MODULE: GENERAL PATHOLOGY

UNIT: GENETIC DISEASES

By Carey Francis Okinda
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OUTLINE

	Topic	Duration (hours)
1.	Introduction to Genetics	3
2.	Genetic Basis of Disease	2
3.	Single Gene Disorders – Autosomal Dominant	2
4.	Single Gene Disorders – Autosomal Recessive	3
5.	Sex Linked Disorders	2
6.	Chromosomal Disorders	2
7.	Mitochondrial and Metabolic Disorders	2
8.	Somatic and Multifactorial Disorders	4
	TOTAL	**20**

TOPIC 1: INTRODUCTION TO GENETICS

Learning Objectives

At the end of the lesson the learner will be able to: -
1) Describe the structure and function of chromosomes and genes
2) Describe the processes of cell division and protein synthesis

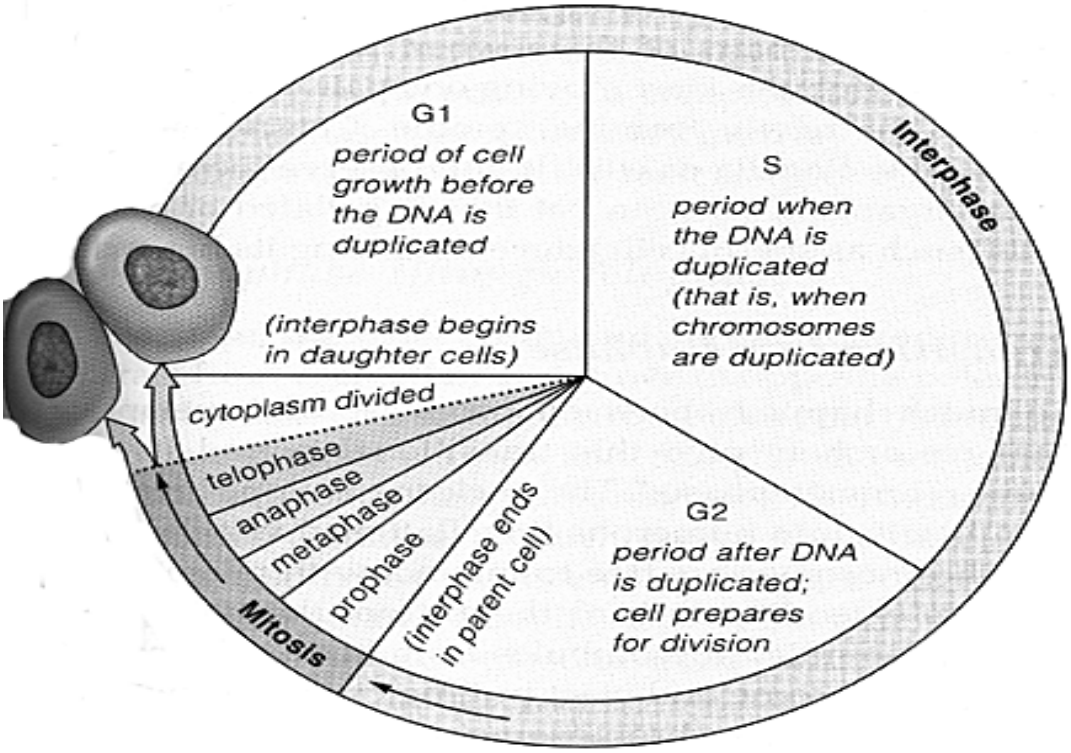
1.0 INTRODUCTION

- Genetics is the scientific study of heredity (passing of characteristics from parents to their offspring) through particles called genes
- Molecular genetics is the study of chemical basis of heredity

2.0 CELL CYCLE

- Cell growth and reproduction are fundamental processes responsible for continued survival (growth, repair and replacement) and creation of new organisms
- The two processes constitute the **cell life cycle**
- Cell growth depends on genetic information from the DNA which contains blueprints that specify construction of proteins such as hormones and structural proteins
- The cell cycle has four sequential phases - G1, S, G2 and mitosis

Diagram 1.1: The Cell Cycle



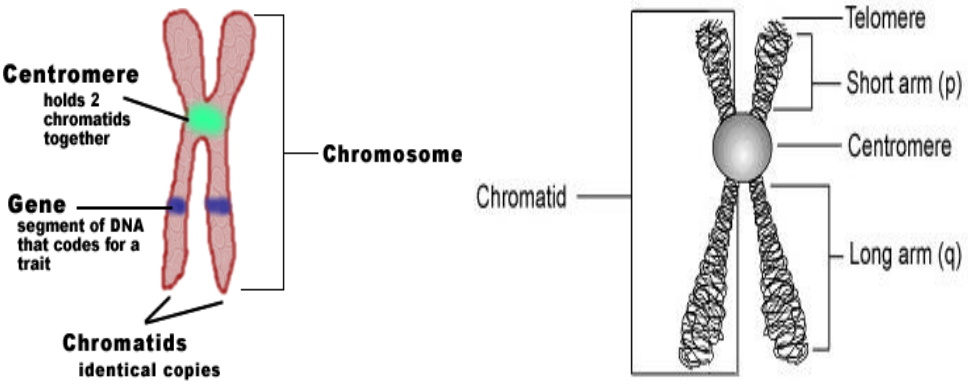
3.0 CHROMOSOMES

- Are structures that transmit hereditary traits from one generation to the next and control synthesis of all proteins in the body
- Normal human cell nucleus contains a set of 23 pairs of chromosomes (Greek *chromos* = coloured; *soma* = body) of which 22 pairs are autosomal and a pair of sex chromosomes (called chromosomes because of their ability to take up colour stains)
- Each chromosome contains a DNA molecule, histone and non-histone proteins
- Histones are small electro-positively charged molecules that form a large protein mass in the chromosome
- Many **histones** are organized into bobbin like cores onto which the DNA helixes are coiled
- Histone cores regulate the DNA activity because tightly packed DNA cannot function as a template for formation of RNA or for replication of a new DNA
- Non-histone proteins form essential as structural proteins, activators, inhibitors and enzymes

Structure of the Chromosome

- Each chromosome has a narrow waist called **centromere**, which divides the chromosome into short and long arms labelled p and q respectively and it is also the region where the two chromatids cross each other
- Distal end (the tip) of each chromosome is called the **telomere**.
- Chromosomes can be seen under the light microscope only when the cell is ready to divide. It contains many **DNA units called genes**

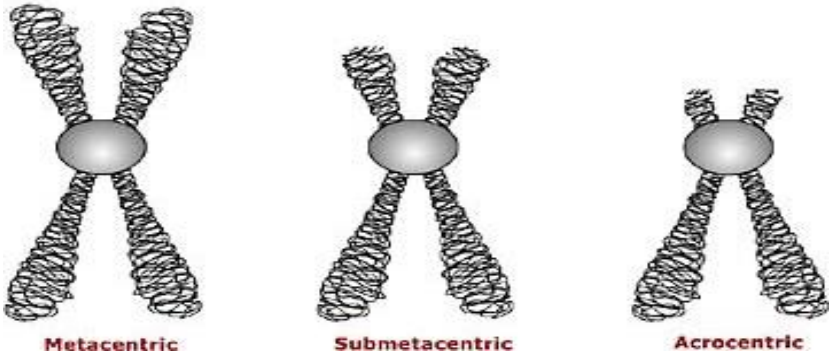
Diagram 1.2: Chromosome structure



Classification

- Based on the location of the centromere
  - i) Metacentric chromosomes –centromere is exactly in the middle e.g. chromosomes number 1, 3, 16, 19 and 20
  - ii) Sub metacentric chromosomes – centromere divides the chromosome into a short arm (p) and a long arm (q)
  - iii) Acrocentric chromosomes – have a very short arm with a centromere that is located off the centre in an unusual position (eccentric) e.g. chromosomes number 13, 14, 15, 21, 22 and the Y chromosome.

