate acceleration of skeletal age.

The treatment involves the administration of GnRH analogs that suppress the effects of the elevated gonadotropins LH and FSH through down-regulation of the pituitary GnRH receptors, as well as the treatment of cause where applicable.

Gonadotropin-independent early puberty (precocious pseudopuberty)

Precocious pseudopuberty arises, before and independently of the maturation of the hypothalamio-pituitary-gonadal axis. The appearance of secondary sexual characteristics is due to the increased production of female or male hormones. Oestrogens induce isosexual pseudopuberty in girls and heterosexual pseudopuberty in boys; conversely, androgens induce isosexual pseudopuberty in boys and heterosexual pseudopuberty in girls. The hypothalamic-pituitary-gonadal axis is suppressed by the abnormally elevated secretion of androgens or estrogens.

Causes of precocious pseudopuberty

- External factors, such as the therapeutic or accidental ingestion of oestrogens or androgens
- Disturbances of steroid biosynthesis
- Congenital syndromes.
- Tumours: Hormone-secreting tumours of the central nervous system, the adrenal gland, the liver or other organs can be responsible for the development of precocious pseudopuberty.
- Germ-cell tumours secrete human chorionic gonadotropin (hCG), which, in turn, stimulates the LH-receptors of the testes (for example), which then produce testosterone. Tumors of this type can arise in the gonads, the central nervous system (pineal and pituitary glands), the liver, the retroperitoneal space, or the posterior mediastinum, which are the sites of origin of the sex-determining cells during embryonic development.
- Adrenal tumours can produce androgens as well as cortisol and thereby induce iso- or heterosexual precocious pseudopuberty in addition to the clinical signs of Cushing syndrome.
- Leydig cell tumours must also be considered in the differential diagnosis of precocious pseudopuberty.

Pathological absence of puberty

- When puberty does not occur spontaneously, no development of secondary sexual characteristics is observed.
- If pubic hair develops, this is usually due to the secretion of adrenal hormones and does not imply activation of the hypothalamic-pituitary-gonadal axis. The concentrations of the pituitary hormones LH

and FSH are low when the disturbance has its origin in the hypothalamus or pituitary gland (hypogonadotropic hypogonadism); they are high when the cause is ovarian or testicular failure (hypergonadotropic hypogonadism). In either case, the level of the gonadal hormone, oestradiol or testosterone, is low.

- Follicular maturation or sperm production does not occur.
- Further diagnostic evaluation is needed if no breast development has yet occurred in a girl aged 14.5 years or if the testes have not reached a size of 3 mL or more in a boy aged 14.6 years.
- Even at this late age, the major differential diagnosis is constitutional delay of growth and puberty.

Causes of absent puberty

- Hypogonadism, whether it is tertiary (hypothalamic), secondary (pituitary), or primary (gonadal), can be either congenital or acquired.
- The classic example of congenital hypothalamic hypogonadism is Kallmann syndrome, in which hypogonadism is characteristically accompanied by hyposmia or anosmia. Kallmann syndrome is due to an impairment of the normal migration of the GnRH neurons from the region of the olfactory nerve to the ventral hypothalamus.
- The term "functional hypothalamic hypogonadism" refers to a usually reversible dysfunction of the hypothalamic-pituitary-gonadal axis that can arise in the setting of anorexia nervosa, during situations of severe stress, or when the affected person participates in very intense physical activity, including sport.
- Congenital developmental abnormalities of the pituitary gland usually cause a complex deficiency of multiple pituitary hormones; therefore, the diagnosis of hypogonadotropic hypogonadism is often preceded by that of a growth hormone deficiency, pituitary hypothyroidism, and/or pituitary ACTH deficiency.
- Magnetic resonance imaging may reveal hypoplasia or aplasia of the adenohypophysis, a rudimentary or absent pituitary stalk primordium, and/or ectopy of the neurohypophysis.
- Acquired forms are due to autoimmune diseases, radiotherapy, or chemotherapy. These patients have significantly elevated LH and FSH levels because of the lack of the negative feedback mechanism that results from the estrogens or from testosterone, as well as from the inhibins A and B, and that inhibits secretion of the hypothalamic-pituitary hormones.
- Tumours of the hypothalamic-pituitary region, such as craniopharyngioma, germinoma, Langerhans cell histiocytosis, prolactinoma, adenoma, etc.

Disturbances of female menstrual cycle

This includes the following:

1)Dysmenorrhea

This presents as painful cramps during menstruation.

2)Premenstrual syndrome

This refers to physical and psychological symptoms occurring prior to menstruation.

3)Menorrhagia

This is heavy bleeding, including prolonged menstrual periods or excessive bleeding during a normal- length period.

4)Metrorrhagia

This is bleeding at regular intervals, particularly between expected menstrual periods.

5)Amenorrhea

The absence of menstruation.

6)Oligomenorrhea.

This is an infrequent menstrual period.

7)Hypomenorrhea

This refers to light periods.

Pain is the most reported of all the problems associated with menstruation and also cramps. The risk factors includes stress, obesity, smoking and marital status.

Pathophysiology of Conception

For conception to occur, the following conditions must be fulfilled:

1)Sperm transport

The sperm must be deposited and transported to the site of fertilization. The sperm must be capable of propelling themselves through the environment of the female vagina and cervix. This environment, which is under cyclic hormonal control, must be favourable to admit the sperm without destroying them. Also the sperms must possess the capability of converting to a form that can penetrate the cell membrane of the egg (capacitation). Tubal obstruction and azoospermia can affect this stage.

2) Egg transport

Ovulation must occur and the egg must be picked up by the fallopian tube. The egg transport begins at ovulation and ends once the egg reaches the uterus. This involves the picking up of the discharged egg after ovulation by the adhesive sites on the fimbriated or finger- like ends of the fallopian tube and its movement into the fallopian tube. The cilia inside the tube and the tubular muscle contractions then move the egg into the uterus. Conditions like endometriosis can affect this stage as well as obstruction along the tubes will affect this stage. This includes: congenital disorders, surgical obstruction and acquired obstruction from infection.

3)Fertilization and embryo development. A union between the sperms and egg must result. This involves a fusion between the egg and the sperm inside the tube and the formation of a zygote which metamorphoses into a blastocyst. If either the sperm or ovum or both are defective, this stage will be affected adversely.

4)Implantation

The embryo must implant and begin to grow in the uterus. The receptivity of the uterus and the health of the embryo are important for the implantation process. This process is affected by many factors which include: placental shape abnormalities, velamentous cord insertion, maternal vascular malperfusion, abnormally located placentation and morbidly adherent placenta.

Pathophysiology of Lactation

Lactogenesis is the process of developing the ability to secrete milk and involves the maturation of alveolar cells. It takes place in two stages:

a)Stage 1 lactogenesis- Secretory Initiation

This is also called lactogenesis (secretory initiation). This takes place during the second half of pregnancy and is controlled essentially by progesterone.

b)Stage 2 lactogenesis- Secretory Activation

This starts with copious milk production after delivery. At this stage the level of progesterone drops and the levels of prolactin, cortisol and insulin are increased.

Lactation is maintained by regular removal of milk and the stimulation of the nipples by suckling. This triggers the release of prolactin and oxytocin. Any abnormality in the level of the hormones and nipple stimulation, will affect lactation.

Pathophysiology of sensory disturbances and peripheral neuropathies

Peripheral neuropathies result from damage to the peripheral nervous system. These damages arise from many different causes. It may be inherited or arise from physical injury or disorder of organ systems. The commonest causes of peripheral neuropathies include diabetes mellitus, renal disease or hormonal imbalances. There are basically four categories of peripheral neuropathies depending on the particular nerves affected:

1. Motor neuropathies are caused by damage to the nerves that control muscles and movement.
2. Sensory neuropathies are caused by damage to nerves that convey sensory information such as pain, temperature or touch sensations to the central nervous system.
3. Autonomic neuropathies arise from damage to nerves that control autonomic functions including breathing and heartbeat.
4. Combination neuropathies as the name implies involves a combination of other types of neuropathies such as a sensory and motor neuropathy.

Symptoms of peripheral neuropathy are varied depending on part of the body that is affected. Symptoms can range from tingling or numbness in a certain body part to more serious effects such as burning pain or paralysis. Other symptoms include: muscle weakness or twitching, including loss of muscle and bone mass, changes in skin, hair, or nails associated with numbness, loss of bladder control leading to urinary tract infection or urinary incontinence, dizziness, or fainting because of a loss of blood pressure control mechanisms others include diarrhoea, constipation, or incontinence because of nerve damage in the intestines amongst others. Symptoms of peripheral neuropathy may mimic like other medical conditions or medical problems.

Syringomyelia

Syringomyelia may be defined as the presence of abnormal, CSF-filled cavities or syrinx within the adult spinal cord. It is different from other the pathological condition and normal anatomical variants such as persisting embryological central canals in children. Although in adults it is rarely a life-threatening condition, cerebrospinal fluid (CSF) accumulates within the spinal cord, expands the central canal, and forms a syrinx. The enlarged syrinx may occasionally cause damage to the spinal via compression and injury to nerve fibres that carry sensory impulses to and from the brain. Symptoms of spinal cord damage vary and is dependent on the location, size and extent of the syrinx. Symptoms gradually develop and may worsen over many years. They can include: chronic pain, progressive weakness in arms and legs, stiffness in the back, shoulders, neck, arms, or legs, headaches, loss of sensitivity to pain or hot and cold, especially in the hands, a numbness or tingling sensation, loss of balance, loss of both sexual and bowel control and loss of sexual functions.

Neurosyphilis

Syphilis is an infectious disease caused by a spirochete bacteria called *Treponema pallidum* (*T. pallidum*). Neurosyphilis is used to describe the central nervous system (CNS) involvement of the infection with the spirochete bacteria. Syphilis is usually a sexually transmitted infection, but vertical transmission can also occur, and more rarely, blood transfusion-associated transmission can be seen. Neural involvement can occur at any time in the history of infection if not promptly treated. Neurosyphilis exists in five forms which includes: asymptomatic neurosyphilis in which patients are asymptomatic; meningeal neurosyphilis with features and symptoms of diffuse inflammation of the meninges; meningovascular neurosyphilis because of inflammation of the meninges and its vascular supply; general paresis resulting from cerebral atrophy; and tabes dorsalis resulting from degeneration of the posterior (dorsal) column and roots of the spinal cord.

Thalamic syndrome

Thalamic (pain) syndrome also known as Dejerine–Roussy syndrome results from a cerebrovascular accident affecting and causing damage to the thalamus. It typically induces a centralized, neuropathic pain that is commonly and associated with changes in temperature. The spectrum of pain may include hyperalgesia and allodynia. The thalamus relays sensory information between a variety of subcortical areas and the cerebral cortex. Usually, sensory information from environmental stimuli arrives the thalamus for processing and then to the somatosensory cortex for interpretation. Eventually interpreted by the brain as seeing, hearing or feeling.

Thalamic damage results in miscommunication between the afferent pathway and the cerebral cortex leading to changes in sensory perception. These changes result in an incorrect sensation experienced, or inappropriate amplification or dulling of a sensation. Symptoms of thalamic syndrome commonly include numbness in the affected side that is replaced by a burning and tingling sensations accompanied by hypersensitivity to pain. The pain symptoms are neuropathic and include allodynia defined as pain from a stimulus that would normally not cause pain, dysaesthesia an unpleasant and abnormal sense of touch presenting as pain. In this condition it is due to thalamic lesioning. There can be itching, tingling, burning, or searing experienced spontaneously or from various stimuli.

Herpes simplex

This is a viral infection caused by the herpes simplex virus. It may affect the face or mouth (oral herpes), genitals (genital herpes), the eyes (herpes simplex keratitis), the brain (herpes viral encephalitis) or neonates (neonatal herpes). Herpes is usually transmitted via direct contact with body fluids or lesions of an infected individual. Genital herpes may be transmitted sexually and may spread to an infant during childbirth. Herpes is contracted through direct contact with an active lesion or body fluid of an infected person typically through direct skin-to-skin contact or exposure to infected saliva, semen, vaginal fluid, or the fluid from herpetic blisters.

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is a complex unpleasant phenomenon with sensory experiences that include time, space, intensity, emotion, cognition, and motivation. It is a symptom and cannot thus be experienced for another.

The complex phenomena associated with pain is involves a sensory (discriminative) system that helps determine the location, intensity, quality and the and temporal and spatial aspects of pain; a motivational (affective) system that determines approach-avoidance behaviours causing depression and anxiety and a Cognitive (evaluative) system on the thought involving the cause and the significance of the pain. All these may block or modulate the perception of pain.

Types and classification of pain

There are various classifications of pain. Pain may be classified as either somatic or psychogenic if the cause is known or unknown.

In somatic pain the cause of the is known and localised to a particular body tissue. Somatic pain may arise from somatic structures including the internal viscera or be neuropatic thus arising from nerve tissues. Psychogenic pain is pain for which there is no known physical cause and arises from psychological factors.

Pain may also be described as acute or chronic. Acute pain is a protective mechanism that alerts the individual to a condition or experience that is immediately harmful to the body. Onset of acute pain is usually sudden. Chronic pain on the other hand is more difficult to treat and can persist for months or even years.

Pain may also be described as slow or fast depending on how soon the pain sensation is experienced following the noxious stimulation. Fast pain is perceived within 0.1seconds of stimulation and is described as sharp, acute or pricking. Slow pain is perceived within 1second but may slowly increase with time and is described as burning, aching or throbbing.

Pain perception and transmission
The neural mechanisms for the perception and transmission of the pain sensation may be divided into three

areas:

1. The afferent pathways
2. The central nervous system
3. The efferent pathways

The afferent pathways are composed of nociceptors which are usually nerve endings of nociceptive nerve cells, afferent nerve fibres and a spinal cord network.

Perception of pain starts with the pain receptors which are usually free nerve ending and are located the skin and other tissues of the body. These pain receptors are stimulated by several types of stimuli. The stimuli may be mechanical, thermal or chemical. Chemical types of stimuli include agents released during inflammation including bradykinin, histamine, serotonin and proteolytic enzymes. Most pain receptors are non-adapting and would continue to be stimulated in the presence of appropriate stimuli. The following factors can also cause pain: tissue damage, tissue ischaemia, muscle spasm.