Diagram 1.3: Types of Chromosomes



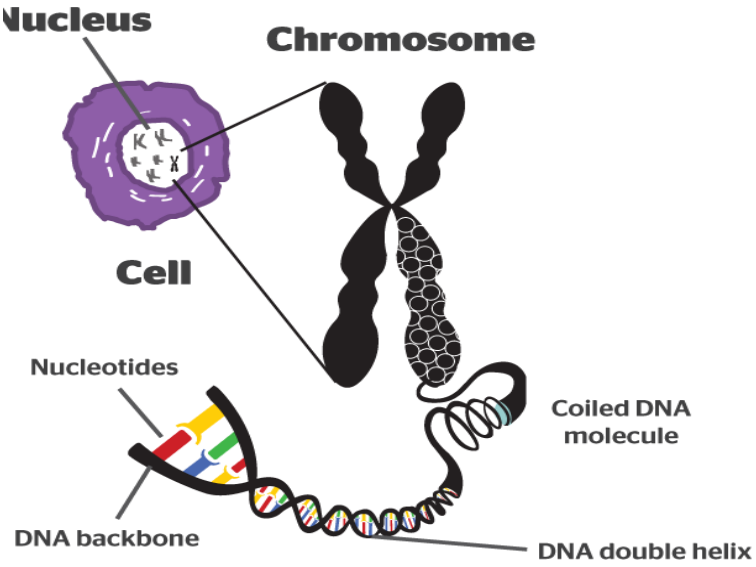
Chromosome numbers

- Each human body cell contains 46 (23 pairs of) chromosomes (two complete sets - 2n) while the one with only one complete set of chromosomes is called a haploid cell (1n) e.g. gametes, eggs and sperm cells
- Human chromosomes are categorized as either sex chromosomes or autosomes i.e. 1 pair of sex chromosomes (XX– females and XY for males) and the 22 pairs of autosome

4.0 DNA

- Is contained on the chromosome
- Cells have powerful internal feedback control systems that maintain homeostatic operations (each gene has a feedback control mechanism) through activation or inactivation of genes or enzyme regulation
- DNA controls protein synthesis by means of the genetic code

Diagram 1.4: Human Chromosome



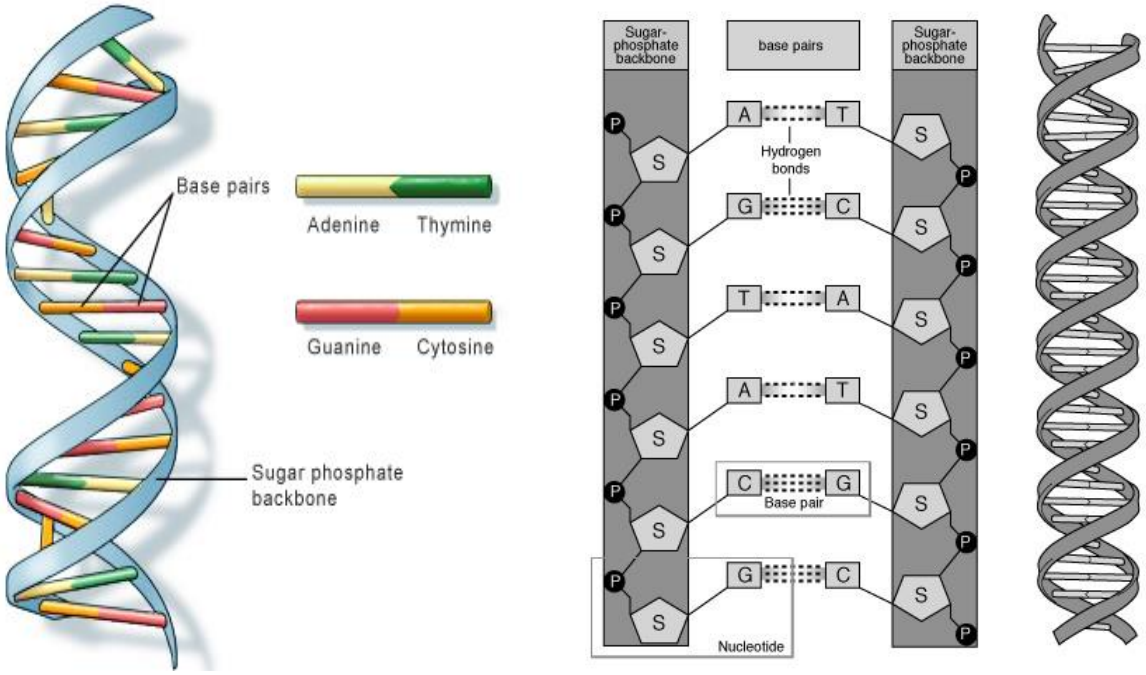
Functions of DNA

1. Carry information of inheritance
2. Protein synthesis
3. Control of biochemical processes in the cells

Structure

- Formed from phosphoric acid, deoxyribose sugar and four nitrogenous bases – two purines (adenine and cytosine) and two pyrimidines (thymine and cytosine)
- DNA molecule consists of two parallel chains twisted (double helix) connected at various points with rings made up of organic bases held together by hydrogen bonds in specific relationship - purines link up with pyrimidines; A–T and C–G.

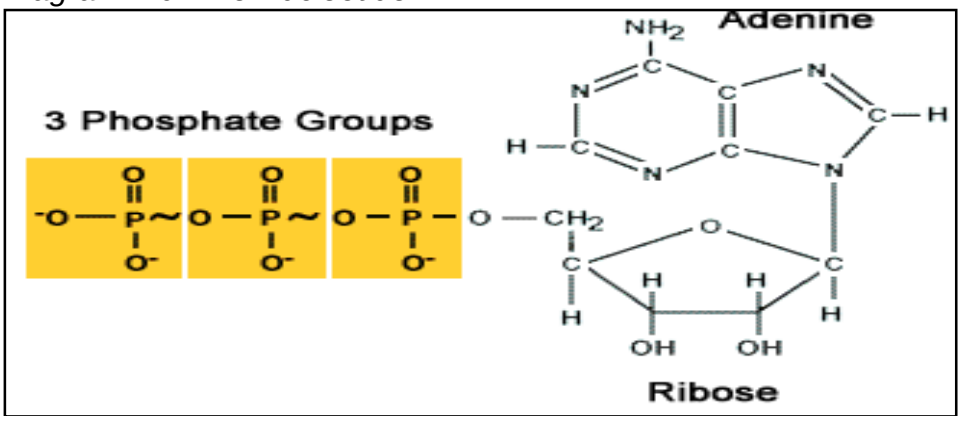
Diagram 1.5: Structure of DNA



Nucleic Acids

- Information carried by genes is usually contained in the **nucleic acids** (compare the nucleic acid to application packages in the computer)
- There are two principal types of nucleic acids– deoxyribonucleic acid (DNA) mainly confined to the nucleus and the ribonucleic acid (RNA) found mainly in the cytoplasm
- Nucleic acids are made up of blocks of complex molecules called nucleotides.
- A nucleotide is made up of three molecules – a 5-carbon sugar (pentose), an organic base and phosphoric acid linked together.

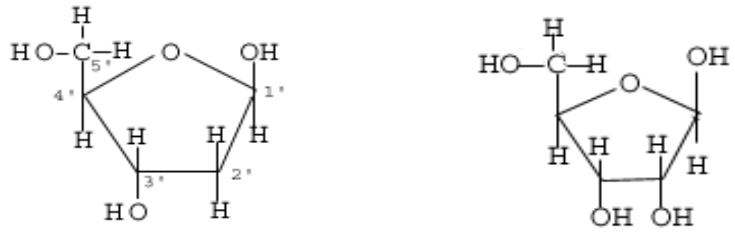
Diagram 1.6: The Nucleotide



The Sugar

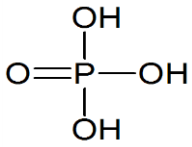
- Is the pentose sugar, either a **ribose sugar** ($C_5H_{10}O_5$) or **deoxyribose sugar** ($C_5H_{10}O_4$) which has lost one molecule of oxygen from a ribose sugar

Diagram 1.7: Ribose and Deoxyribose Sugar



Phosphate group

Phosphate or Phosphoric acid (H_3PO_4)



Organic Bases

- Are complex compounds made up of intricate rings of carbon and nitrogen atoms
- There are five organic bases found in the nucleotides – adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U)
- Adenine and guanine are purines (double rings) and the rest are pyrimidines (single rings)

Diagram 1.8: Purines

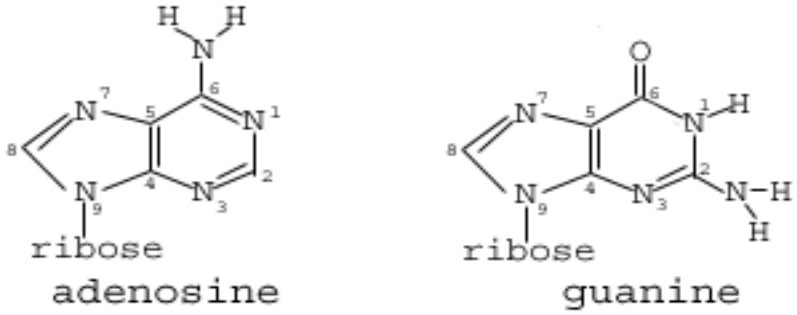
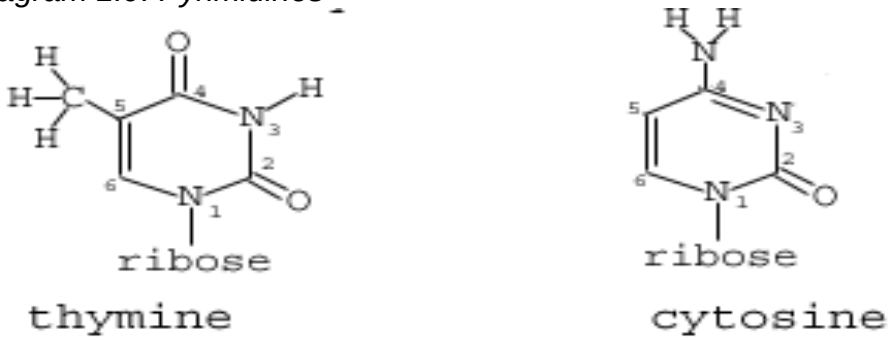


Diagram 1.9: Pyrimidines

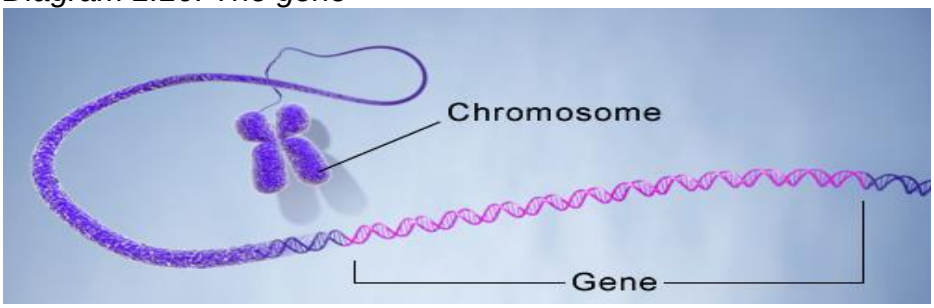


5.0 GENES

Introduction

- A gene is the basic physical and functional unit of heredity
- Contain information needed to synthesize a particular protein molecule
- They are segments of a DNA molecule of a chromosome
- They are an arrangement of different **codons** along the DNA. A codon is a section of 3 successive base pairs (triplet)
- Each codon codes or forms code word (message) for one amino acid
- Determine characteristics living things inherit from their parents e.g. sex, height, hair colour, etc.

Diagram 1.10: The gene



Genetic Code

- Is a set of instructions by which information encoded in genetic material (DNA or RNA sequence) is translated into proteins by cells
- Set of corresponding codons in RNA and amino acids in proteins
- The code defines a mapping between tri-nucleotide sequences [condons] and amino acids)
- A codon defines a single amino acid e.g. AUG (methionine) and UGG (tryptophan)
- There are 64 codons and 20 essential amino acids

6.0 PROTEIN SYNTHESIS

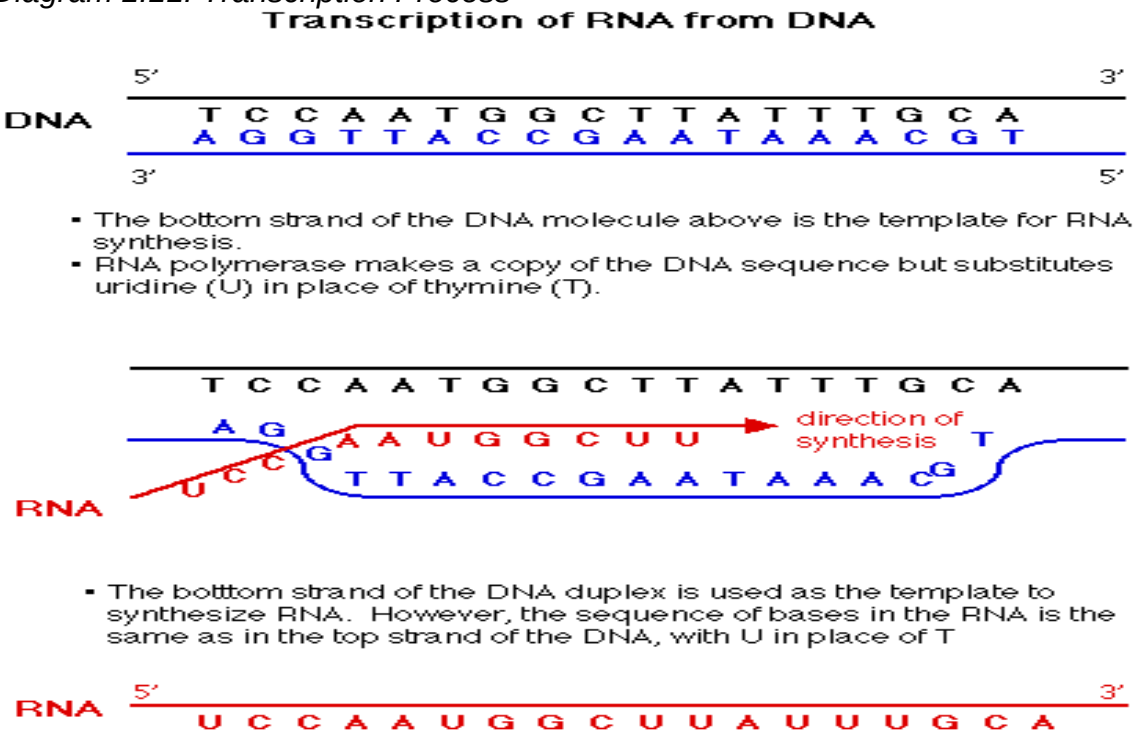
Introduction

- Takes place in **two steps** – **transcription** and **translation**
- Transcription occurs in the nucleus and involves DNA and mRNA and translation takes place in the cytoplasm and involves the tRNA, rRNA and ribosomes

Transcription

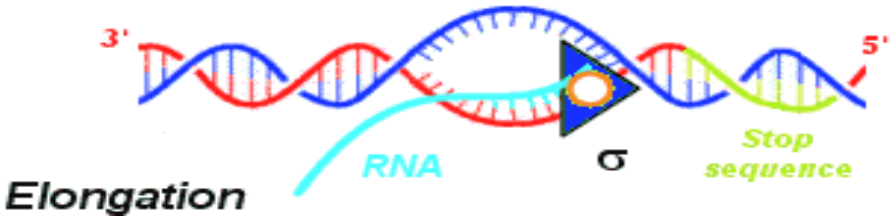
- Is the process of making an RNA copy of a gene sequence from a DNA strand in the cell nucleus - the messenger RNA(mRNA)
- Involves assembly of the RNA chain from activated nucleotides using the DNA strand as a template by adding RNA nucleotides until it encounters a new sequence of DNA nucleotides (**chain terminating sequence**)

Diagram 1.11: Transcription Process



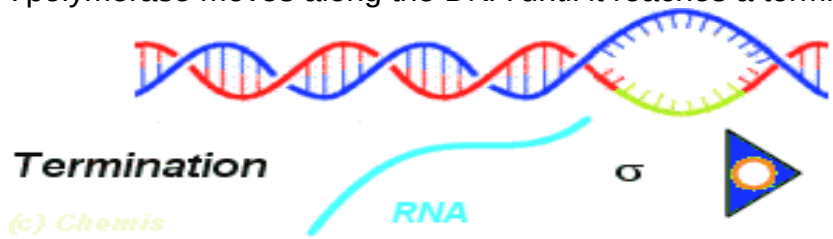
- The chain breaks away from the DNA strands and the DNA chain rebinds with the complementary bases joining up
- The RNA is forced away from the DNA and is released into nucleoplasm
- Takes place in three main steps
  i) RNA Polymerase Binds to DNA
    - DNA is unzipped and partially unwinds into two separate strands
    - One strand acts as a template for mRNA synthesis and the other acts as a cover
    - RNA polymerase attaches to the DNA at a specific area called the **promoter region**
    - RNA nucleotides present in the nucleoplasm attach themselves to the exposed based on the DNA molecule

  ii) Elongation
    - RNA nucleotides align themselves along the DNA bind to each to each other forming a chainlike strand called ***messenger RNA (mRNA)*** under the influence of *RNA polymerase*
    - mRNA strand peels away from the DNA (**a transcript of a gene**)



iii) Termination

- RNA polymerase moves along the DNA until it reaches a terminator sequence.