Once the receptors for pain is stimulated, impulses are generated and the transmitted to the central nervous system. There are basically two pathways the fast-sharp pain pathway and a slow-chronic pain pathway. The fast-sharp pain is elicited by mechanical or thermal stimuli and are transmitted via myelinated Aδ fibres while the slow-chronic pain is stimulated by chemical or thermal stimuli and transmitted via unmyelinated type C fibres. On entering the cord, these afferent pathways terminate in the dorsal horn of the spinal cord as first order afferent neurons. The second afferent neuron creates spinal part of afferent system. From thence, two different pathways transmit pain impulses to the brain. There are two pathways:

1. A neospinothalamic tract
Transmit impulses from the myelinated Aδ fibres for acute pain. Nerve impulses usually pass to the opposite side of the brain and transmit to the thalamus and then the higher brain centres. The impulses are described as localised and sharp.

2. A palaeospinothalamic tract
Transmit impulses from the unmyelinated type C fibres for chronic pain sensation to the substantia gelatinosa and then through the opposite side of the brain to higher brain centres. The impulses are described as diffuse burning or aching.

The portion of CNS involved in the interpretation of the pain signals are the limbic system, reticular formation, thalamus, hypothalamus and cerebral cortex; they are important for the conscious appreciation of pain. Particularly, the cerebral cortex for the interpretation of the pain sensation.

There is also an efferent pathway connecting the reticular formation, midbrain and substantia gelatinosa involved in different behavioral and psychological responses and the possible modulation of the pain sensation.

Analgesia system of the nervous system

Pain afferents on their way to CNS send branches to periaqueductal gray matter surrounding the cerebral aqueduct in the midbrain, and stimulates the neurons via activation of efferent (descendent) anti-nociceptive pathways from there the impulses are transmitted through the spinal cord to the dorsal horn there thay inhibit or block transmission of nociceptive signals at the level of dorsal horn

Theories of pain

There are a number of theories attempting to explain the production and modulation of the pain sensation. However, the most widely accepted and rational explanation is the Gate control theory. This theory proposes that nociceptive impulses are transmitted to the spinal cord either through myelinated Aδ fibres and small unmyelinated type C- fibres. Both of these fibres create synapses with neurons in the substantia gelatinosa and the cells here function as a gate regulating transmission of pain impulses to higher portions of the brain. Stimulation of larger myelinated Aδ fibres causes the cells in substantia gelatinosa to 'close the gate' for transport of painful information centrally. A closed gate leads to decreases stimulation of the second afferent neuron decreasing transmission of impulses and diminishing pain perception. Stimulation of small unmyelinated type C-fibres inhibits cells in substantia gelatinosa and 'opens the gate'. An open gate increases the stimulation of and transmission of impulses and enhances pain perception. The gate control theory may also explain modulate pain perception by the nervous system.

Types of pain: referred, visceral, neuropathic, hyperalgesia and algesia

Referred pain: This is pain perceived at a location different from the site of the origin of the painful stimulus. It arises from the complex network of interconnecting sensory nerves supplying many different tissues. Injury at a particular site in the network may cause wrongful signal interpretation in the brain as the sensation are experienced as arising from the surrounding nervous tissue

Visceral pain: This is pain arising from internal organs within the thoracic, abdominal, or pelvic cavities. It is opposed to somatic pain arising from Musculo skeletal structures. Visceral organs include the intestines, the uterus, the heart and the ureter and urethra.

Neuropathic pain: This occurs as a result of injury to or dysfunction of the peripheral or central nervous system. The nerve injury may be caused by associated pathology of surrounding tissue. Neuropathic pain may mimic somatic pain and is characterized as disesthetic pain (e.g. uncomfortable, unfamiliar sensation) causing a burning or shock-like tingling sensation. Neuropathic pain may be associated with reffered pain or allodynia.

Hyperalgesia and allodynia: Hyperalgesia refers to an increased sensation or perception of pain from a stimulus that normally provokes pain. Its pain of a higher intensity that would ordinarily be associated with that particular stimulus. On the other hand, allodynia is pain due to a stimulus that does not normally elicit pain. It is characterised by painful sensations induced by ordinarily non-noxious stimuli. The impulses of allodynia are transmitted by fast- conducting nerve fibres.

Hyperpathia: This is an augmented response to any sensory stimuli. Hyperalgesia and hyperpathia are similar. The difference is that hyperalgesia is an increased response is to ordinarily a less painful stimuli.

PATHOPHYSIOLOGY OF HEADACHE

Headache is a common neurologic disorder that affects more than 90% of the population at some time in their life. It is usually a benign symptom, though can be associated with serious diseases such as brain tumor, meningitis and cerebrovascular diseases.

There are two categories of headache:

(a) Primary headache disorders, not associated with structural anomalies or systemic diseases, they include: migraine, cluster, paroxysmal hemicrania, and tension headache.

(b) Secondary headache disorders , are symptomatic of an underlying abnormality such as intracranial tumor, aneurysm, drug withdrawal, etc. The characteristic features of the main types of headache are summarized in Table 14.1 .

Feature	Migraine with or without aura	Cluster headache/proxysmal hemicrania	Tension-type headache
Age of onset	Childhood, adolescence or young adulthood	Young adulthood, middle age	Young adulthood, middle age
Gender	Female	Male	Not gender specific
Family history of headache	Yes	No	Yes
Onset and evolution	Slow to rapid	Rapid	Slow to rapid
Time course	Episodic	Clusters in time	Episodic, may become constant.

Quality	Usually throbbing	Steady	Steady
Location	Variable, often unilateral	Orbit, temple, cheek	Variable
Associated features	Prodrome, vomiting	Lacrimation, rhinorrhea, Horner syndrome	None

Migraine

Pathophysiology of Migraine

Migraine is the most common multifactorial and multidisciplinary neurologic condition of the primary headaches syndrome, characterized by unilateral, throbbing headaches, usually associated with nausea, vomitting, photophobia, and phonophobia. It occurs either in episodic or in chronic form, with or without aura. Prior to the onset, a plethora of transient motor and somatosensory disturbances such as visual disturbances, unilateral numbness, weakness, and language dysfunction are common in this condition.

In the early years, the pathophysiology of migraine was mainly based on neurological and vascular mechanisms, but now, metabolic mechanisms have been added. Migraine has four phases: premonitory, aura, headache and postdromal. These phases may occur sequentially or may overlap.

The main pathophysiology of migraine has been linked with the trigeminovascular system, controlled by the brain stem and diencephalic nuclei. Trigeminovaascular system consists of efferent neurons that supply vascular networks and afferent neurons that feed information to the trigeminal nucleus caudalis. Meningeal inflammation and vasodilation due to activation of these networks lead to headache.

Neurotransmitters, such as serotonin, play significant roles in the pathophysiology and management of migraine. Serotonin triggers an intracellular network cascade that causes inhibitory or excitatory neurotransmission. Drugs for managing migraine have been tailored to modulate serotonin receptors. The modulation is aimed at amplifying the serotonin signal, leading to pain relief via vasoconstriction of blood vessels and inhibition of peptides such as Substance P and calcitonin gene-related peptide(CGRP).

Premonitory phase

This is the first phase of the typical migraine headache and the accompanying symptoms precede the headache phase. The symptoms of this phase include irritability, food cravings, mood swings, faitque, stiff neck, and phonophobia; and they may persist into the aura and headache phases. This possible overlap indicates the association between the premonitory phase and the hypothalamic origin. Sleep deprivation, bright light and hunger can trigger migraine attacks.

Aura phase.

This phase is seen in about 30% of migraine patients. Migraine aura has been described as a spreading, focal, neurologic disturbance that manifest as visual, sensory, or motor symptoms. The pathophysiological mechanism is unclear, but appears to be a cortical spreading depression(CSD), decreased electrical activity, and a decrease in blood flow that slowly spreads across the cerebral cortex from the occipital region.

Headache phase

This phase is marked by unilateral, pulsating, pain of moderate to extreme severity. It may last from 4-72 hours. The exact mechanism is unknown but the following have been proposed:

a. Activation of trigeminal cervical afferent neurons that innervate cerebral vessel nociceptors, (leading to activation of trigeminal sensory nerves to release vasoactive peptides, that cause sterile inflammatory response around vessels in the meningis;

b. Abnormal processing of trigeminal pain from the dural vessels and upper cervical muscles by the diencephalon(thalamus, and hypothalamus), brain stem, or high cerebral spinal cord;

c. Central sensitization from an increased of thalamic neurons to stimulation-allodynia;

d. Dilation of the terminal branches of the external carotid artery.

Postdromal Phase

This is least reported and studied of the headaches syndrome. Migraine patients may present with tiredness, muscle weakness, mood changes, difficulty in concentration and decreased appetite. The mechanism is likely due to persistent activation of the brainstem and diencephaly while and after processing the pain stimuli.

Cluster headache

Cluster headache belong to a group of disorders called trigeminal autonomoic cephalagia. They are commoner in men between 20 and 50 years. Other names of cluster headache are histamine cephalagia, Horton syndrome, and erythromelagia. They occur in clusters for a period of days followed by a long remission period. The pathologic mechanisms include release of vasoactive peptides, formation of neurogenic inflammation, and activation of pain matrix.

Cluster headache usually starts without warning and is characterized by severe, unilateral tearing; and burning, perorbital, and retrobulbar or temporal pain, lasting 30 -120 minutes. There could several attacks in a day, usually same of the day or night. Cluster headache is associated with symptoms such as lacrimation, reddening of the eyes, nasal stuffness, eyelid ptosis, and nausea.

Chronic paroxysmal hemicrania(CPH)

This is a cluster-type headache characterized by unilateral head pain, high daily frequency(4-12 in a day) and shorter duration(20-120 minutes). It is commoner in women, usually after pregnancy.

Tension-Type Headache

Among the primary types of headache, it is the most prevalent and commoner in the second decade of life. Its usually mild to moderate with a characteristic sensation of tight band or pressure around the head. The onset of tension-type headache is typically gradual and not aggravated by physical activity.

The exact pathophysiological mechanism of TTH is unknown, although, there is genetic predisposition. However, head pain is seen as the sum of nociceptive input from vascular structures, similar input from myofascial and muscular sources, and descending supraspinal modulations.

PATHOPHYSIOLOGY OF DEEP TENDON REFLEXES

The deep tendon reflexes are used to assess and diagnose neurologic disorders affecting the afferent nerves, spinal synaptic connections, motor nerves, and descending pathways. The table below is a summary of the deep tendon reflexes showing the muscles involved, nerve supply and the segmental innervations.

Type of reflex	Muscle involved	Nerve supply	Segmental innervation
Biceps reflex	Biceps brachii	Musculocutaneous	C5-6
Brachioradialis reflex	Brachioradialis	Radial	C5-6
Triceps reflex	Triceps brachii	Radial	C7-C8
Patellar (knee-jerk)	Quadriceps femoris	Femoral	L2-L4
Achilles reflex(ankle-jerk)	Gastrocnemius, soleus	Tibial	S1-S2

The National Institute of Neurological Disorders and Stroke (NINDS) grading of deep tendon reflexes:

0: Reflex absent

1: Reflex small, less than normal, includes a trace response or a response brought out only with reinforcement

2: Reflex in the lower half of a normal range

3: Reflex in the upper half of a normal range

4: Reflex enhanced, more than normal, includes clonus if present, which optionally can be noted in an added verbal description of the reflex.

Hyperreflexic deep tendon reflexes are usually seen upper motor neuron lesions. Hyper-reflexia manifest in corticospinal tract abnormalities or other descending pathways influencing the reflex arc due to a suprasegmental lesion.Hyperactive deep tendon reflexes may be evoked by a much lighter tendon tap than normal, have short latency, and reflex activity can be seen motor neuron pools of synergistic muscles. For example, a tendon tap to the biceps brachii can elicit wrist pronation.

Hypoactive or absent deep tendon reflexes are common in lower motor neuron lesions. Hypoactive deep tendon reflexes are seen in some disease conditions like hypothyroidism, hypothermia, cerebellar dysfunction, or beta-blockade.

Absent deep tendon reflexes points to a lesion within the reflex arc. Absence of a reflex plus sensory loss within the nerve distribution of the reflex indicates the presence of a lesion involving the afferent arc of the reflex, either the nerve or dorsal horn. Absence of a reflex plus paralysis, fasciculations, and muscle atrophy indicates the presence of a lesion involving the efferent arc, either the anterior horn cells, efferent nerve, or both. The

commonest cause of areflexia is peripheral neuropathy, and is caused by diabetes, alcoholism, uremia, vitamin deficiencies, amyloidosis, or toxins.

Specific peripheral nerve injuries have also shown decreased or absent deep tendon reflexes. Femoral nerve lesions can affect the patellar reflex, tibia nerve injury can affect the ankle reflex, radial nerve injury can affect the triceps or brachioradialis.

PATHOPHYSIOLOGY OF CEREBRAL PALSY

Cerebral palsy(CP) is a heterogenous group of neurodevelopmental disorder of movement, muscle tone, or posture caused by nonprogressive injury or abnormal development in the immature brain, before, during or after birth up to 1 year of age. The motor impairments are usually associated with symptoms such as altered sensation or perception, intellectual disability, communication and behavioral difficulties, seizures and musculoskeletal complications.

Several factors , alone or in combination have been implicated in the aetiology of CP. Prenatal factors include impaired embryo implantation, chromosomal abnormalities, infection, trauma, radiation exposure, maternal toxaemia, diabetes mellitus, and maternal nutritional deficiencies. During the perinatal period, anoxia, trauma, and infections are common factors. Physical trauma can also occur during child birth.

The impairments associated with CP can be grouped based on the areas of the brain that are damaged and the part of the body that is affected. Brain damage affecting the pyramidal system causes spastic CP, while damage to the extrapyramidal system leads to dyskinetic, ataxic, or hypotonic CP.