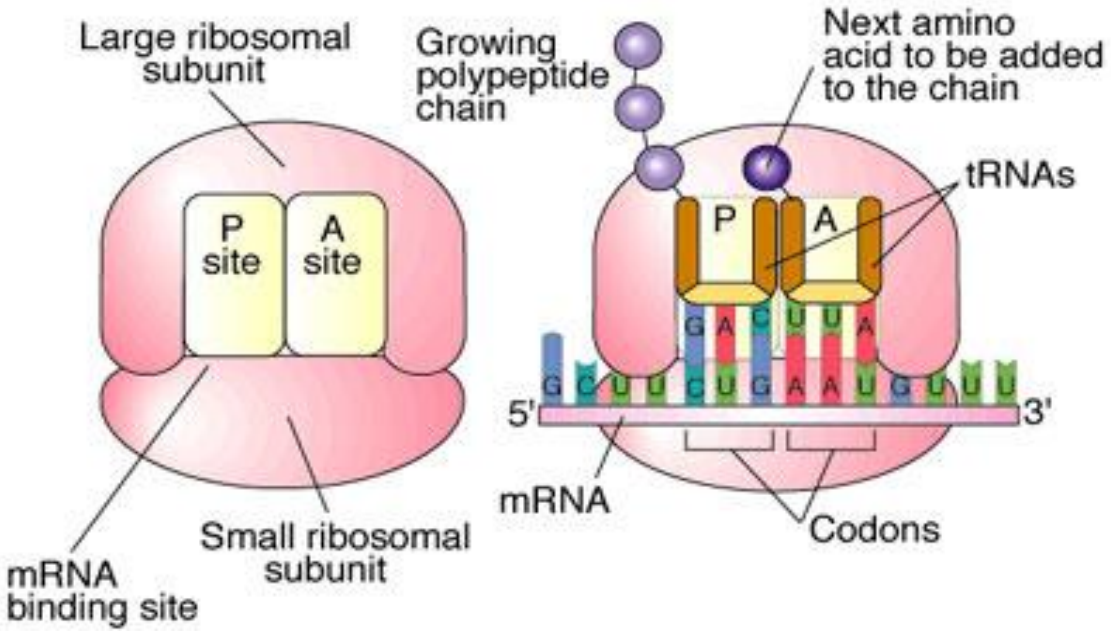


- When the single helix mRNA is complete it will separate from the DNA and the DNA will re-zip into the double helix
- mRNA is proofread and edited by the **spliceosome** removing non-coding portions (**introns**) and putting together the remaining pieces (**exons – coding regions**)
- Edited mRNA is transported out of the nucleus through the pores in the nuclear envelope.

Translation

- Is the process of translating the sequence of a messenger RNA(mRNA) molecule to a sequence of amino acids during protein synthesis in the cytoplasm
- The mRNA, rRNA and tRNA all come together
- The rRNA consists of two parts – the **large ribosomal unit** (with the A and P sites) and the **small ribosomal** unit for polypeptide synthesis and elongation
- The tRNA molecules have an amino acid attachment site and it also carries an anticodon (complementary nucleotide sequence to a given codon)
- Steps
  i. mRNA attaches to two subunits of ribosomes which sandwich it
  ii. As the mRNA moves through the rRNA from the 5' 9(with AUG) to the terminating codon at the 3' end, the tRNA picks up the appropriate amino acid in the cytoplasm that is coded for by the mRNA that its anticodon matches
  iii. The first codon AUG will start in the A site and the tRNA with the appropriate anticodon (UAC) will meet up to start codon bringing
  iv. Once completed the complex moves to the site P site
  v. The next codon will move in a and a new amino acid brought in
  vi. The two amino acids in the rRNA will then form a peptide bond
  vii. The first tRNA will disconnect from its UAC amino acid and go back to the cytoplasm while the 2nd tRNA will move to the P site with third tRNA getting to A site
  viii. As the ribosomes move along the mRNA strand more amino acids are added until the end of the mRNA.
  ix. mRNA is degraded in the cytoplasm by a combination of endonucleases and exonucleases

Diagram 1.12: Polypeptide Synthesis Process



TAKE AWAY

Explain the following terms

- Alleles, chromosome, gene, dominant and recessive genes, genotype and phenotype, heredity, heterozygous and homozygous, mutation

ASSIGNMENT

Read about

1) Mutation and causes of mutation
2) Patterns of gene inheritance

TOPIC 2: GENETIC BASIS OF DISEASE

Learning Outcomes

At the end of the lesson the learner should be able to: -

1) Describe the mechanisms of genetic disease development
2) Explain the inheritance patterns in genetic diseases
3) Classify genetic disorders

1.0 INTRODUCTION AND HUMAN GENOME

- Genetic disorder – illness or disease caused by one or more abnormalities of the genome(gene)
- The human genome is the entire "treasury of human inheritance."
- The 46 human chromosomes (22 pairs of autosomal chromosomes and 2 sex chromosomes) between them house almost 3 billion base pairs of DNA that contains about 20,500 protein-coding genes
- The coding regions make up less than 5% of the genome (the function of all the remaining DNA is not clear) and some chromosomes have a higher density of genes than others
- Most genetic diseases are the direct result of a mutation in one gene
- However, one of the most difficult problems ahead is to further elucidate how genes contribute to diseases that have a complex pattern of inheritance, such as in the cases of diabetes, asthma, cancer, hypertension and mental illness

2.0 MITOSIS

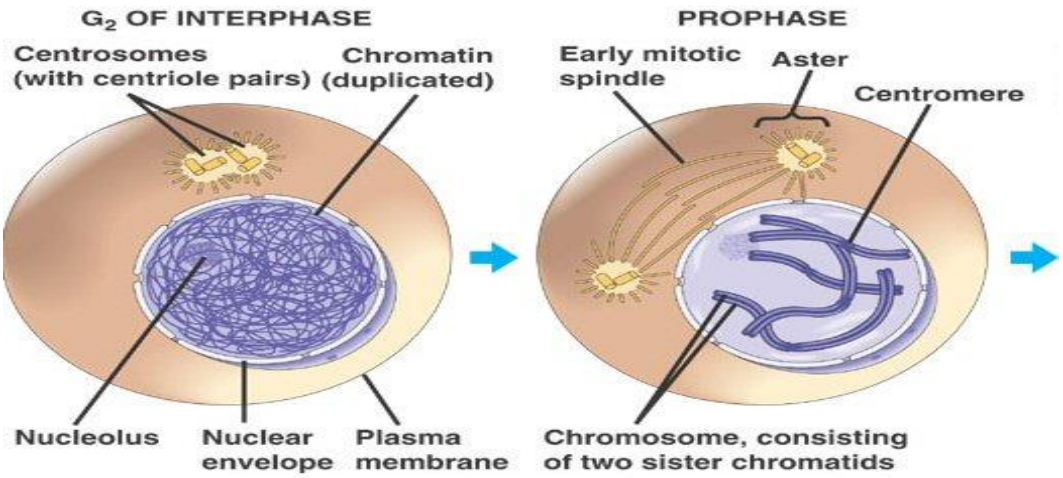
Introduction

- Is the division of the ***nucleus into 2 identical nuclei***, which occurs during cell division
- Involves organization and distribution nuclear DNA
- Takes place in four phases - prophase, metaphase, anaphase, and telophase

Phase 1- Prophase

- Prophase means "*before phase"*
- Nucleus envelope falls apart and the paired (sister) chromatids coil up to form dense compact chromosomes
- Sister chromatids are joined together by the centromere
- Nucleolus and nuclear membrane disappear and two structures called **centrosomes** appear next to the disappearing nucleus.
- Centrosomes move toward opposite poles of the cell and as they separate
- Spindle fibers form (two types kinetochore and polar fibers)

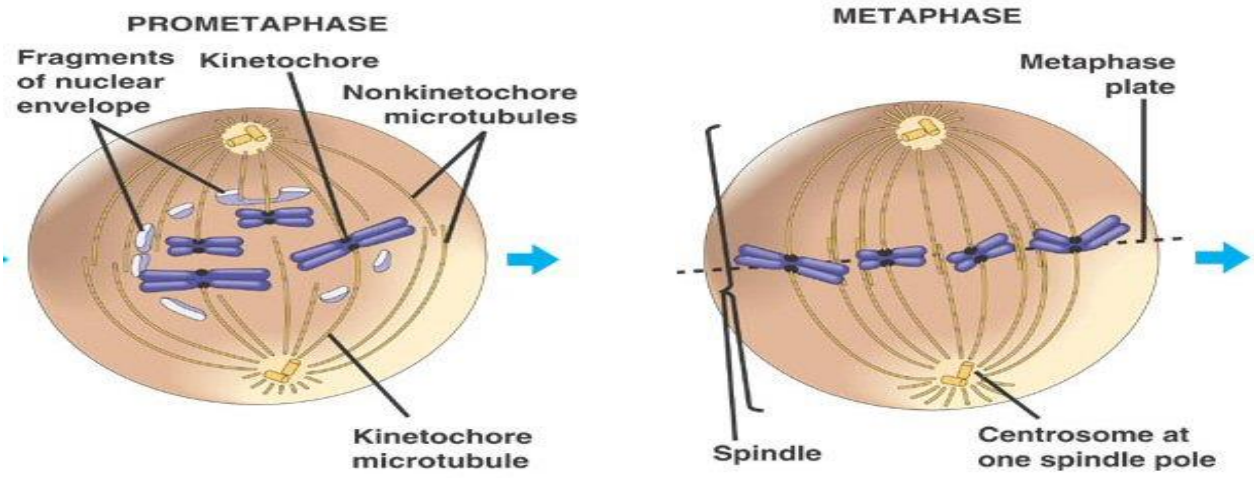
Diagram 2.1: Prophase



Phase 2 - Metaphase

- Metaphase – “position-changing phase”
- Chromosomes are moved and aligned along a plane at the equator of the cell midway between the centriole pairs at opposite poles of the cell (equatorial plane) by the kinetochore fibers attached to the centromeres
- One chromatid of each chromosome faces one pole of the cell and its identical sister chromatid faces the opposite pole
- Each chromatid then attaches to a spindle fibre

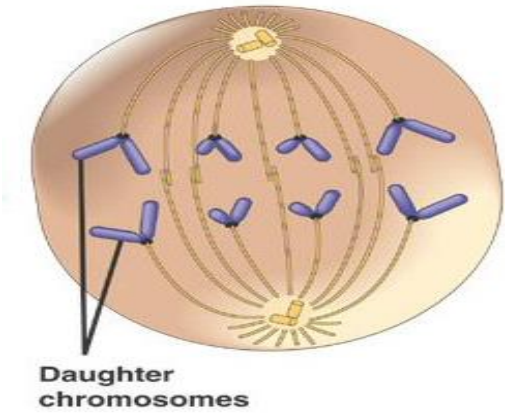
Diagram 2.2: Metapahse



Phase 3 - Anaphase

- Anaphase – “apart phase”
- Centromere of each chromosome splits to form two chromosomes each consisting of a single DNA molecule
- Each chromosome is pulled toward the opposite poles (centromeres)
- Sister chromatids move apart and are thus separated from each other and are now considered to be individual chromosomes.