Pyramidal or Spastic cerebral palsy ccounts for 70% of cases, results from damage or defects in the brain's corticospinal pathways(upper motor neuron) in either one or both hemispheres. The features of spastic cerebral palsy include increased muscle tone, prolonged primitive reflexes, exaggerated deep tendon reflexes, clonus, rigidity of extremities, scoliosis, and contractures. When the spasticity affects the whole body, we have spastic quardriparesis and hemiparetic cerebral palsy, if it occurs primarily in one half of the body.

Furthermore, infants with unilateral spastic CP, mostly of middle cerebral artery origin, also have sensory impairments such as tactile perception(light touch) and discrimination, stereognosis and proprioception.

Nonspastic/Extrapyramidal cerebral palsy accounts for about 30% of cases, results from damage to cells in the basal ganglia, thalamus, or cerebellum. It has subtypes: dyskinetic and ataxic cerebral palsy. Dyskinetic cerebral palsy results from injury to basal ganglia or thalamus and manifests with extreme difficulty in fine motor coordination and purposeful movements. The associated movements are jerky, uncontrolled, and abrupt.

Ataxic cerebral palsy arises from damage to the cerebellum and manifests with gait disturbances and instability. An infant can present with features of both types of cerebral palsy.

PATHOPHYSIOLOGY OF BASAL GANGLIA LESIONS

The basal ganglia has three distinct biochemical pathways, that their optimal performance, must act in a balanced fashion. These are:

(a) the nigrostriatal dopaminergic system,

(b) (b) the intrastriatal cholinergic system, and

(c) (c) the GABAergic system.

Typically, motor abnormalities manifest when one or more of these pathways become dysfunctional. Basal ganglia lesions can lead to: Parkinsonism, Hutington's chorea, athetosis, hemiballismus, and Wilson's disease.

Pathophysiology of Parkinson Disease

Parkinsonism, also called Paralysis agitans, is the most common disease of the basal ganglia. It is characterized by the triad of rigidity, hypokinesia or bradykinesia, and tremor at rest. The main feature of parkinsonism is degeneration of the basal ganglia involving the dopaminergic nigrostriatal pathway.

The main pathologic features of PD are loss dopaminergic pigmented neurons in the substantia nigra(SN) pars compacta with dopaminergic deficiency in the putamen portion of the striatum. Dopamin loss in other brain areas such as brainstem, thalamus and cortex has also been observed. Neurodegeneration of the dopaminergic nigrostriatal pathway to the basal ganglia leads to reduced activity of the direct pathway(normally facilitates movement and increased activity of the indirect motor loop(usually inhibits movement).Consequently, motor cortex is inhibited, manifesting with bradykinesia and rigidity. The overactivity activity of the subthalamic nucleus(STN) also affects the limbic system, accounting for the emotional signs and symptoms associated with PD. The pathophysiological mechanisms of cell dyfunction include oxidative stress, altered protein handling, mitochondrial dyfunction and inflammatory changes with autophagy and apoptosis.

Other markers of neurodegeneration such as Lewy bodies, fibrillar intracellular eosinophilic inclusions, high concentrations of alpha-synuclein, ubiquitin, tau protein, tuberculin, and other proteins are found in the substantia nigra(SN), locus cerulus(LC, and other areas of the brain.

Molecular mechanisms associated with PD include mitochondrial dysfunction, oxidative stress, abnormal folding and accumulation of alpha-synuclei, abnormal phosphorylation, and dysfunction of ubiquitin proteasome system.

There is also genetic predisposition in Parkinson disease. Autosomal dominant genes linked with PD include SNCA-PARK8 and LRRK2-PARK8 while autosomal reccesive genes include PARK2 oncogene DJ-1 and PINK1.

PATHOPHYSIOLOGY OF CHOREA, ATHETOSIS AND HEMIBALLISMUS

CHOREA
Chorea or Hutington disease(HD) is an inherited autosomal dominant trait neurodegenerative disease by mutations of a gene called huntingtin(htt), usually located on the short arm(p) of chromosome 4, CAG expansion mutation. It is characterized by unusual movements, cognitive and psychiatric disorders. HD occurs between the age of 25 and 45 years, and in all races.

The main pathophysiological feature of HD is unknown. However, molecular genetics, oxidative stress, excitotoxicity, mitochondrial dysfunction, neuroglia dysfunction, protein aggregation, and altered UPS leads to HD.

HD develops slowly and is usually triggered by sudden changes in the HD protein huntingtin(htt). Any extension within the CAG repeat tract can cause mutation in htt, leading to longer lengths of polyglutamine(polyQ) in the encoded protein. The abnormally long polyglutamine tract in the Huntingtin protein is toxic to neurons and is caused by a cytosine-adenine-guanine(CAG) trinucleotide repeat expansion(40-70 repeats instead of 9-34).

In HD, there is severe degeneration of the basal ganglia, especially the caudate and putamen nuclei, and the frontal cerebral cortex. The excitotoxic theory of striatal and cortical degeneration suggests that the mutated hungtintin protein produces excitatoxic pathways mediated by glutamate function that also induces concomitant dysregulation of dopaminergic function. Furthermore, the huntingtin protein can also alter mitochondrial function, which in turn stimulates the apoptotic pathways, leading to neuronal death. In the plasma of Chorea patients, the levels of IL-6, matrix metallopeptidase 9, vascular endothelial growth factor(VEGF), and TGF-1 are significantly elevated, while the levels of IL-18 are greatly decreased.

Patients with HD have also demonstrated varying degrees of visual impairments such as retinal thinning, thinning of the temporal retinal nerve fiber layer, deletion of retinal ganglion cells, poor colour vision, and poor motion perception.

ATHETOSIS

Athetosis is nonrhythmic, slow, writhing, sinuous involuntary movements predominantly in distal muscles, particularly the arms.

It has been associated with lesions in the putamen and caudate nuclei of the basala ganglia. It has also been linked with peripheral neuropathy, vascular lesions, vitamin B12 deficiency, and syringomyelia.

Athetosis is an involuntary movement disorder characterized by slow, smooth, sinuous, writhing movements, particularly involving the hands.

HEMIBALLISMUS

Hemiballismus has been described as a hyperkinetic involuntary movement disorder characterized by intermittent, sudden, violent, involuntary, flinging, or ballistic high amplitude movements involving the ipsilateral arm or leg caused by malfunction in the CNS of the contralateral side. It is most severe form of movement disorder seen in clinical practice.

It is usually due to lesions in the nuclei masses of the basal ganglia especially subthalamic nucleus,and caudate nucleus, involved in the inhibitory pathways. Decreased excitatory transmission of the globus pallidus internus(GPi) and the disinhibition of the thalamus, creates an overactivation of the corticospinal and corticobulbar tracts with random firing. Consequently, efferent innervation is sent to the muscles on the contralateral side.

Other neuropathological features depends on the causative agents. For example, in hyperglycemia syndrome, basal ganglia show fibrosis and dilation of small perforating arteries, macrophage infiltration with small lunar infarcts. Other inflammatory findings include protein and iron deposition and astrocytic gliosis.

In stroke or intracranial haemorrhage, cranial nerve signs include anisocria, ptosis, facial droop, dysarthria, and headaches.

PATHOPHYSIOLOGY OF PARKINSON DISEASE

Parkinsonism is a motor disorder characterized by rigidity, tremors and bradykinesia. A typical example of Parkinsonism is Parkinson's disease (PD). Parkinson disease (PD) is one of the disorders of the basal ganglia which form part of the extrapyramidal system, which is concern with integration and regulation of motor activities. It occurs in elderly people due to a steady loss of dopamine and dopamine receptors with age.

Parkinson disease is a slowly progressive degenerative disease of the nervous system associated with destruction of brain cells which produce dopamine. It is named after discoverer James Parkinson. It is also called Parkinsonism or paralysis agitans

Parkinson disease occurs due to lack of dopamine caused by damage to basal ganglia. Mostly due to widespread destruction of the portion of the substantia nigra (the pas compacta) that sends dopamine-secreting fibres to the caudate nucleus and putamen through the neurostriatum. The dopamine neurons which use the D_2 receptors are degenerated. There is an imbalance between excitation and inhibition in the basal ganglia created by the loss of dopaminergic inhibition of the putamen. Due to the fact that dopamine is an excitatory neurotransmitter, there is over-activity of the inhibitory pathway from the striatum to the globus pallidus.

Damage to basal ganglia usually occurs due to Injury to basal ganglia, cerebral arteriosclerosis, brain infection by virus e.g., encephalitis, destruction or removal of dopamine in basal ganglia, Idiopathic which is destruction of BG due to unknown causes.

Signs and symptoms

Parkinson's disease has both hypokinetic and hyperkinetic features. It cardinal features are triad of akinesia, rigidity and tremor of which akinesia is a hypokinetic feature, while rigidity and tremors are hyperkinetic features.

1. Akinesia or hypokinesia: the patient is unable to initiate the voluntary movements (akinesia) or the voluntary movement is decreased (hypokinesia).

Manifestations of akinesia or hypokinesia include:

i. Delayed motor initiative

ii. Slow performance of voluntary movements (bradykinesia)

iii. Musk-like facial expression due to decrease in movement of facial muscles

iv. Shuffling or festinant-type gait, in which the patient is bent forward and walks quickly with short steps.

2. Rigidity: refers to increase in tone of the muscles due to the removal of inhibitory influence on gamma motor neurons. It affects both flexor and extensor muscles. So the limbs become more rigid and the condition is called lead-pipe rigidity.

3. Tremors: have the following characteristics:

i. Present at rest but disappear during activity and it is popular known as resting (static tremor)

ii. Frequency ranges from 4-6 times/s

iii. There are suppressed during sleep and exaggerated by stress, anxiety and excitement.

PATHOPHYSIOLOGY AND CAUSES OF COARSE TREMORS AND FINE TREMORS

Introduction

Tremor is defined as either fine or coarse depending on the range of oscillatory movement in the affected body part(s). A coarse tremor has a large displacement, whereas a fine tremor is barely noticeable. Tremor is divided into two subtypes, namely fine tremor with a frequency greater than 6 Hz and amplitude lower than 3 cm, and coarse tremor with lower frequency rate and higher amplitude (equal or greater than 3 cm). Various lesions in the brain stem, extrapyramidal system, and cerebellum can cause tremors.

Pathophysiology and causes of fine tremors

Physiologic tremor

Tremor can be physiological or pathological. Physiologic tremor is a very-low-amplitude and high frequency fine tremor (6 Hz-12 Hz) that is invisible or occasional. The tremor is typically postural and is thought to arise from the resonant oscillation of a limb as a result of mechanical factors affecting it.

Physiological tremor can also be enhanced (the so-called increased physiological tremor) under the influence of vigorous exercise, fatigue, anxiety, stress, certain medications, excessive caffeine consumption, hypoglycaemia, and hypermetabolic states (hyperthyroidism),

The important mechanisms underlying these tremors are a mechanical component activated by a stretch reflex component. However, alternatively (or additionally), this tremor can also be caused by an enhanced central tremor oscillation that is also seen in normal subjects.

Orthostatic Tremor

The key phenomenological characteristics include high frequency, low amplitude tremor when the individual stands up and tremor resolves immediately after sitting or lying down. Very low amplitude and high frequency of OT may not be often obvious to the eyes. The mechanism of subjective unsteadiness in OT has been attributed to a tremulous disruption of the proprioceptive feedback from the lower limbs.

Pathophysiology and causes of coarse tremors

Intention tremors

Intention tremors are as a result of cerebellar lesions are evident during purposeful movement and diminish or disappear with rest.

Holmes Tremor

Holmes tremor is usually of low frequency, high amplitude, irregular, present at rest, worsens with posture, and additionally intensifies with action. Holmes tremor almost always occurs in the context of pathologies in the brainstem or diencephalon. The aetiologies of this tremor vary widely, including cerebrovascular events, tumours, demyelination and infections.

It is suggested that the affected brain regions in Holmes tremor are connected to a common brain circuit with nodes in the red nucleus, thalamus, globus pallidus, and cerebellum. It is also suggested that Holmes tremor occurs mainly as a result of impairment of dopaminergic nigrostriatal system and cerebellothalamocortical or dentato-rubro-olivary pathways.

Myorhythmia

Myorhythmia is a slow tremor in a patient with dystonia. This is an uncommon movement disorder which is characterized by slow, rhythmic, repetitive jerky movements of 1–4Hz frequency, involving the cranial or limb muscles. The pathophysiology of tremor in dystonia likely involves the cerebello-thalamo-cortical pathway and its connections to basal ganglia.

Neuropathic Tremor

A neuropathic tremor is a form of tremor observed in some patients with severe peripheral neuropathies in the absence of any other movement disorders. Certain peripheral neuropathies, especially demyelinating polyneuropathies, have a higher predilection than other neuropathies for neuropathic tremor.

Parkinson's tremors

Parkinson's resting tremor is associated with increased cerebral activity in the cerebello-thalamo-cortical circuit. Degeneration of dopaminergic neurons in the retrorubral area (RRA) of the midbrain, more so than in the substantia nigra pars compacta, may correlate with the generation of tremor in PD. Loss of dopaminergic projections from the RRA to the subthalamic region, the basal ganglia, and the ventrolateral thalamus result in dopamine depletion in these regions and represent one of the main neurochemical bases of tremor generation in PD.

PATHOPHYSIOLOGY OF GAIT CHANGE

Normal gait requires precise control of limb movements, posture, and muscle tone, an extraordinarily complex process that involves the entire nervous system. Specialized groups of neurons in the spinal cord and brainstem generate rhythmic activity and provide output to motor neurons, which in turn activate muscles in the limbs. The cerebral cortex integrates input from visual, vestibular, and proprioceptive systems; additional input is received from the brainstem, basal ganglia, cerebellum, and afferent neurons carrying proprioceptive signals from muscle stretch receptors (as may be damaged in peripheral neuropathy). Together, these systems allow individuals to walk not only in a straight, unencumbered line but to adapt their gait to avoid obstacles and adjust posture to maintain balance. Abnormalities of any portion of the nervous system can therefore give rise to a gait disorder.

Pathophysiology of gait change

Gait disturbances/changes are described as any deviations from normal walking or gait. Numerous etiologies cause these disturbances. Gait problems can be subdivided into episodic and chronic disturbances. Continuous or chronic gait disturbances are those that the patient had adapted due to the chronicity of the neurological dysfunction. Episodic disturbances include those that occur suddenly, and the patient has not adapted to them and is a frequent cause for complications like unexpected falls. Examples of episodic disturbances include freezing gait, festinating gait, and disequilibrium. Most other gait disturbances belong to the chronic category.

Neurological causes are more common than non-neurological causes. Sensory ataxia caused by polyneuropathy, Parkinsonism, subcortical vascular encephalopathy, and dementia is among the most common neurological causes. Hip and knee osteoarthritis causing pain and limit motion are common non-neurological causes of gait disorders. Gait disturbances have a tremendous impact on patients, especially on the quality of life, morbidity, and mortality.

Musculoskeletal gait disorders

In musculoskeletal gait changes, pathological gait patterns results from musculoskeletal arthritis, excessive hip flexion, hip abductor weakness, hip adductor contracture, weak hip extensors, hip flexor weakness, knee pathologies (weak quadriceps, severe quadriceps weakness, knee flexion contraction), ankle pathologies (ankle dorsiflexion weakness, calf tightening or contractures), foot pathologies (hallux rigidus) and leg length discrepancy.

Knee hyperextension gait

Quadriceps muscle weakness results in knee hyperextension during the early stance phase. Initial contact may occur with a flat foot. The knee is stabilized by the posterior ligaments. Increased ankle plantar flexion and hip extension serve to extend and advance the affected leg during the stance phase.

Neuromuscular and myelopathic gait disorders

Waddling gait

The waddling gait can be seen in cases of proximal muscle weakness, such as myopathy. In normal gait the gluteal muscles serve to stabilize the pelvis, elevating the non–weight-bearing side with each step. With weakness of these muscles, and particularly the gluteus medius, instability of the weight-bearing hip instead causes the non–weight-bearing side to drop (Trendelenburg's sign). This leads to excessive side to-side trunk motion, giving the gait a waddling appearance. Individuals with proximal muscle weakness often have difficulty rising from a chair without using their arms.

Steppage gait

The steppage gait is caused by weakness of ankle dorsiflexion, also known as a foot drop. When the muscles that lift the foot are paretic the patient must lift the leg higher than usual during the swing phase. Individuals with a steppage gait lift the swinging leg higher to compensate for the toes' inability to clear the ground with each step; the foot landing often has a slapping quality

Myelopathic gait

Cervical spondylotic myelopathy is a relatively common cause of gait disturbance in the elderly. Degenerative osteophytes and ligamentous hypertrophy lead to narrowing of the spinal canal and mechanical compression of the cervical spinal cord. Gait and balance problems are the main clinical manifestations. The gait is stiff and paraparetic spastic but may also be spastic ataxic due to dorsal column dysfunction. Cervical pain, upper limb sensory symptoms and loss of dexterity are common but may be absent in a minority of affected patients. In severe cases, urinary urgency may occur. Compressive cervical myelopathy tends to be progressive and surgical decompression should be considered in symptomatic cases.

Cautious gait

Cautious gait (sometimes termed senile gait) refers to an excessive degree of age-related changes in walking and fear of falling. The walking difficulties seem out of proportion when considering the patient's actual sensory or

motor deficits. The gait appears slow, with a wider base than normal, reduced arm swing bilaterally and a slightly stooped posture. This type of gait change often occurs after the first time a patient has fallen. Without treatment, excessively cautious gait may lead to considerable handicap.

Spastic Gait

Spastic gaits are caused by lesions in the corticospinal tract at any level and may be unilateral or bilateral. When unilateral, the affected leg is held in extension and plantar flexion; the ipsilateral arm is often flexed. There is circumduction of the affected leg during the swing phase of each step. Common causes include stroke or other unilateral lesions of the cerebral cortex. If bilateral, the spastic gait may appear stiff-legged or scissoring owing to increased tone in the adductor muscles, such that the legs nearly touch with each step. Common causes of bilateral spastic gait (spastic paraparesis) include cerebral palsy, cervical spondylotic myelopathy, and multiple sclerosis, among many others, and are often accompanied by signs of myelopathy, such as bowel and bladder dysfunction, increased reflexes, and Babinski signs. Antispasticity agents such as baclofen or tizanidine are variably effective in improving gait but may reduce painful spasms. Botulinum toxin injections may be useful in cases of focal spasticity.

Parkinsonian Gait

The parkinsonian gait is among the most common gait disorders in the elderly. The classic “shuffling” appearance is caused by a decrease in both step length and height; posture is stooped, arm swing is reduced, and the base is narrow to normal. Parkinsonian turns are characterized by simultaneous rotation of the head, trunk, and pelvis, the so called en bloc turn; in normal individuals, the head rotates first, followed by the trunk then pelvis. Parkinson’s disease is typically asymmetric at onset, so arm swing and step length are diminished more on the affected side. Asymmetric shuffling can often be heard as scuffing of one foot more than the other. Freezing of gait and festination are features of more advanced Parkinson’s disease. Freezing is defined as “an episodic inability (lasting seconds) to generate effective stepping” despite the intention to walk. Affected individuals feel as if their feet are stuck to the floor, often associated with alternating trembling of the legs. Freezing is commonly seen while initiating gait, turning, or approaching a destination but can also be provoked by features of one’s environment, such as narrow hallways, doorways, or even large crowds. Freezing is a major contributor to fall risk. Freezing may improve with optimization of dopaminergic medications. If freezing persists despite medication adjustment, symptoms may improve with visual or auditory cueing. Festination describes a phenomenon in which steps become increasingly rapid and short, so that gait takes on the appearance of running. The center of gravity moves forward. Festination may precede freezing but also occurs independently and further contributes to fall risk.

Functional (Psychogenic) Gait Disorder

Functional gait disorders, formerly referred to as “psychogenic,” frequently co-occur with other functional neurologic disorders and are common in clinical practice. Though their presentation is heterogeneous, functional gait disorders are typically abrupt in onset, fluctuate over time, and are both suggestible and easily distractible. Common patterns include excessive slowing of gait or buckling of the knees, usually without falls. Abnormal twisting or muscle contractions may superficially resemble dystonia. Astasia-abasia describes an inability to stand or walk without support, despite ability to otherwise use the legs normally.

Pathophysiology of other gait changes

Dystonic gait disorder: The abnormal posture of the foot in dystonic gait typically involves inversion, plantar flexion and tonic extension of the big toe. In many patients complex types of walking, such as walking backwards and running are paradoxically less impaired than walking forward and may seem completely unaffected.

Choreatic gait disorder: Choreatic gait disorders may also occur in levodopa-induced dyskinesia in PD, in tardive dyskinesia and, less frequently, with hypoxic lesions in the basal ganglia, e.g. following cardiopulmonary bypass surgery ("post pump" chorea). Typical choreatic gait is impaired by sudden involuntary movements affecting knee and hip flexion and it appears irregular, dance-like and swaying.

Myoclonic gait disorder: Myoclonus of the trunk and the lower limbs may cause gait difficulties and insecurity on standing up, sudden giving way of the hips and knees and falls. A typical cause of this clinical syndrome in older age groups is generalized cerebral ischemia or hypoxia.

PATHOPHYSIOLOGY OF SOCIAL BEHAVIOUR

Pathophysiology associated with social behavior

Role of Oxytocin

Oxytocin (OT) has been most widely studied, and appears to exert modulatory functions associated with pro-social behavior. Oxytocin is an important regulator of the social brain. OT and its signaling pathway, the OT system, are important regulators in the development of the social brain, suggesting that OT plays a role in both childhood and adult neuropsychiatric disorders characterized by social cognition impairment.

Role of Acetylcholine

The neurotransmitter acetylcholine has a trophic role in many cell types including neurons. It regulates neuronal circuits in the developing brain. Hence deficits in cholinergic neurotransmissions will result in several neurodevelopmental disorders and social behavior eventually.

Role of Dopamine

Genetic or environmental perturbation in the dopaminergic neurotransmission system is associated with an array of neurodevelopmental disorders including Attention Deficit-Hyperactivity Disorder, Schizophrenia, and Autism spectrum disorders which are associated with deficit in social behavior.

Role of serotonin

Denervation of serotonin neurons in the mature brain lead to damaged synapses and de-maturation of that area. Examples Down's syndrome, and ASD are neurodevelopmental disease due to

Role of immune system in pathophysiology of social disorders

Dysfunctional immune responses are associated with increased impairments in behaviors characteristic of core features of ASD, in particular, deficits in social interactions and communication. Elevated pro-inflammatorycytokine profiles in the CSF and blood, increased presence of brain-specific auto-antibodies and altered immune cell function are the dysfunctional immune response.

Social Anxiety Disorder

Social anxiety disorder (SAD) includes the essential feature of marked fear or anxiety of one or more social situations during which the individual may or may not be under scrutiny by others. The amygdala is an essential region in anxiety disorders.

Additionally, multiple neurotransmitter systems, including serotonin, dopamine, and glutamate are important in the pathogenesis of social anxiety disorder. Brain imaging of those with social anxiety disorder reveals the increased activity of para-limbic and limbic circuitry.

Attention Deficit Hyperactivity Disorder

Attention Deficit-Hyperactivity Disorder (ADHD) is a psychiatric condition that has long been recognized as affecting children's ability to function. Individuals suffering from this disorder show patterns of developmentally inappropriate levels of inattentiveness, hyperactivity, or impulsivity. The numbers of dopaminergic receptors are decreased in the frontal lobes in individuals with ADHD. Attention Deficit-Hyperactivity Disorder (ADHD) is associated with cognitive and functional deficits that relate to diffuse abnormalities in the brain, the anterior cingulate gyrus and dorsolateral prefrontal cortex (DLFPC). These changes account for the deicits in goal-directed behavior.

Autism spectrum disorders

Autism spectrum disorders (ASD) are a group of neuro-developmental diseases. The cause of ASD is unknown, but several genetic and non-genetic risk factors have been characterized that, alone or in combination, are implicated in the development of ASD.

It has been linked to alterations in the lateral occipital lobe, the pericentral region, the medial temporal lobe, the basal ganglia, and proximate to the right parietal operculum. There are anormalities in the cytoarchitecture of the brain e.g., decreased number of cerebellar Purkinje cells.

Obsessive-Compulsive Disorder

Obsessive-compulsive disorder (OCD) is often a disabling condition consisting of bothersome intrusive thoughts that elicit a feeling of discomfort. OCD is characterized by the presence of obsessions and/or compulsions.

There is a genetic predisposition, as 45 to 65% of the variance of OCD is attributable to genetic factors. OCD has been linked to cortico-striato-thalamo-cortico circuitry. Aggression

Biological causes include genetics, medical and psychiatric diseases, neurotransmitters, hormones, substances of abuse, and medications. Psychological causes include bipolar affective disorder, schizophrenia, major depression, general anxiety disorder, and antisocial personality.. Reduced activity of the prefrontal cortex (medial and orbitofrontal regions), is associated with violent aggression. If there is an overactive amygdala that is coupled with a less active prefrontal cortex, the potential for violence increases.

Serotonin in both excess and deficiency has been correlated with aggression. Excess dopamine has been demonstrated to be involved in aggression.

Narcissistic Personality Disorder

Narcissistic personality disorder (NPD) is a pattern of grandiosity, need for admiration, and lack of empathy. The etiology of narcissistic personality disorder is multifaceted. Gray matter abnormalities in the prefrontal and insular regions and in the right prefrontal and anterior cingulate cortices and the white matter of the frontal lobe as well.

Anorexia Nervosa

Anorexia nervosa is an eating disorder defined by restriction of energy intake relative to requirements, leading to a significantly low body weight. Patients will have an intense fear of gaining weight and distorted body image with the inability to recognize the seriousness of their significantly low body weight.

Patients with anorexia nervosa have altered brain function and structure. Tthere are deficits in neurotransmitters dopamine and serotonin with differential activation of the cortico-limbic system, and diminished activity among the frontostriatal circuit

Bipolar Disorder

Bipolar disorder (BD) is a chronic and complex disorder of mood that is characterized by a combination of manic, hypomanic, and depressive episodes, with subsyndromal symptoms extant in between the mood episodes.

The prefrontal cortex, anterior cingulate cortex, hippocampus, and amygdala are important areas for emotion regulation, conditioning of responses, and behavior response to stimuli. Abnormal hyperintensities in the subcortical regions, especially the thalamus, basal ganglia, and the periventricular area are affected.

Schizophrenia

Schizophrenia is a psychotic disorder characterized by hallucinations, delusions, and disturbances in thought, perception, and behavior. The development of schizophrenia results from abnormalities in multiple neurotransmitters, such as dopaminergic, serotonergic, and alpha-adrenergic hyperactivity or glutaminergic and GABA hypoactivity. Genetics also plays a fundamental role - there is a 46% concordance rate in monozygotic twins and a 40% risk of developing schizophrenia if both parents are affected.

PATHOPHYSIOLOGY OF ATAXIA

A kind of movement disorder, ataxia is a common clinical symptom that has various origins; it presents through difficulties in the smooth and accurate execution of movements, balance disorders, and a lack of muscle control during voluntary activity. Muscle strength is normal, but the coordination of the patient's actions is disrupted, making it impossible to accurately perform activities that require the smooth interaction of several muscle groups.

Pathophysiology of Ataxia

Cerebellar Ataxia

The term cerebellar ataxia is used to indicate ataxia due to dysfunction of the cerebellum. Cerebellar lesions result in an abnormality of movement called ataxia. The ataxia is due to error in rate, range, force and direction of movement. Cerebellar dysfunctions are characterized by ataxia, hypotonia, asynergy, dysmetria, dyschronometria, nystagmus, dysdiadochokinesia, tremor, and cognitive dysfunction. How and where these

abnormalities manifest themselves depends on which cerebellar structures, such as vestibulocerebellum, spinocerebellum or cerebrocerebellum, have been damaged.