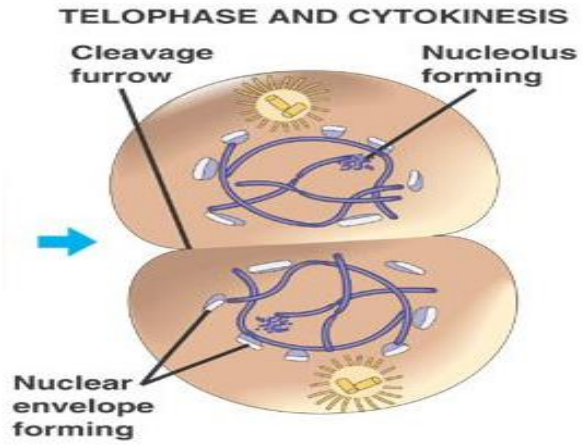
Diagram 2.3: Anaphase



Phase 4 - Telophase

- Telophase – “end phase” or “completion phase”
- Chromosomes reach opposite ends of the cell
- Spindle fibers disassemble and the chromosomes return to its original form and location within the cell
- A new nuclear envelope forms around the chromosomes at each end of the cell.

Diagram 2.4: Telophase



3.0 MEIOSIS

Introduction

- Meiosis is a process of nuclear division that reduces the number of chromosomes in new cells to half the number in the original cell (produces four haploid cells)
- One parent cell divides twice to produce four haploid daughter cells
- Proceeds in two main stages namely **meiosis I** and **meiosis II** (the sister chromatids of each chromosome are separated)

Meiosis I

- Homologous pairs are separated

Prophase I

- Chromosomes become thick and visible and **each homologous pair is tangled together**
- Portions of chromatids may break off and attach to adjacent chromatids on the homologous chromosome in a process called **crossing-over**
- Crossing-over results in genetic recombination by producing a new mixture of genetic material
- Each pair consists of four chromatids, because each chromosome in the pair had replicated before meiosis began
- The nucleoli and the nuclear envelope disappear and the spindle fibers form

Metaphase I

- Homologous pairs (tetrads) are still together and arrange in the middle of the cell.

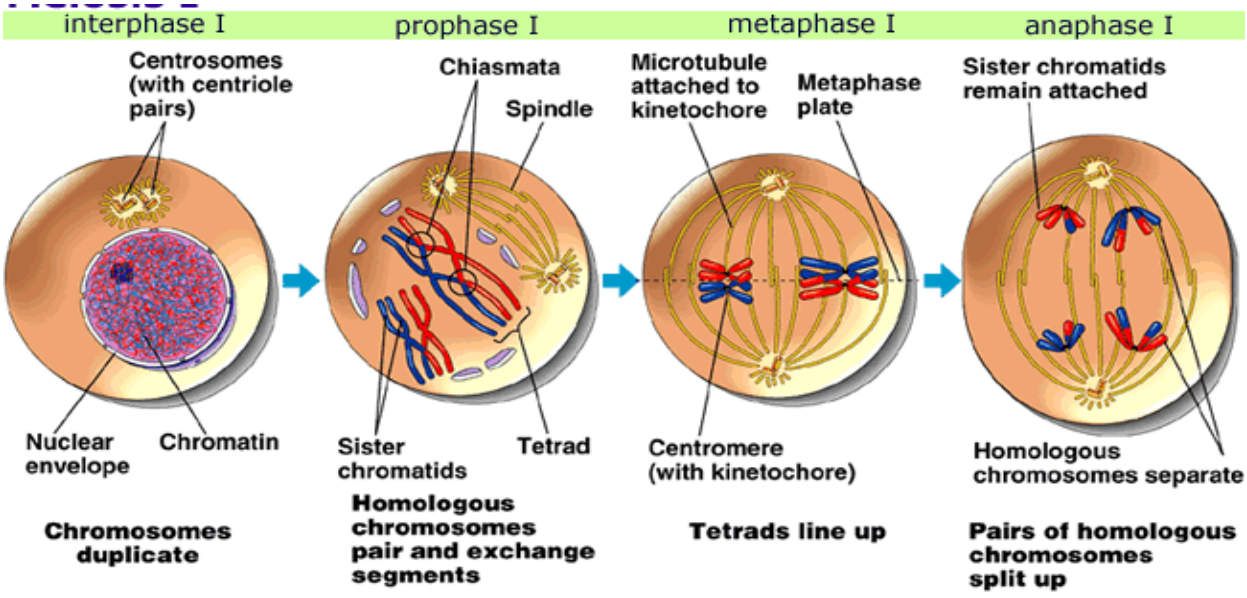
Anaphase I

- Homologous pairs of chromosomes separate from each other and the spindle fibers pull one member from each pair to opposite ends of the cell

Telophase I

- Cytokinesis takes place and each new cell is haploid, containing one chromosome from each pair

Diagram 2.5:: Meiosis I



Meiosis II

- Chromosomal replication does not occur between meiosis I and meiosis II
- Meiosis I proceeds directly to meiosis II without going through interphase
- Resembles mitosis
- Begins with two haploid cells and ends with four haploid cells

Prophase II Metaphase II

- Chromosomes align on the metaphase plate during metaphase II in preparation for centromeres to divide in the next phase

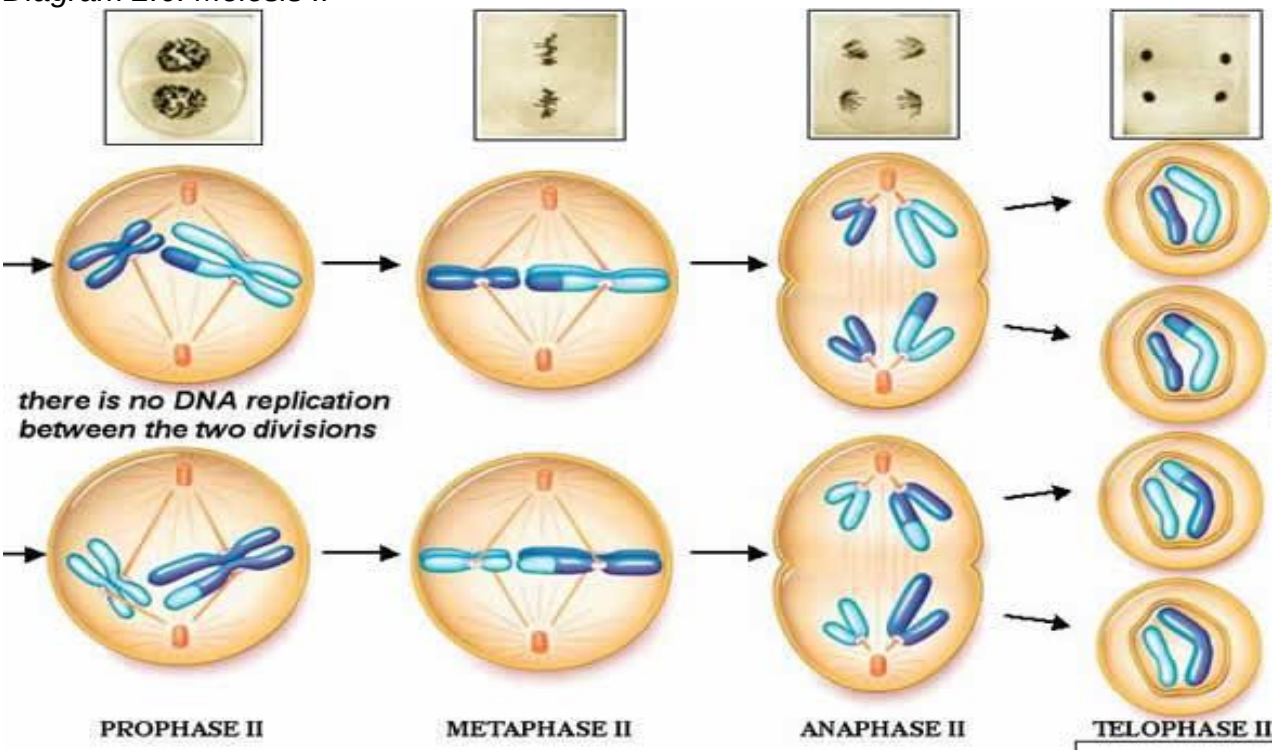
Anaphase II

- Chromosomes divide at the centromeres and the resulting chromosomes each with one chromatid move towards the opposite plates of the cell

Telophase II and Cytokinesis

- Four haploid nuclei (containing chromosomes with single chromatids) are formed
- Division of the cytoplasm cytokinesis results in four haploids cells
- Spindle fibers reform and attach to centromeres in prophase II

Diagram 2.6: Meiosis II



4.0 PATHOGENESIS OF GENETIC DISEASES

- Occur as a result of **inheritance** or **acquisition** of altered genetic material

> **Talking Point**
> 1. Explain how genetic composition determines causation of disease
> 2. What determines the magnitude of the clinical features of genetic disorders

4.1. Inheritance of Genetic Diseases

- Mode of inheritance is the manner in which a particular genetic trait or disorder is passed from one generation to the next

- Inheritance patterns trace the transmission of genetically encoded traits, conditions or diseases to offspring
- Genetic conditions caused by a mutation in a single gene follow predictable patterns of inheritance within families
- Modes of inheritance include single gene (Mendelian), multifactorial and mitochondrial

Single gene (Mendelian) Inheritance

- Single gene inheritance is also referred to as Mendelian inheritance as they follow transmission patterns
- There are four types of Mendelian inheritance patterns namely autosomal dominant, autosomal recessive, X-linked dominant and x-linked recessive
- Several laws guide Mendelian inheritance
  1. Mendel's First law - The law of segregation
     - States that during the formation of reproductive cells (gametes), pairs of hereditary factors (genes) for a specific trait separate so that offspring receive one factor from each parent
  2. Mendel's Second law - The law of independent Assortment
     - States that chance determines which factor for a particular trait is inherited.
     - Each of the two alleles of one gene may combine with either of the alleles of another gene.
     - This brings in the concept of probability in that transmission of genes occurs as independent events with different chance of fusion.
  3. Mendel's Third law - The law of Dominance
     - States that one of the factors for a pair of inherited traits will be dominant and the other recessive, unless both factors are recessive

Multifactorial Inheritance

- Also called complex or polygenic inheritance
- Are caused by a combination of environmental factors and mutations in multiple genes
- For example, different genes that influence breast cancer susceptibility have been found on chromosomes 6, 11, 13, 14, 15, 17, and 22
- Some common chronic diseases are multifactorial disorders e.g. heart disease, arthritis, Alzheimer's disease, obesity
- Multifactorial inheritance also is associated with heritable traits such as fingerprint patterns, height, eye color, and skin color.

Mitochondrial Inheritance

- Is caused by mutations in the non-nuclear DNA of mitochondria
- Mitochondria are organelles found in the cytoplasm of cells
- Mitochondria are unique in that they have multiple copies of a circular chromosome.
- Mitochondria are only inherited from the mother's egg, thus only females can transmit the trait to offspring, however they pass it on to all of their offspring
- The primary function of mitochondria is conversion of molecule into usable energy

- Thus many diseases transmitted by mitochondrial inheritance affect organs with high-energy use such as the heart, skeletal muscle, liver, and kidneys

4.2. Acquisition of Genetic Diseases

- Caused by acquired mutations or changes in parts of the DNA
- Mutation due to exposure to environmental factors – drugs, radiations, metals, infections
- Only become heritable if the mutation occurs in the germ line (germline cells include the gametes and the cells that produce the gametes)
- A person suffers from a genetic condition may be determined to some degree by environmental factors

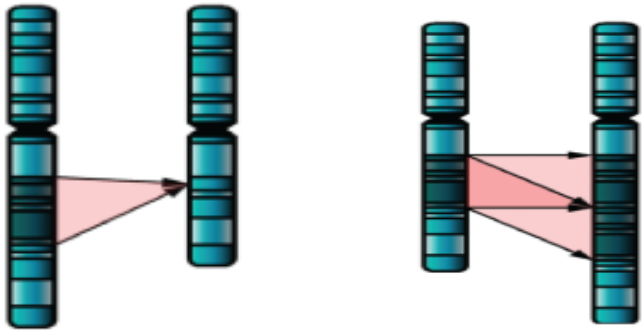
5.0 PATHOPHYSIOLOGY OF GENETIC DISEASES

5.1. Mutation

- Mutation is a permanent alteration in the DNA sequence that makes up the gene
- Can range from a single DNA building block to a large segment of a chromosome that include multiple genes
- Mutations may be spontaneous or induced
- Classification
  i) Hereditary mutations
    - Inherited from a parent and are present throughout a person's life
    - Also called germ-line mutations because they are present in the parent's egg/sperm
  ii) Acquired (somatic) mutations
    - Happen in a single cell early in embryogenic development
    - Genetic changes are not present in a parent's egg or sperm cells

- Broadly there are two types of mutations namely length and point mutations
  i) Length mutations involve gain or loss of genetic material through deletions, duplications and insertions

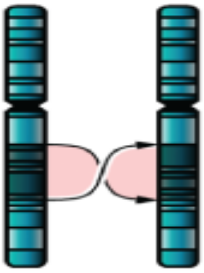
Diagram 2.7: Pathology of Length Mutation



Deletion Duplication/insertion

  ii) Point mutations result in alteration of the genetic code with no gain or loss of genetic material where a single nucleotide base is replaced by a different nucleotide base

Diagram 2.8: Pathology of Point Mutations



Inversion

- Mistake results in an incorrect polypeptide chain and eventually protein thus affecting the structure and/or function of the protein in question and process the protein is/are involved in
- There are four categories of mutation
  i) DNA base substitution, insertion and deletion
  ii) Unequal crossing-over and related structural modifications of chromosomes
  iii) Partial or complete gene inversion and duplication
  iv) Irregular number of chromosomes

5.2. Protein synthesis defects

- Defects in protein synthesis results in
  1) Enzyme defects/deficiencies
  2) Receptor protein defects
  3) Structural protein defects

6.0 CLASSIFICATION OF GENETIC DISORDERS

1) Monogenic Disorders - Mendelian (Single Gene) disorders
   a. Autosomal Disorders - autosomal dominant disorders and autosomal recessive disorders
   b. Sex (X-linked) disorders - X-linked dominant disorders and X-linked recessive disorders
2) Chromosomal (Cytogenic) disorders -
   a. Numerical abnormalities – aneuploidy and polyploidy
   b. Structural abnormalities - translocations, deletions and inversions
3) Mitochondrial Disorders
4) Metabolic (In borne errors) disorders
5) Somatic cell disorders
6) Multifactorial Inheritance Disorders

Study Questions

1) Explain the difference and relationship between congenital disease and genetic disease

TOPIC 3: AUTOSOMAL SINGLE GENE DISORDERS

Learning Objectives

At the end of the lesson the learner will be able to: -
1) Classify single gene autosomal disorders
2) Explain the pathology of single gene autosomal dominant disorders

1.0 INTRODUCTION

- Result from mutation of a single gene that has a large effect
- Mutations may occur in one or both members of a pair of genes causing a permanent change in the DNA of the cell
- Autosomal disorders are usually carried on the somatic cells and they are usually transmitted to the next generation

2.0 CLASSIFICATION OF SINGLE GENE DISORDERS

- Single gene disorders are classified according to whether the
  i. Location of the mutation
     a. On an autosome – Autosomal disorders
     b. On the sex chromosome – Sex linked disorders (X and Y Linked disorders)
  ii. Number of mutant genes
     a. Heterozygous - one mutant and one normal gene in a pair
     b. Homozygous - both members of the pair are affected
  iii. Genotype expression
     a. Recessive disorders
     b. Dominant disorders

3.0 AUTOSOMAL DISORDERS

- The mutation occurs on the autosomes
- Can be classified as autosomal dominant disorders and autosomal recessive disorders