Vestibular Ataxia

Vestibular ataxia develops as a result of vestibular dysfunction. Its clinical aspect depends on the speed with which lesion develops, the extent of the lesion such as unilateral or bilateral, and the degree of vestibular compensation. Vestibular ataxia can also develop due to central vestibular lesions such as medullar stroke (Wallenberg's syndrome), migraine, and multiple sclerosis; and peripheral vestibular diseases such as Meniere's disease, benign paroxysmal positional vertigo, or vestibular neuronitis.

Sensory Ataxia

The term sensory ataxia indicates ataxia due to loss of proprioception, the loss of sensitivity to the positions of joint and body parts. This is generally caused by dysfunction of the posterior columns of the spinal cord. In some cases, the cause of sensory ataxia may be dysfunction of the cerebellum, thalamus, parietal lobes, and sensory peripheral nerves.

Sensory ataxia presents itself with an unsteady "stomping" gait with heavy heel strikes, as well as a postural instability that is usually worsened when the lack of proprioceptive input cannot be compensated for visual input. In patients with sensory ataxia, they usually complain of loss of balance in the dark. When their eyes are closed, instability is worsened markedly, producing wide oscillations and possibly a fall (positive Romberg's test). Sensory ataxia is distinguished from cerebellar ataxia by the presence of near-normal coordination, and marked worsening of coordination when the eyes are closed. On the other hand, sensory ataxia also lacks the associated features of cerebellar ataxia such as pendular reflexes, cerebellar dysarthria, nystagmus and abnormal pursuit/saccadic eye movements.

Frontal Ataxia

Frontal ataxia is also called as gait apraxia, and is observed in frontal lobe lesions such as tumors, abscesses, cerebrovascular disorders and normal pressure hydrocephalus. Patients with frontal ataxia have a difficulty in erect position. A wide stance base, increased body sway and falls, the loss of control of truncal motion, locomotor disability with gait ignition failure, start hesitation, shuffling, small steps, and freezing are also encountered in frontal ataxia

Ataxic-hemiparesis

Although ataxic- hemiparesis is mainly caused by the pontine or internal capsule/corona radiata lesions, it also occurs in the midbrain, diencephalic-mesencephalic junction, thalamus, parietal lobe, and the precentral gyrus lesions. Ischemic infarct is the most frequent cause of the syndrome, but hemorrhagic, neoplastic and demyelinating disorders have also been reported.

Optic Ataxia

Optic ataxia usually follows damage to the posterior parietal cortex, and is the inability to conduct meaningful movements or movements on command in the absence of paralysis or other sensory and cerebellar impairments. Optic ataxia occurs when the patient has a deficit in reaching under visual guidance that can not be explained by cerebellar, motor, somatosensory, visual field defects or acuity deficits.

Visual Ataxia

Visual ataxia is unsteadiness due to visual disturbances. Human being is very dependent on vision for balance and gait. Foveal vision appears to be the most important for this function, but peripheral vision also contributes to balance. The central area of the visual field as compared with the peripheral retina dominates postural control. Visual acuity causes a linearly increasing postural instability. Abnormalities in visual acuity or visual field defects increase body sway, disturbances of equilibrium, and predispose the person to fall down.

Mixed Ataxia

Mixed ataxia occurs when the symptoms of two or more types of ataxia such as the occurrence of symptoms of sensory and cerebellar ataxia, are observed together. All types of ataxia can have overlapping causes, and therefore can coexist. In some neurologic diseases, mixed ataxia may be observed frequently. For instance, cerebellar, vestibular and sensory ataxia may be observed together in multiple sclerosis, whereas in cases of spino-cerebellar ataxias, cerebellar and sensory ataxia may be seen together. Frontal, vestibular and cerebellar ataxia can also be coexisted in some degenerative neurologic disorders such as multiple system atrophy. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome (CANVAS) is also a mixed ataxia syndrome.

PATHOPHYSIOLOGY OF MEMORY DISTURBANCES

Memory disturbances occur as a result to the neuroanatomical structures that hinders the storage, retention and recollection of memories. Memory disorders can be progressive, including Alzheimer's disease, or they can be immediate including disorder resulting from head injury.

Memory is defined as the ability to recall past experience or information. It is also defined as retention of learned materials. There are various degrees of memory. Some memories remain only for few seconds, while others last for hours, days, months or even years together. Synapse for memory coding is slightly different from other synapses. Memory is stored in brain by the alteration of synaptic transmission between the neurons involved in memory.

1. *Short-term memory:* Short-term memory is the recalling events that happened very recently, i.e. within hours or days. It is also known as recent memory. Short-term memory may be interrupted by many factors such as stress, trauma, drug abuse, etc. There is another form of short-term memory called working memory. It is concerned with recollection of past experience for a very short period, on the basis of which an action is executed.

2. *Long-term memory:* Long-term memory is the recalling of events of weeks, months, years or sometimes lifetime. It is otherwise called the remote memory. Long-term memory is more resistant and is not disrupted easily.

Dementia

Dementia is the progressive deterioration of intellect, emotional control, social behavior and motivation associated with loss of memory. It is an age-related disorder. Usually, it occurs above the age of 65 years. When it occurs under the age of 65, it is called presenile dementia. Dementia occurs due to many reasons. Most common cause of dementia is Alzheimer disease. In about 75% of cases, dementia is due to this disease. Other

common causes of dementia are hydrocephalus, Huntington chorea, Parkinson disease, viral encephalitis, HIV infection, hypothyroidism, hypoparathyroidism, Cushing syndrome, alcoholic intoxication, poisoning by high dose of barbiturate, carbon monoxide, heavy metals, etc. Common features are loss of recent memory, lack of thinking and judgment and personality changes. As the disease progresses, psychiatric features begin to appear. Motor functions are also affected.

Alzheimer Disease

Alzheimer disease is a progressive neurodegenerative disease. It is due to degeneration, loss of function and death of neurons in many parts of brain, particularly cerebral hemispheres, hippocampus and pons. There is reduction in the synthesis of most of the neurotransmitters, especially acetylcholine. Synthesis of acetylcholine decreases due to lack of enzyme choline acetyltransferase. Norepinephrine synthesis decreases because of degeneration of locus ceruleus. Dementia is the common feature of this disease.

Agnosia

Agnosia is a disturbance of perception characterized by the lack of recognition of objects, people, sounds, shapes, smell already known in the absence of memory disturbances and the absence of system lesions elementary sensory. It can occur separately about each of the five senses and for each sense different types of afnosia can be found; in essence, the person suffering from agnosia can use a fork instead of spoon thinking that they have chosen the spoon, or a shoe instead of a cup or a penknife instead of a pencil.

Pathophysiology of Balance and Equilibrium, Complete and Incomplete Section of Spinal Cord. Causes of Aphasia. Pathophysiology of Corneal Opacity, Cataract, Glaucoma

Physiologic Anatomy of the Ear

The ear is one of the organ of the special senses. It serves two sensory functions

- Auditory function is essentially performed via cochlea
- Balance- Vestibular apparatus

The cranial nerve VIII (vestibulocochlear nerve also called auditory nerve is central to this function

The ear consist of three parts

- Outer ear- made up of the pinna which help to determine the direction of the sound especially if from front or back. Inflammation may occur in the external ear called otitis externa, which may produce watery discharge as there are no mucinous glands there.
- Middle ear- this is separated from the outer ear by the tympanic membrane. It is air filled and contains the ear ossicles, ossicular muscles and eustachian tube. Infection of the middle ear is called otitis media with a mucous discharge, if discharge is serosanguineous it suggest granular mucosa of chronic otitis media but if offensive it may be cholesteatoma. Cerebrospinal fluid leak (CSF otorrhoea) may be as a result of trauma or surgery.

- ✓ The eustachian tube equilibrates the pressure on either side of the tympanic membrane by connecting the middle ear and the pharynx. Barotrauma (aerotitis) may result if the tube is occluded, then middle ear pressure cannot be equalized during descent in an aircraft or diving hence causing damage. There is a severe pain as the drum becomes indrawn, this may be caused by inflammation or infection. Barotrauma in the inner ear causes tinnitus, vertigo and deafness. To prevent this, individuals need not fly while having upper respiratory tract infection (URTI), also, may practice repeated yawning or use decongestants as preventive measures.

- ✓ The ossicles are the malleus, incus and stapes with the handle of the malleus attached to the tympanic membrane while the foot plate of the stapes is attached to the oval window- (oval window is found at the intersection of the middle ear and the inner ear and in direct contact with stapes).Transmission of vibration to the oval window leads to movement of fluid within the cochlea and activation of receptors of hearing.

- ✓ The ossicular muscles are stapedius and tensor tympani which are attached to the stapes and malleus respectively. These muscles play important role by contracting or tensing the tympanic membrane and oval window to very loud sound.

- ● Inner ear- contains the cochlea and the vestibular apparatus.

Cochlea - has two membranes Reissner's membrane and basilar membrane which divides the cochlear duct into three fluid-filled chambers

- ✧ Scala vestibuli- found in the space above the Reissners membrane and is filled with perilymph

- ✧ Scala media-is found between the two membrane and it is in the middle. It is filled with endolymph. The organ of Corti (receptors for hearing) are located in the scala media towards the side of the basilar membrane.

- ✧ Scala tympani- this is found below the basilar membrane and it is filled with perilymph.

The part of the cochlear apex where the scala tympani and scala vestibuli meets is called the helicotrema. It allows fluid to move between the two chambers and it is believed to slightly impede the travel of sound.

The endolymph is very rich in K^+ and low in Na^+ while the perilymph is rich in Na^+ but low in K^+ (like ECF). This results in a potential difference called endocochlear potential which is positive inside the scala media,

Organ of Corti is responsible for the transduction of sound waves into electrical impulse for the generation of action potential which relays to the spiral ganglia. It consist of the hair cells, basilar membrane with the hair cells embedded in it, supporting cells, reticular lamina and the tectorial membrane.

Pathophysiology of Balance and Equilibrium

The vestibular system is very important in the coordination of the position of the head and the movement of the eyes. The organs in the inner ear that help in this function are the labyrinth: the semicircular canals, which respond to rotational movements (angular acceleration); and the utricle and saccule within the vestibule, which respond to changes in the position of the head with respect to gravity (linear acceleration)

The earlier scientists were impressed with the observation that orientation of the semi circular canal lie in three planes at right angle to one another (superior, posterior, and horizontal), and believed that the canals must be designed for localizing the source of sound in the environment in a three-dimensional space. However, it was French experimental neurologist Marie-Jean-Pierre Flourens, who in 1824 observed abnormal head movement in pigeons after cutting each of the semicircular canals in turns. It was then recognized that semicircular canals are sense organs specifically concerned with the movements and position of the head.

Disorder of Vestibular Apparatus

The vestibular apparatus of the two ears relate to each other in a reciprocal way. When the head is turned to the left, the discharge from the left horizontal canal is decreased, and when head is turned to the right the reverse happen. Normal posture is the result of their acting in cooperation and in opposition. When the vestibular system of one ear is damaged, the unrestrained activity of the other causes a continuous false sense of turning (vertigo) and rhythmical, jerky movements of the eyes (nystagmus), both toward the uninjured side. When the vestibular hair cells of both inner ears are injured or destroyed, as can occur during treatment with drugs, there may be a disturbances of posture and gait (ataxia) as well as severe vertigo and disorientation.

There is a marked increase in the study of the vestibular system due to an increasing need for space travels. Of particular interest is the concern of the well being of persons exposed to microgravity of spaceflight as compared with the gravitational field of the earth

The vestibular function can be assessed by stimulation of the semicircular canals to elicit nystagmus and other vestibular ocular reflexes. The vestibular system may react to unusual stimulation from the motion of an aircraft, a ship, or a vehicle to produce a sense of unsteadiness, abdominal discomfort, nausea, and vomiting which is likened to motion sickness.

Symptoms of Ear disease

i. Aural pain (otalgia)

ii. Discharge (otorrhoea)

iii. Hearing loss

iv. Sensation of sound in the absence of an appropriate auditory stimulus (tinnitus)

v. Sensation of abnormal movement (vertigo)

Role of cerebellum in balance

The cerebellum is a part of the brain that helps to coordinate and regulate the functions and processes in the brain and body. It is a small in size compared to the entire brain, however, it more than half of the neurons in the nervous system is found there.

The cerebellum receives afferent fibres from the spinal cord, vestibular system, basal ganglia and cerebral cortex. It modulates movement mainly through its connections, via the thalamus, with the basal ganglia and cerebral cortex.

The cerebellum play particularly important in control of movement and crucial role in balance and locomotion. It does not initiate but modulates the tone and movements in the joints. The most characteristic signs of cerebellar damage is walking ataxia.The most distinctive clinical sign of cerebellar damage is impairments of balance and gait. Balance abnormalities are characterized by increased postural abnormalities, poor control of equilibrium during motions of other body parts. Gait ataxia, or walking in-coordination, is often described as a "drunken or zig-zag gait "

Cerebellar Connections

a. With motor cortex (cerebrocerebellum)

b. Proprioceptors in the joints (spinocerebellum)

c. Special senses (vestibulocerebellum)

d. Other nuclei concerned with voluntary movements

Features of Cerebeller Lesion

- Lesions of the cerebellum cause in coordination (Ataxia)
- Reduced muscle tune (hypotonia)
- Ataxia of trunk making the person have difficulty in sitting and standing
- Paralysis not a feature
- Tendon reflexes are not usually increased.
- Pendular knee jerk
- Nystagmus

Disturbances of Voluntary Movement

- Intention tremor- tremor that is absent at rest (unlike Parkinsonism) but manifests with voluntary action
- Dysdiodochokinesia - inability to terminate a movement and follow it with the opposite movement eg alternating pronation and supination
- Dysarthria- difficulty in articulation of speech
- Dysmetria-a problem of overshooting or undershooting a target due to inability to to stop a movement at the desired point
- Zig-zag gait

Complete and Incomplete Transection of Spinal Cord.

The spinal cord extends from the foramen magnum caudally to the interspace between the 12th thoracic and 1st lumber spine, however the thecal membrane continue as far as the body of the 2nd sacral vertebra. The largest portion is at the 5th cervical vertebra.