4.0 AUTOSOMAL DOMINANT DISORDERS

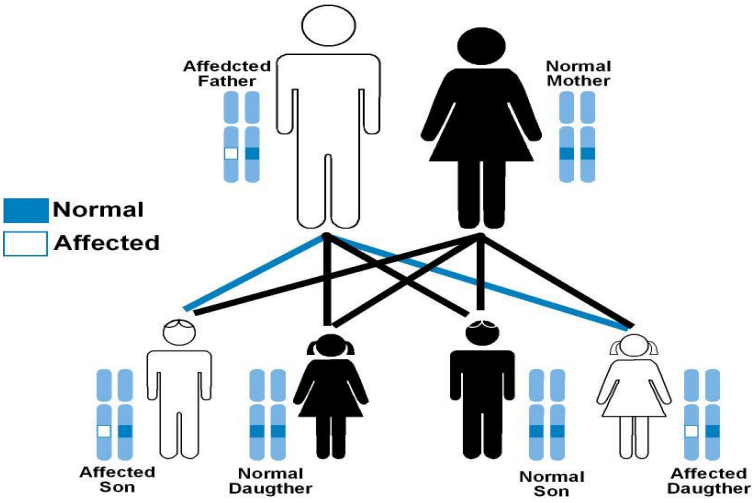
4.1. Introduction

- Requires that only one mutant gene be passed onto the child from the mother or father
- Only occurs if one or both parents have the resulting genetic disease
- The mutated gene that determines the abnormal phenotype is dominant to that coding for normal development
- Presence of the abnormal gene leads to disease
- Tend to occur in every generation of an affected family or may not be transmitted to the next generation
- Mutations affect structural proteins e.g. collagen or regulatory proteins such as receptors
- There is reduced ability of the gene to express itself or its effects and variation in the expressions

- Usually the onset of clinical features is later than in autosomal recessive disorders

4.2. Transmission (Mode of Inheritance) of Autosomal Dominant

Diagram 3.1: Mode of Inheritance



4.3. Pathology

- Main effects of autosomal dominant disorders result from abnormalities arising in **proteins** responsible for cell membrane, enzymes, enzyme inhibitor receptors, transport of oxygen, ions, extra cellular structures of cells, homeostasis and growth regulation

4.4. Examples

- Achondroplsia; Adult polycystic kidney; Familial hypercholesterolaemia; Familial polyposis coli; Hereditary spherocytosis; Huntington disease; Marfan's syndrome; **Neurofibromatosis** (von Recklinghausen's disease); Osteogenesis imperfect; Von Willibrand disease

5.0 INDIVIDUAL AUTOSOMAL DOMINANT DISORDERS

1. HEREDITARY SPHEROCYTOSIS

- Caused by intrinsic defects in the red cell membrane that render the red cells spheroid, less deformable and vulnerable to spleenic sequestration

Cause
- Mutation of the gene **SPTBN1** on chromosome 1 which results in deficiency of the structural protein of the red cell membrane called **spectrin** resulting in spheroidal contour and smaller size of red cells that are not flexible

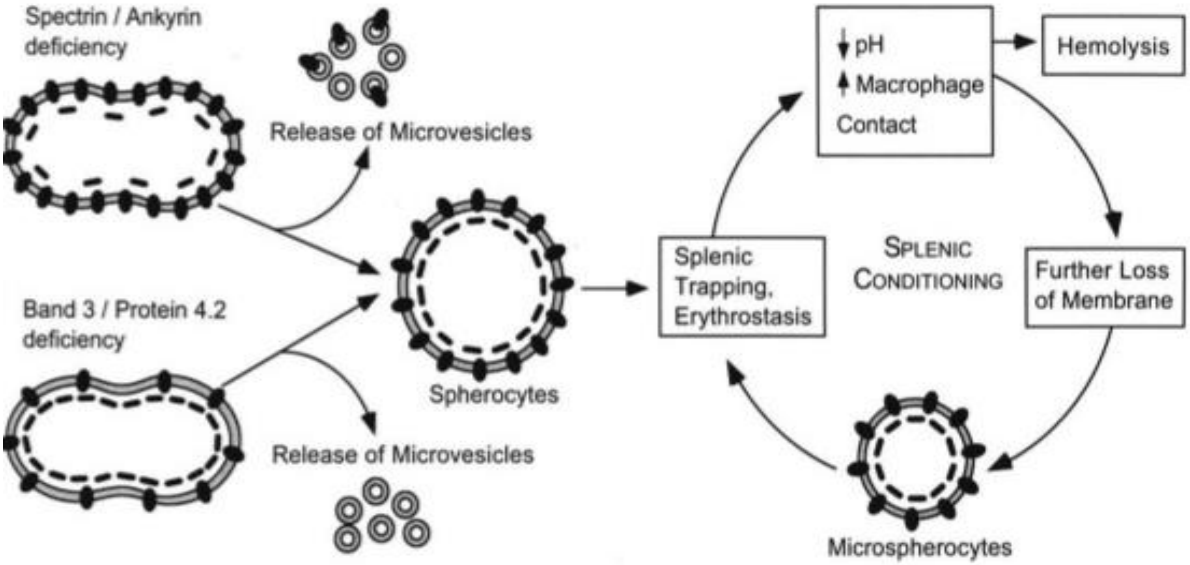
Pathology
- Defective cell membrane of the red blood cells

Pathogenesis
- Inheritance of mutant **SPTBN1** gene that codes for structural protein spectrin

Pathophysiology

- Defects in membrane structural proteins result in the weakening of vertical linkages between membrane surface proteins and the phospholipid layer
- Reduced phospholipid and cholesterol content favours excessive permeability to Na^+ resulting in loss of surface membrane area relative to volume
- This alters the shape of the red cells to become spherical with reduced flexibility (**increased rigidity**) and increased permeability (causes osmotic fragility)
- This process is countered by increased glycolytic process producing ATP needed by Na pump in order to pump Na ions from the cell resulting in an increase cell turnover and loss of membrane lipid producing micro-spherocytes
- In the spleen there is less glucose available hence the destruction of cells due to lack of deformability characteristic to enhance their passage in the red pulp of the spleen
- Red cells with decreased deformability are retained in the spleenic pulp for unduly long time or the cells find the environment of acidic pH and low glucose concentration in the spleenic pulp unfavourable.

Diagram 3.2: Pathophysiology of HS



Clinical Features

- Features of haemolytic anaemia – pallor, jaundice, hyperbilirubinaemia, increased reticulocyte count, splenomegaly, gall stones

2. OSTEOGENESIS IMPERFECTA (OI)

- Also called Brittle bone disease (disorder of bone fragility)
- OI means imperfectly formed bone
- Inheritance can be autosomal-dominant, autosomal-dominant with new mutations, or autosomal-recessive

Cause

- Results from mutations on genes COL1A1 (on chromosome 17) and COL1A2 (on chromosome 7) which carry instructions for making type 1 collagen

Pathogenesis

- Inheritance of a mutant gene

Pathophysiology

- Mutations result in failure of synthesis of collagen leading to formation of brittle bone due to failure of osteoblasts to synthesize bone tissues

Pathology

- Defective bone formation

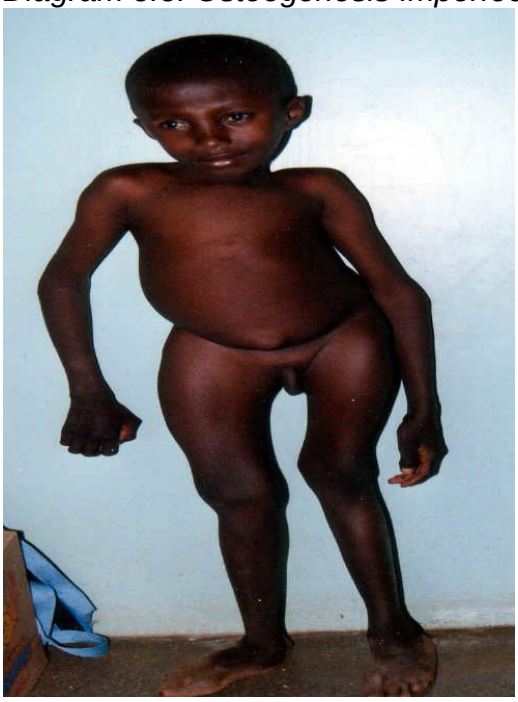
Types

Type	Description and Pathology
1	• Mildest and most common form of brittle bone disease • Body produces quality collagen but not enough resulting in mildly fragile bones • Typically have bone fractures due to mild traumas • Such bone fractures are much less common in adults • Teeth may also be affected, resulting in dental cracks and cavities
2	• Most severe form of brittle bone disease (can be life-threatening) • Body either doesn't produce enough collagen or produces collagen that's poor quality • Cause bone deformities (a narrowed chest, broken or misshapen ribs), or underdeveloped lungs
3	• A severe form of brittle bone disease • Causes bones to break easily • Body produces enough collagen but its poor quality • Bone deformities are common and may get worse as your child gets older
4	• Most variable form of brittle bone disease • Symptoms range from mild to severe • Body produces enough collagen but the quality is poor • Children with type 4 OI are typically born with bowed legs, although the bowing tends to lessen with age.