Cord transection is the most severe form of cord injury as it results in complete and irreversible loss of all neural functions. Generally, it is a result of unstable spinal fractures.

Spinal cord transection results from injury sustained during road traffic accidents, a fall from a height, a gun shot injury or injury to the vertebral column, producing mechanical compression or distortion of the spinal cord. Secondary damage can result from ischemic, inflammatory, and other mechanisms. It can also be made experimentally in laboratory animals. Immediately after the injury, there is a temporary cessation of all reflexes carried by the part of the cord below the section.This gives the spinal shock syndrome.

Injury could results from right or left-sided hemisection of the spinal cord. Transection of the corticospinal and dorsal column nerve tracts leads to ipsilateral loss of motor function, tactile sensation, proprioception, and vibratory sensation below the level of injury

The transection to the spinal cord could be complete or incomplete. In complete spinal cord injuries, the spinal cord is fully severed and function below the site of the injury is eliminated. In comparison, incomplete spinal cord injuries occur when the spinal cord is compressed or injured, but the brain's ability to send signals below the site of the injury is not completely removed.

Symptoms of Spinal Cord Injuries

i. numbness,

ii. tingling, or

iii. a loss of or changes in sensation in hands and feet.

iv. Paralysis that may happen immediately or develop over time as swelling and bleeding affects the spinal cord.

v. Pain or pressure on the the head, neck, or back.

Cervical spinal cord injuries affecting the head and neck region above the shoulders is the most severe level of spinal cord injury because it is not compatible with life. Thoracolumber injuries are rare. The level of the transection determines the manifestations of the symptom because of the organs that may be involved. The degree of neurological compromise corresponds with the degree of cord transection. In a incomplete transection, there may still be some sensory-motor function retained, whereas in complete transection, there is a complete loss of function.

Classification of Spinal Cord Injury (SCI)

Spinal cord injury can be classified according to the spinal cord level and the severity of neurological deficits. Most traumatic spinal cord injuries (TSCIs) involve the cervical spinal cord and results in quadriparesis or quadriplegia. Spinal cord injury (SCI) at C3 level can affect the muscles involved in respiration which, could be

fatal if immediate medical attention is not available. This is because the diaphragm which is the primary muscle of respiration, is controlled by the C3-C5 spinal nerves.

Stages of Spinal Cord Injury

i. Acute injury phase - less than 48 hours after the traumatic injury

ii. Sub acute injury phase - 48 hours to 14 days after

iii. Intermediate injury phase - 14 days to six months after.

iv. Chronic injury phase - six months after and beyond

Can Spinal Cord Injury Recover?

As the spinal cord recovers from the shock of the injury, some progress may be made with movement of the part of the body and/or improved sensation. Although progress and adaptation is possible, it need to be stated that there is not yet any effective repair available for spinal cord injury. Therefore, due to the limited ability of the central nervous system to repair itself following injury, many deficits remain permanent in the individuals.

Aphasia

Aphasia is a disorder that affects individuals ability to use language, whether in speaking, writing or comprehending. It may affect both written and spoken language. This usually happens suddenly after a stroke or a head injury. It may also result gradually from a slow-growing tumor or a progressive permanent damage from a degenerative disease.

Causes

i. Stroke- commonest cause

ii. Head injury

iii. Brain tumour

iv. Infection

v. Dimentia

Everyday use of language includes the following

- The ability to comprehend spoken speech
- The ability to read to oneself (not aloud)
- The ability to write
- The ability to comprehend other symbols eg mathematical or musical symbols

Speech defects can be analysed as disturbances of articulation, fluency, verbal comprehension, naming, repetition, reading and writing. The defect in any of these can be used to localize the part of the brain that is affected. For example:

- ✓ Disturbance of fluency, verbal comprehension,repetition and writing are all prominent in left anterior temporal lobe lesion (amnestic or Wernicke's aphasia)
- ✓ Disturbance of articulation and fluency more than other language categories is associated with left frontal lesion
- ✓ Impairment of reading (visual language function) is mostly from parieto-occipital lesion
- ✓ Left parietal lesion impair several other associative functions but especially writing.

It is important to note that lateralization of speech corresponds to handedness, but most left-handed people have left hemisphere dominance.

Pathophysiology of Corneal Opacity, Cataract, Glaucoma

The Cornea

The transparent part of the eye that covers the iris and pupil and allows light to enter the inside. It is more convex than the sclera (which is opaque and tough) and is made of collagen fibrils in a mucopolysaccharide matrix it is covered anteriorly by a stratified epithelium which is continuous with the conjunctiva covering the exposed sclera and line the inner surface of the eyelids. The cornea is smooth, clear, strong and durable. The sclera transitions anteriorly to become cornea.

The cornea is avascular, therefore oxygen for its metabolism is from atmospheric air and the free nerve endings are from 5th cranial nerve

Functions of Cornea

i. It shields the rest of the eye (structural barrier) from germs, dust and other harmful matters just like the eyelids, socket etc

ii. Acts as eyes outermost lens

iii. Functions like a window that controls and focuses the entry of light into the eyes

iv. Contributes to the focusing power of the eye through refraction (contributes two-third of refractive power)

v. Optical degradation

Layers of the Cornea

i. Epithelium

ii. Bowmans membrane

iii. Stroma

iv. Dua's layer

v. Descemet's membrane

vi. Endothelium- very important, keeps the cornea clear by pumping out excess fluid. Conea swelling and clouding results if fluid builds up as occurs in Fuch's corneal dystrophy.

Causes of Corneal Disease

- ✓ Infection- bacterial, fungal, viral. Bacterial infections can result to massive inflammatory response with pus in the anterior chamber (hypopyon) this may progress to endophthalmitis which is sight threatening. Inflammation of the cornea is called keratitis.
- ✓ Injury- this may be superficial or deep (interstitial), the resulting scar or discoloration interferes with vision by blocking or distorting lights as it enters the eye.
- ✓ Age - aging process affects clarity and health of cornea
- ✓ Cataract
- ✓ Hereditary
- ✓ Contact lenses
- ✓ Eye trauma
- ✓ Certain eye diseases- retinitis pigmentosa, retinopathy of prematurity, vernal conjunctivitis etc

Cornea response to injury

It copes well with minor injuries by growth of healthy cells almost immediately to protect from infection or cause problem with vision. If the injury is penetrative, it results in pain, blurred vision, tearing, redness and extreme sensitivity to light.

Diseases of the Cornea

Corneal disease is a serious condition that can cause clouding, distortion, scaring and eventual blindness

- ✧ Keratoconus- It is a progressive thinning of the cornea and most prevalent in teenagers, this results from the bulging outwards of the the dome-shaped part of the cornea. It is the commonest cornea disease causing blurring of vision and sensitivity to light. It has strong genetic association. Vigorous rubbing of the eyes have been implicated as a risk factor.
- ✧ Arcus senilis a crescentic opacity near the periphery of the cornea. It usually starts at the lower part and extends to form a complete circle. It is common in old people but may occur in the young (arcus juvenilis)

Cataract

They are lens opacities or cloudy areas which develop with ageing as a result of braekdown of proteins and fibres in the lens. It is among the four major causes of blindness in the world (cataract, vitamin A deficiency, trachoma and onchocerciasis)

Causes

- ✓ Exposure to bright light in fair-skinned people
- ✓ Diabetes mellitus
- ✓ Post trauma
- ✓ Associated with hyperclolestrolaemia
- ✓ Features of certain hereditary diseases- dystrophia myotonica

Classification

This is based on the appearance of the lens

- ✧ Immature cataract- red reflex still occur
- ✧ Dense cataract- no red reflex
- ✧ Nuclear cataract- changes the lens refractive index and are common in old age
- ✧ Polar cataract- are localized, commonly inherited and lie in the visual axis

There may be subscapular opacities a a result of the use of steroids, usually deep to the lens capsule along the visual axis or dot opacities are common in normal lenses but are also seen in fast growing cataracts in diabetics.

Glaucoma

This a chronic, progressive eye disease caused by damage to the optic nerve which leads to visual field loss resulting from, raised eye pressure (intraocular pressure). It is called 'ocular hypertension'. The abnormality in the eyes drainage system causing fluid to accumulate

Types

Open angle glaucoma- usually has no symptom other than slow loss of vision, there may be patchy blind spots in peripheral vision and later difficulty seeing things in central vision.

Acute angle- closed glaucoma- is rare but when present is a medical emergency presenting with eye pain, nausea and sudden visual disturbance. It is a cause of red eyes. It occurs in middle age or later in life. The acute uniocular attack which is often preceded by blurred vision or haloes around light it is caused by blockage of drainage of aqueous humor from the anterior chambers through the canal of Schlemn. Dilatation of the pupil at night worsens drainage block. Intraocular pressure (IOP) then rises from the normal value of 15-20mmHg to 60mmHg or 70 mmHg

Normal tension glaucoma- no symptoms in the early stage are reported but there is gradual blurred vision and later loss of side vision.

Glaucoma in Children (congenital glaucoma) - a dull or cloudy eyes in infants, with increased blinking, blurred vision nearsightedness that gets worse should increase ones suspicion in children.

Pigmentary glaucoma- seeing halos around light, blurring of vision during exercise and accompanying gradual loss of side vision.

Causes

i. Blockage of the flow of aqueous humour- this usually flows out through a mesh-like channel. The cause may be unknown but may be inherited

ii. Excessive production of aqueous humour

iii. Blunt or chemical injuries to the eyes though less common

iv. Severe eye infection

v. Blocked blood vessels inside the eyes

vi. Inflammatory eye conditions

People at higher risk of glaucoma

- ✓ African American over 40 years
- ✓ Positive family history
- ✓ People living with diabetes mellitus

Pathophysiology of Refractive Errors

Refraction refers to bending of light to focus image of the object on the retina for visualization. The refractive media in the eyes includes the cornea and the lens. Of the two refractive media, the cornea has the greatest refractive power but its shape cannot be changed unlike the lens which changes shape to focus on far or near object on the retina. Refractive errors include myopia, hypermetropia, astigmatism and presbyopia.

Myopia

Myopia occurs when the globe of the eyes is too long and the image is formed in front of the retina. An individual myopia can see near object clearly but finds it difficult to see far object clearly.

Hypermetropia

Hypermetropia occurs when the globe of the eye is too short and the image is formed at the back of the retina. An individual with hypermetropia can see far object clearly but finds it difficult to see near object clearly.

Astigmatism

Astigmatism occurs due to irregular curvature of the surface of the cornea or the lens. When the cornea is affected, it is called corneal astigmatism when the lens is affected, it is called lenticular astigmatism. The abnormal curvature of the cornea or the lens results in failure of convergence of the light rays from an object on a single focus on the retina resulting in blurred vision.

Presbyopia

Presbyopia occurs due to loss of flexibility of the lens due to age-related hardening. With less flexibility, the lens loses the ability to focus near object on the retina.

Pathophysiology of Visual Pathway Disturbances

The visual pathway consists of the neural network for transmission of visual impulses from the eyes to the cerebral cortex. The visual pathway includes the retina, optic nerves, optic chiasm, optic tracts, lateral geniculate nuclei, optic radiations and cerebral cortex. Visual impulses are generated by the photoreceptor cells in the retina and propagated through the optic nerves to the optic chiasm where the medial fibres of each side decussate to join the lateral fibres of opposite sides to form the optic tracts which projects to the lateral geniculate nuclei from where fibres emanate as optic radiations which project to the visual cortex at the occipital lobes of each cerebral hemispheres. Interruption of impulse transmission along the pathways results either a blind spot in the visual field(scotoma) or absence of sight called anopia which can be partial or complete. The variety of visual loss experience with interruption of visual pathway are given below (Table 14.2 and Fig. 14.2).

Table 14.2. Visual field defects

Level of Lesion	Visual Field Defect
Retina	Central Scotoma (blind spot in the visual field)
Optic nerve	Monocular vision loss
Optic chiasm	Bitemporal hemianopia
Optic tract, optic radiation and primary visual cortex	Contralateral homonymous hemianopia

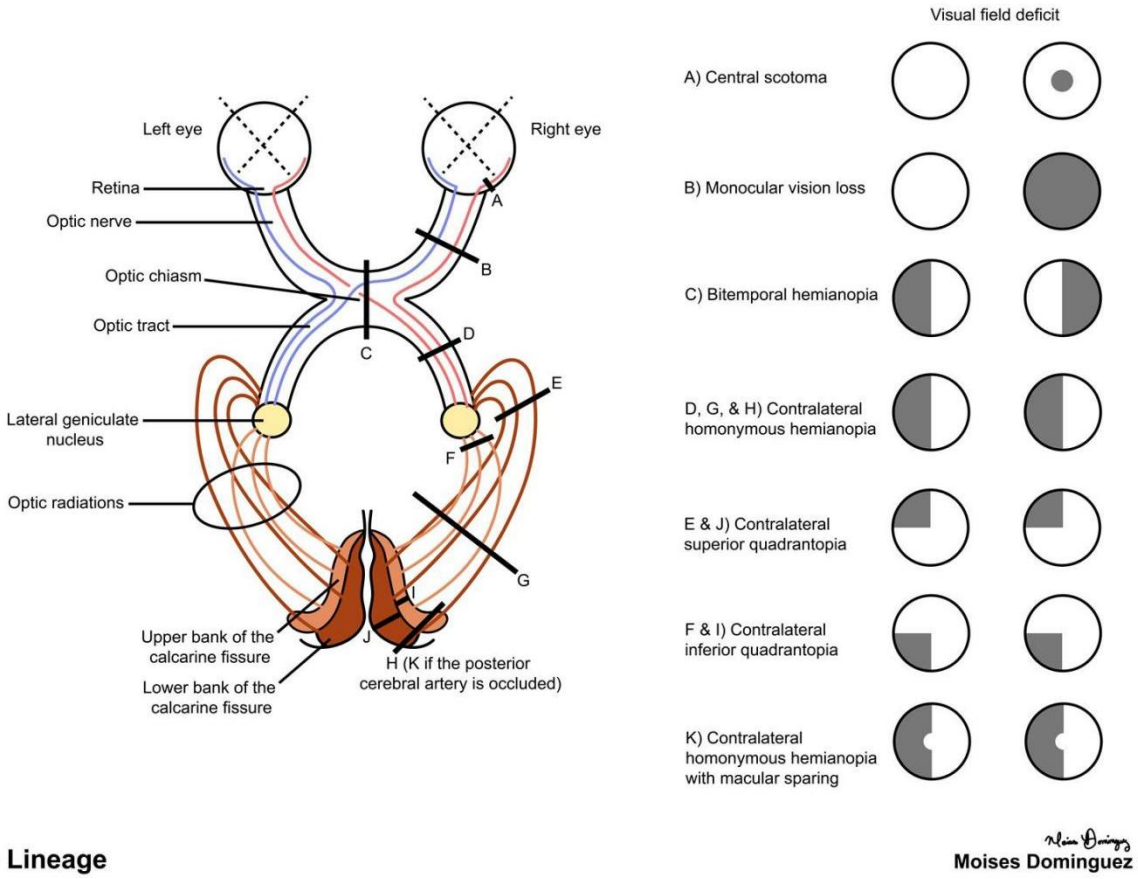

Fig. 14.2: Disorders of visual pathway

Disturbances colour vision

The photoreceptors cells in the retina for perception of colour are the cones. There are three types of cones depending on their visual pigment; red, green and blue cone pigment. Most humans are trichomats with ability to recognise red, green and blue colours. A few are dichromats with ability to recognise only two primary colours. Very few are monochromats. The red and green cone pigments are encoded on the X chromosome while the blue cone pigment is encoded on chromosome 7. Colour blindness refers to the inability to recognise certain colour or colours. The most severe form is inability to see any colour. This is called achromatopsia. Mutation in the genes encoding red and green cone pigments results in red-green colour blindness. This is common among males but rare among females because it is X-linked disorder. Mutation in the genes encoding blue cone pigment results in blue colour blindness.

Colour blindness can also occur as a result of disease of retina, optic nerve or stroke involving the occipital lobe.

Deafness

Hearing loss is defined as a reduced ability to perceive sound. It can be mild, moderate or severe. Deafness is a severe form of hearing loss. With deafness, an individual is cannot understand speech or perceive sound, even with amplification. It can be unilateral or bilateral.

Pathophysiology of Hearing Disturbances

Most of the hearing disturbances involve interruption of the transmission of sound waves or impairment of sound signal transduction and/or propagation along the auditory pathway. The most common hearing disturbances can be classified into four groups;

1.Conductive hearing loss

2. Sensorineural hearing loss

3. Mixed hearing loss

4. Auditory neuropathy spectrum disorder

Conductive hearing loss occurs due to primary lesions in the external auditory canal, tympanic membrane and/or middle ear. The lesions impair transmission of sound waves to the inner ear. Conduction hearing loss may be due to excess ear wax or disorders of the ear ossicles.

Sensorineural hearing loss results from damage to the hair cells within the inner ear(sensory) or the auditory pathway(neural). The mechanisms for sensorineural hearing loss include;

1. Cochlear structural abnormality; acquired or congenital.
2. Abnormality of ionic transport channels within the inner ear.
3. Interruption of vascular supply to the cochlea.
4. Abnormalities of basilar membrane impairing motility of the outer hair cells motility and or transduction capabilities of the internal hair cells.
5. Noise trauma due to loud noise increases vibrational shift between the tectorial and basilar membranes with resultant damage to the stereocilia of the outer hair cells.
6. Interruption of neuronal network of the auditory pathway

The mixed hearing loss involves mechanisms of conduction and sensorineural hearing losses.

Auditory neuropathy spectrum disorder occurs following damage to the auditory nerve and may be related to prematurity or genetic predisposition.

PATHOPHYSIOLOGY OF ANOSMIA, HYPOSOMNIA

Anosmia

Anosmia is defined as the inability to perceive smell. It can be temporary or permanent and acquired or congenital. Many viral infections cause nasal obstruction, congestion and rhinorrhea, thereby impeding odorant access to the sensory epithelium and preventing the binding of the odorants to olfactory receptors. Lesions to the Olfactory Nerve and/or to the Olfactory Pathway can lead to anosmia. Anosmia can also be congenital (present at birth), idiopathic (no known cause), or related to dementia such as Parkinson disease or Alzheimer disease. Diabetes, Addison disease, Cushing syndrome, and hypothyroidism are some of the endocrine diseases associated with smell dysfunctions. Blunt force trauma to the face, as in road traffic accidents can lead to the loss of the olfactory nerve, and subsequently, loss of the sense of smell. Congenital anosmia is a condition in which people are born with a lifelong inability to smell. It may occur as an isolated abnormality or be associated with a specific genetic disorder (such as Kallmann syndrome or congenital insensitivity to pain). Treatment of anosmia depends on the cause of the abnormality.

Hyposmia

Hyposmia is a diminished smell sensation. Decreased sense of smell can lead to significant impairment of quality of life, including taste disturbance and loss of pleasure from eating with resulting changes in weight and difficulty in avoiding health risks such as spoiled food or leaking of natural gases. Hyposmia can also be a sign of neurological diseases such as; Parkinson's disease, multiple sclerosis (MS) or Alzheimer's disease. Treatment of hyposmia depends on the underlying pathology.

Hyperosmia

Hyperosmia is an increased olfactory acuity (heightened sense of smell), usually caused by a lower threshold for odor. This disorder arises when there is an abnormally increased signal at any point between the olfactory receptors and the olfactory cortex. Tumors such as nasal polyps and some neurological disoders such as Parkinson's disease, epilepsy, Alzheimer's, multiple sclerosis can cause hyperosmia. Treatment of hyperosmia depends on the cause of the abnormality. If a growth like a polyp or tumor is causing hyperosmia, surgical removal may alleviate the symptoms. Migraine medications can help treat hyperosmia when migraines are the root cause.

PATHOPHYSIOLOGY OF TASTE DISTURBANCES, AGEUSIA, HYPOGEUSIA, DISGEUSIA

Ageusia

Ageusia is defined as the complete loss of taste sensation. It may be caused by different physiologic and diseased conditions. Senility predisposes an individual to lose some of the taste buds, and the available ones present have reduced sensitivity especially after the age of 60 years. Damage to the chorda tympani and the glossopharyngeal nerves and deficiencies in the B vitamins, especially B12, as well as certain minerals like zinc have been associated with loss of taste. Also some infections of the gum, or oral dentures, certain medications e.g. aspirin,furosemide, lisinopril and nutritional deficiencies can leave a bad taste in the mouth and change the way food tastes. Treating the underlying cause of ageusia can restore the taste to normal. Also, regualar brushing of the teeth, flossing, and using mouthwash can help improve the taste sensation.

Hypogeusia

Hypogeusia Is defined as a reduced ability to perceive various taste modalities. It is caused by acute viral illness, traumatic brain injury, liver disease, allergic rhinitis and certain neurologic disorders such as multiple sclerosis, Alzheimer's disease, and Parkinson's disease.

Dysgeusia

Dysgeusia is defined as a distorted sense of smell. It is caused by many factors, such as infection, some medications and vitamin deficiencies. Treatment involves addressing the underlying cause of the dysgeusia.

PATHOPHYSIOLOGY OF MYASTHENIA GRAVIS, MUSCLE DISTROPHY, INTESTINAL COLIC, SYMPATHOMIMETIC AND SYMPATHOLYTIC

Myeasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder in which antibodies destroy the communication between nerves and muscle, resulting in weakness of the skeletal muscles. Myasthenia gravis affects the voluntary muscles of the body, especially those that control the eyes, mouth, throat and limbs. In myasthenia gravis, autoantibodies bind to the receptors, preventing acetylcholine from binding to them and thus preventing the muscle from responding to the nerve signal. Myasthenia gravis is a rare long-term condition that causes muscle weakness. Treatments include blocking the acetylcholinesterase (AChE), an enzyme that breaks down ACh, and immunomodulatory therapies.

Muscle dystrophy

Muscular dystrophy is a group of diseases that cause progressive weakness and loss of muscle mass. In muscular dystrophy, abnormal genes (mutations) interfere with the production of proteins needed to form healthy muscle. The primary cause for various forms of muscular dystrophies is the mutations in individual genes that encodes a wide variety of proteins, including extracellular matrix (ECM) proteins, transmembrane and membrane-associated proteins, cytoplasmic enzymes, and nuclear matrix proteins. There are four types of muscular dystrophies; Facioscapulohumeral, Limb-Girdle, Myotonic and Oculopharyngeal. Muscle biopsy is the standard approach to diagnosis. Treatments of muscular dystrophies include the use of steroid medications to maintain muscle strength as long as possible; stretching and other exercises specifically designed for the type of muscular dystrophy; braces and splints; assistive devices such as wheelchairs, computer technology, and lifting devices to help alleviate the disorders.

Internal colic

Intestinal colic is a cramp-like pain that originates in the small or large intestine. It is caused by a blockage that keeps food and liquid from passing through the body. Blockages can occur from outside the lumen as ones seen in the formation of scar tissue from previous abdominal or pelvic surgery or it can be intramural, due to fecal impaction of colonic tumors. Kidney and gall blaader stones also lead to inter colic. Other causes include; food allergies or intolerances, overfeeding, underfeeding or infrequent burping. Gas produced by bacteria in the intestines can produce abdominal cramps and distention. Symptoms of excessive gas production include

fussiness, enlarged abdomen, and passage of excessive gas through burping or flatulence. Treatment depends on the cause of the colic.

Sympathomimetics

Sympathomimetic drugs are agents which in general mimic responses due to stimulation of sympathetic nerves. These agents are able to directly activate adrenergic receptors or to indirectly activate them by increasing norepinephrine and epinephrine (mediators of the sympathoadrenal system) levels. Sympathomimetic drugs are used to treat cardiac arrest and low blood pressure, or even delay premature labor. Prolonged sympathomimetic drug use can induce hypertension, hyperthermia, myocardial infarction, cardiac arrhythmias, strokes and even dissections of thoracic and mesenteric blood vessels. In addition, intravenous use of these agents also may lead to endocarditis. Sympathomimetic drugs include; cocaine, amphetamines, phencyclidine hydrochloride (PCP), and lysergic acid diethylamide (LSD), all can precipitate a hypertensive emergency. Treatment of prolonged sympathomimetic use includes the use of activated charcoal for sympathomimetic agents ingested orally, as long as the patient is alert. In hypertension unresponsive to the benzodiazepines, should be managed with a shorting antihypertensive like labetalol or nitroprusside. The main medication for symptomatic treatment is a benzodiazepine.

Sympatholytics

Central sympatholytic drugs reduce blood pressure mainly by stimulating central α_2 -adrenergic receptors in the brainstem centers, thereby reducing sympathetic nerve activity and neuronal release of norepinephrine to the heart and peripheral circulation. Sympatholytic drugs include alpha- and beta-adrenergic receptor antagonists (alpha blockers and beta blockers) as well as centrally acting agents such as clonidine, guanabenz, methyldopa, minoxidil, and reserpine. Most prominent among undesirable side effects are the central nervous system findings of sedation, altered thought process, depression, and orthostatic or exercise hypotension. Sexual problems, especially in men leading to erectile dysfunction, are also prominent. Treatment of sympatholytic over dose includes the use of activated charcoal if taken orally, maintaining the airway and support respiration if necessary. Symptomatic treatment is usually sufficient even in massive overdose. Maintain blood pressure with intravenous fluids.

Demyelinating Disease

Demyelination is the process in which the nerve fibre loses its myelin sheath as a result injury or degenerative process affecting the myelin. This results in poor conduction of action potentials, impaired neuronal signalling and, in some cases, partial or complete neuronal loss. Moderate to severe pain is a common feature of demyelinating disorders. Causes of demyelination include infections, ischemia, metabolic disorders like diabetes, alcohol consumption, folate deficiency or hereditary and autoimmune diseases. Lead is a common environmental pollutant that causes hypomyelination and demyelination. Example of demyelinating diseases includes; multiple sclerosis (MS), optic neuritis, acute disseminated encephalomyelitis etc. Magnetic Resonance Imaging is used to diagnose demyelinating conditions which shows plaques in the brain areas affected.

Muscle Denervation

Muscle denervation is the loss of nervous connection to the organ it supplies. This results in an increased number of acetylcholine receptors thereby making the muscle to be hypersensitive to acetylcholine, and becomes liable to depolarize spontaneously. Denervation can be caused by injury to the myelin sheath as a result of trauma, or destruction of the neuromascular junction as a result of autoimmune disease or it may be due to age-related loss of motor neurons. Denervation leads to the activation of the catabolic pathways and oxidative stress which ultimately results in skeletal muscle atrophy and weakness. After denervation, muscle passes through three stages of recovery; immediate loss of voluntary function and rapid loss of muscle mass, increasing atrophy and loss of muscle organization, and finally muscle fiber degeneration and replacement of muscle by fibrous connective tissue and fat. Regeneration time depends on how seriously the nerve was injured and the type of injury encountered. Various modalities are employed to restore the muscle function, these include; the use of braces or splints to keep the affected area in a proper position; use of electrical stimulation to activate muscle while the nerve regrows; Physical therapy and exercise.

PATHOPHYSIOLOGY OF BOTULINUM AND TETANUS TOXOID, EATHON-LAMBERT SYNDROME

Botulinism

Botulism is caused by sporeforming rod like gram(+) clostridium. They are anaerobic bacteria, opportunistic pathogens responsible for some of the deadliest diseases including botulism and tetanus.

E-Botulinu- caused by closteridium is an anaerobic gram positive, rod shaped sporeformer which produces a protein neurotoxin found mainly in soil, sediments of lakes, ponds and decaying vegetation, intestinal tracts of birds, mammals and fish. It is divided into A,B,C,D,E, F and G. transmission is by spores which is heat resistant, requires anaerobic environment and can be by eating uncooked foods containing spores.

Botulinum Toxin

It binds to peripheral nerve receptors acetylcholine neurotransmitters which inhibits nerve impulses causing flaccid paralysis leading to death due to respiratory and cardiac failure. It can be used as a bioweapon 10nanogram can kill a normal adult.

Route of entry: food borne and infant wound.

TETANUS

This is caused by clostridium tetani which is an anaerobic bacteria found worldwide. Occasionally, it is found in the intestinal flora of human s and animals. It causes tetanus or “lock jaw” when the spores are introduced into wounds by contaminated soil or foreign objects such as nails or glass splinters.

PATHOPHYSIOLOGY

This is mainly an exogenous infection with no invasiveness. It produces two exotoxins; tetanolysin and tetanospasmin (A neurotoxin). Tetanospasmin are complex and involved in three components of the nervous system; central motor control, autonomic function and neuromuscular junction. Tetanospasmin disseminates systematically by binding to ganglioside receptors inhibitory neurons in the CNS glycine, neurotransmitter which

stops nerve impulse to impulse to muscles leading to spastic paralysis, severe muscle contractions and spasms can be fatal

EATON-LAMBERT SYNDROME

This is one of the autoimmune disorders at the neuromuscular junction. It is caused by pathogenic auto-antibodies to presynaptic voltage gated calcium channels (VGCCs) in the membrane of the motor nerve terminal, impairing acetylcholine release thereby causing weakness of skeletal muscles.

Pathophysiology:

Normally ACh is synthesized and stored in vesicles at the motor nerve terminal, ACh is released into the nerve terminal following stimulation by an action potential which travels down the motor nerve, ACh release is dependent on calcium ions influx via the voltage-gated calcium channel (VGCC). ACh then binds to the ACh receptors on the postsynaptic neuron, leading to the rapid entry of cations which produces depolarization at the end plate region of the muscle fiber and generating an action potential and subsequent muscle contraction.Acetylcholine within the synaptic cleft is rapidly broken down by the enzyme acetylcholinesterase. In Lambert-Eaton myasthenic syndrome, VGCC is reduced due to the IgG antibody-mediated cross-linking of the channels. More specifically, antibodies are directed towards the P/Q subtype of VGCC. 85% of patients with Lambert-Eaton myasthenic syndrome demonstrate antibodies against the P/Q type VGCC. Rarely, antibodies against the N-type VGCC has been found in malignancy-associated Lambert-Eaton myasthenic syndrome.

PATHOPHYSIOLOGY OF SCHIZOPHRENIA AND DEPRESSION

SCHIZOPHRENIA is a serious mental disorder in which people interpret reality abnormally. Schizophrenia may result in some combination of hallucinations, delusions, and extremely disordered thinking and behavior that impairs daily functioning, and can be disabling. People with schizophrenia are characterized by the presence of delusional beliefs, hallucinations, and disturbances in thought, perception, and behavior. Traditionally, symptoms have been divided into two main categories: positive symptoms, which include hallucinations, delusions, and formal thought disorders, and negative symptoms such as anhedonia, poverty of speech, and lack of motivation.

Pathophysiology some studies have postulated that the development of schizophrenia usually results from

a. Abnormalities in multiple neurotransmitters, such as dopaminergic, serotonergic, and alpha-adrenergic hyperactivity or glutaminergic and GABA hypoactivity.

b. Genetics also plays a fundamental role. The gene neuregulin (NGR1), which is involved in glutamate signaling and brain development, has been implicated, alongside dysbindin (DTNBP1), which helps glutamate release, and catecholamine O-methyl transferase (COMT) polymorphism, which regulates dopamine function.

c. Some postulates that schizophrenia is a neurodevelopmental disorder based on abnormalities present in the cerebral structure, an absence of gliosis suggesting in utero changes, and the observation that motor and cognitive impairments in patients precede the illness onset.

d. There are some risk factors associated with schizophrenia like environmental factors associated with increased risk e.g. complications during delivery, the season of birth, severe maternal malnutrition, maternal infection with viruses such as influenza in pregnancy, family history, childhood trauma, social isolation, cannabis use, and urbanization

Diagnosis: mainly base on history taking which the patient will have some history of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms.

DEPRESSION is a state of low mood and aversion to activity can affect a person's activity. Mainly cause by genetic disposition and familial like variant gene encoding serotonin transporter protein, dysfunction of neurotransmitter- norepinephrine, serotonin and dopamine, psychosocial stress- unemployment, death of loved ones and divorce. Chronic diseases like cancer, AIDS and diabetes. Endocrine disorders like hypothyroidism

Types of Depression

a. Unipolar Depression

b. Bipolar Depression

Unipolar depression is divided into two

i. Reactive depression

ii. Endogenous depression

Reactive depression is due to stressful life like loss of loved one or divorce while endogenous depression is unrelated to external stress due to endogenous factors.

Bipolar depression also known as manic depressive disorder has a cyclical manifestation of depression followed by mania. Its pathophysiology is mainly due to two hypotheses;

i. Neuropathic hypothesis: this is associated with a drop in brain derived neurotrophic factor due to low levels in the cerebrospinal fluids and serum

Monoamine Hypothesis: this is due to the association between clinical effects of various drugs that cause alleviation of symptoms of depression and their known neurochemical effects on monoaminergic transmission in the brain. In this hypothesis, depression related to defieciency in the amount or function of cortical and limbic serotonin (5-HT), norepinephrine and dopamine.

Summary

Tremor is the most commonly encountered movement disorder in clinical practice and is defined as either fine or coarse depending on the range of oscillatory movement in the affected body part(s). A coarse tremor has a large displacement, whereas a fine tremor is barely noticeable. Fine tremors are with a frequency greater and lower amplitude lower (physiologic tremor and orthostatic tremor) and coarse tremor are with lower frequency rate and higher amplitude (Intention tremor, Holmes tremor, dsytonia tremor, neuropathic tremor, and parkinson's tremor).

Speech is defined as the expression of thoughts by production of articulate sound, bearing a definite meaning. Speech disturbances occur as result damage to the central speech apparatus or the peripheral speech apparatus.

Gait disorders/changes are a major source of disability, morbidity, and may be neurologic or non-neurologic in origin. Non-neurological/musculoskeletal gait changes are often caused by soft tissue imbalance, joint alignment or bony abnormalities. When neurologic in origin, gait disorders may arise from lesions in any part of the nervous.

Memory is defined as the ability to recall past experience or information. It is also defined as retention of learned materials. Memory disturbances occur as a result to the neuroanatomical structures that hinders the storage, retention and recollection of memories.

Parkinsonism is a motor disorder characterized by rigidity, tremors and bradykinesia. The tremor is the hallmark of Parkinson's disease. It involves degeneration of the dopamine neurons of the basal ganglia. It has both hypokinetic and hyperkinetic features.

Ataxia resulting from damage to the cerebellum and its connections is described as incoordination and balance dysfunction in movements, and abnormal postural control. Clinically, ataxias can be subdivided into cerebellar, vestibular, sensory, frontal, optic, visual, mixed ataxia and ataxic-hemiparesis.

Male infertility is the inability of the man to get his partner pregnant after one year of frequent and regular sexual intercourse.The major causes of male factor infertility are infections and hormonal abnormalities.

Azoospermia is the absence of sperm cells, while oligospermia is the markedly reduced number of sperm cells in a semen specimen. They are indicators of male infertility.Klinefelter's syndrome (typically 47, XXY male) is a common cause of male hypogonadism.

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage. It is a complex unpleasant phenomenon with sensory experiences that include time, space, intensity, emotion, cognition, and motivation.

Headache is the commonest neurologic symptom of ailments. It is categorized into two: primary headaches syndrome and secondary headaches syndrome. Primary headache is further divided into migraine, cluster headache, tension-type headache. Migraine headache has four phases: premonitory phase, aura phase, headache phase and postdromal phase. Migraine is the most studied type of primary headache.

Migraine is a debilitating neurovascular disorder characterized by (a) unilateral throbbing head pain; (b) many neurological symptoms such as hypersensitivity to light, sound, and smell; nausea; and © a variety of autonomic, cognitive, emotional, and motor disturbances.

Basal ganglia is the center for the integration and regulation of motor activities of the brain. It has five nuclear masses namely caudate nucleus, putamen, globus pallidus, substantia nigra and subthalamic nucleus. It controls motor and non-motor functions through the direct and indirect nigrostriatal dopaminergic pathways. The pathophysiologic mechanisms associated with Parkinson disease include (1) neurodegeneration of the nigrostriatal dopaminergic neurons involving the basal ganglia; (2) molecular mechanisms such as oxidative stress, mitochondrial dysfunction, abnormal phosphorylation, and dysfunction of ubiquitin proteasome system.There is genetic predisposition involving genes such as SNCA-PARK8, LRRK2-PARK8, PARK2 oncogene DJ-1, and PINK 1.

Huntington disease is a neurodegenerative disease that results from a mutation in the Huntingtin (htt) gene on the short arm of chromosome 4, causing abnormal repetition of the DNA sequence CAG, which codes for the amino acid, glutamine.

Athetosis is nonrhythmic, slow, writhing, sinuous involuntary movements predominantly in distal muscles, particularly the arms.

Hemiballismus is a hyperkinethic involuntary movement disease that manifests as intermittent, sudden, violent, flinging or ballistic high amplitude movements involving the ipsilateral arm and leg, due to dysfunction in the central nervous system of the contrlateral side. It is a rare disorder and the most dramatic of all the movement disorders in clinical practice.

Cerebral palsy is a common neurodevelopmental condition due to damage or defect of the brain before, during, and after birth, leading to disturbances of movement, muscle tone and posture. There are two main types of cerebral palsy: pyramidal or spastic cerebral palsy and extrapyramidal/non-spastic cerebral palsy.In spastic cerebral palsy, the defect is in the corticospinal pathway of the brain, manifests increased muscle tone, prolonged primitive reflexes, exaggerated deep tendon reflexes, clonus, rigidity of extremities, etc. It also presents with sensory impairments.

Non-spastic or extrapyramidal cerebral palsy results from damage to basal ganglia, thalamus or cerebellum. Has two subtypes: dyskinetic cerebral palsy and ataxic cerebral palsy.

Deep tendon reflexes used to examine and diagnose neurologic diseases affecting afferent nerves, spinal cord synaptic connections, motor nerves, and descending pathways. The main deep tendon reflexes are the triceps, biceps, brachioradialis, knee-jerk and ankle-jerk reflexes. They are used to assess upper and lower motor neuron lesions.

This chapter explains in very simple terms the role of the ear in the maintenance pof balance and equilibrium in human. The functions of the vestibular apparatus and other structures that link the cerebellum and other parts of the brain. The common disorder associated with the malfunctioning of these organs and their pathophysiology were well elucidated. Furthermore, the problem of transection of the spinal cord which may result from road traffic accident, fall from a height of trauma resulting from violence was also dealt with whether resulting in complete or incomplete transection and their various presentations at different level of the vertebral column was also explained. Additionally, the common problems of vision including cornea opacities, cataract and glaucoma were also explained.

EXERCISE

1. Define fine tremors and coarse tremors
2. Mention the cause of physiologic tremors and orthostatic tremors
3. Describe the pathophysiology of holmes tremors and parkinson's tremors.
4. Explain the pathophysiology of aphasia.
5. Explain the pathophysiology of anarthria and dysphonia
6. Differentiate between musculoskeletal gait changes and neuromuscular gait changes.
7. Mention 2 examples of musculoskeletal gait changes and the causes.

8. Write briefly on 4 neuromuscular gait disorders
9. Explain the pathophysiology of Alzheimer disease
10. What is Parkinsonism?
11. Explain the pathophysiology of Parkinson's disease
12. Define ataxia.
13. Briefly explain the pathophysiology of cerebellar and sensory ataxia.
14. Describe the role of the hypothalamus and anterior pituitary gland in the control of other endocrine glands in the body
15. Describe the pathophysiological mechanisms involved in:
16. Gigantism and acromegaly
17. Dwarfism
18. Infantilism
19. Simmond's disease
20. List the causes of male infertility.
21. Describe the different abnormalities that may be seen in sperm analysis.
22. List the male chromosomal abnormalities and differentiate between them.
23. Explain impotence and list the probable causes.
24. Define the different pubertal disturbances you know.
25. Describe the pathophysiology of refractive errors
26. Describe the pathophysiology of colour blindness
27. Write short note on the lesions of the visual pathway
28. Define deafness
29. Highlight the pathophysiology of hearing disturbances
30. Briefly explain the basic pathophysiology of the following conditions:
    a. Sensory disturbances and peripheral neuropathies
    b. Syringomyelia
    c. Neurosyphilis

d. Thalamic syndrome

e. Herpes simplex

31. Define terms associated with the physiology of pain
32. What are the types and classification of pain?
33. Outline the pathway for pain perception and transmission
34. Explain the most plausible theory of pain
35. What analgesia system is available in the nervous system?
36. Define the following terms: referred pain, visceral pain, neuropathic pain, hyperalgesia and hyperpathia
37. State the components of primary headaches syndrome.
38. Explain the phases of migraine headache
39. Outline the differences between the the three classes of headache.
40. Mention the hallmark features of Parkinsonism
41. Explain the three possible pathophysiological mechanisms associated with Parkinsonism.
42. State examples of genes linked with Parkinson disease.
43. Explain the main pathophysiologic mechanism associated with Huntington disease.
44. Enumerate the clinical features of Chorea.
45. State the visual impairments associated with Huntington disease
46. Define hemiballismus
47. Explain the pathophysiological processes associated with hemiballismus
48. Describe cerebral palsy
49. Explain the two main types of cerebral palsy
50. Mention the manifestations of spastic or pyramidal cerebral palsy
51. State the sensory impairments of spastic cerebral palsy.
52. State the primary deep tendon reflexes
53. Mention three specific peripheral nerve injuries and their effects on the deep tendon reflexes.
54. Outline five disease conditions that manifest hypoactive deep tendon reflexes.

55. Describe the physiologic anatomy of the ear, highlighting the important structures in each part?
56. Explain the organs important in maintaining equilibrium and balance?
57. What are the components of the vestibular apparatus?
58. What are the features of cerebellar lesion?
59. What are the common presentation of incomplete transection of the spinal cord?
60. What are the causes of aphasia?
61. Describe the different types of glaucoma?
62. What are the common causes of corneal opacity?

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