Clinical Features

- Four major clinical features
  i) Osteoporosis with abnormal bone fragility – weak bones, pathological fractures, bone deformities. Bow legs (genu vara) and arms, kyphosis, scoliosis
  ii) Blue sclera
  iii) Dentinogenesis imperfect
  iv) Hearing impairment – deafness
- Other features include ligamentous laxity and hypermobility of joints, short stature, and easy bruising, flat feet
- Heart defects and respiratory defects

Diagram 3.3: Osteogenesis Imperfecta



Complications

1) Multiple pathological fractures
2) Hearing loss
3) Heart Failure
4) Recurrent Chest infections
5) Deformities – chest, spinal cord

3. ACHONDROPLASIA

- Achondroplasia means without cartilage formation
- There is failure of ossification of bones at the epiphyseal plates of long bone resulting in severe short-limb dwarfism
- Long bones are abnormally short but the skull grows normally leading to a relatively large skull

Pathophysiology

- Caused by mutations in the FGFR3 gene (located on chromosome 4 and 14) which encodes a protein called **Fibroblast Growth Factor Receptor 3**(receptor site of action of a major growth factor responsible for lengthening bones)
- Retards growth of long bones resulting in abnormally shaped shorter bones and thus a shorter stature

Risk Factors

- A parent with achondroplasia
- Advanced paternal age causing spontaneous mutations

Diagram 3.4: Achondroplasia

Clinical Features

- Short stature, a long trunk, and shortened limbs, which are noticeable at birth
- Large head with a prominent forehead
- Underdeveloped portions of the face
- Knock-knee or bowed-leg deformity
- Hands and the feet appear large, but the fingers and toes are short and stubby
- Excessive curve of the lower back and a waddling walking pattern
- Dental problems
- Weight control problems
- Dental problems from overcrowding of teeth
- Neurologic and respiratory problems
- Fatigue, pain, and numbness in the lower back and the spine

4. MARFAN'S SYNDROME

- A genetic disorder that causes connective tissues—which provide substance, shape and support to many parts of the body—to be weaker than they should be
- Often weakens the aorta creating the risk of an aortic tear, leak or aneurysm
- Results from abnormality of the structural protein - collagen an essential connective tissue in the body affecting the skeleton, eyes and the cardiovascular system
- A serious condition that can affect many parts of the body - including the heart and blood vessels, lungs, bones, joints, eyes and skin.

Pathology

- Inheritance of mutant FBN1 which codes for glycoprotein fibrilin-1

Pathophysiology

- Glycoprotein fibrilin-1 is the main constituent of the microfibrils of the extracellular matrix glycoprotein
- Reduced or abnormal fibrilin-1 leads to tissue weakness, increased transforming factor β signalling and loss of cell-matrix interactions

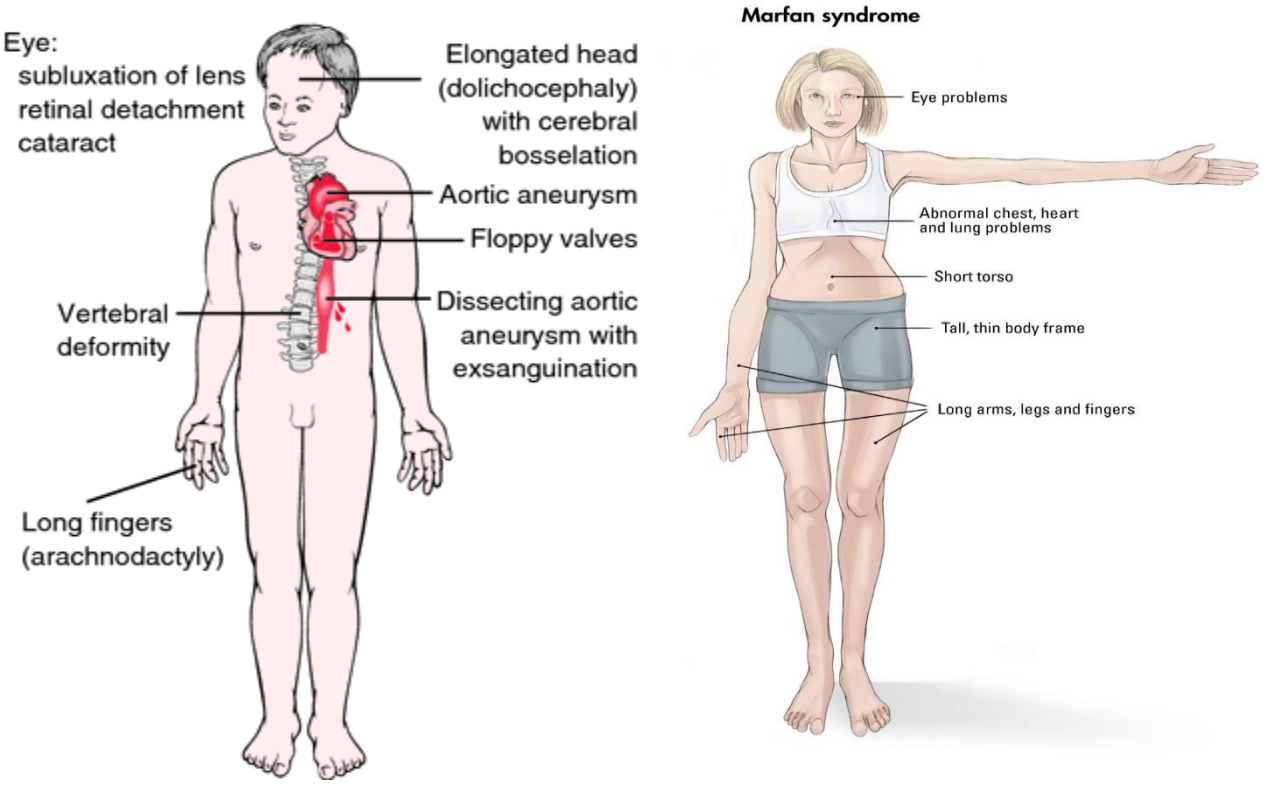
Pathology

- Poor formation of the extracellular matrix

Clinical Features

- Tall and slender build with disproportionate long arms, legs, fingers and toes
- Exceptionally long extremities (lower and upper limbs), long tapering fingers and toes (arachnodactly)
- Heart murmurs (weakness of heart valves – AV valves and aortic)
- Extreme near-sightedness - ectopia lentis (dislocation or subluxation of the lens)
- Flat feet
- An abnormally curved spine (laxity of joints resulting in hyper extensibility of the joints and spinal deformities such as kyphosis (forward bending) and scoliosis (lateral bending)
- A high arched palate and crowded teeth
- Pectus excavatum or cavinatum

Diagram 3.5: Marfan's Syndrome



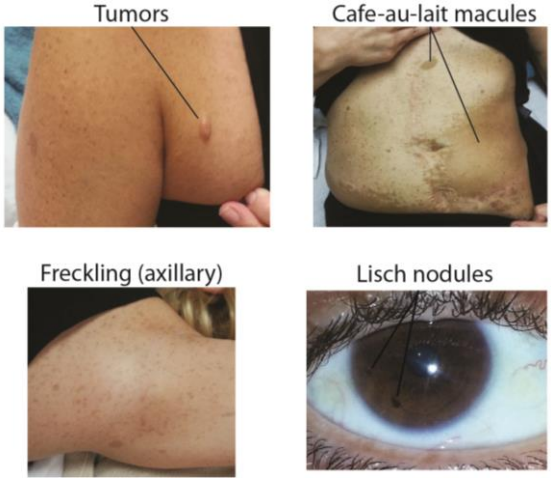
5. NEUROFIBROMATOSIS

- NF is a genetic disorder causing lesions in the skin, nervous system and skeleton
- Characterized by changes in skin colouring (pigmentation) and growth of tumours affecting the brain, spinal cord, nerves and skin

Pathophysiology

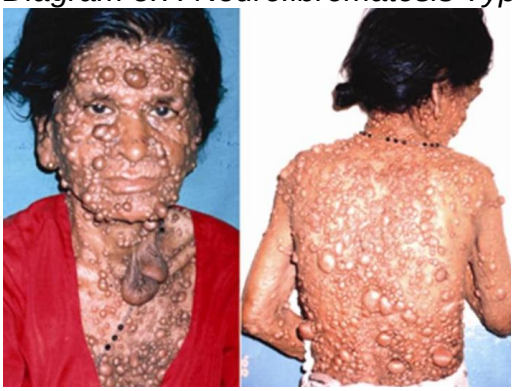
- Result from a mutation in or deletion of the **NF1** gene located on chromosome 17q (von Recklinghausen disease) or NF2 (merlin protein) located on chromosome 22p
- NF1 codes for neurofibromin protein.
- Neurofibromin serves as a tumour suppressor thus decreased production results failure to regulate growth of cells leading to formation of tumours on the nerves
- There are three types –
  i) Type 1 - von Recklinghausen's disease
    - More common form Neurofibromin, the gene product

Diagram 3.6: Neurofibromatosis Type 1



ii) Type 2 - presents with multiple neural tumours involving nerve trunks in the skin and internal organs

Diagram 3.7: Neurofibromatosis Type 2



Clinical Features

1) Dermal features
   - Café-au-lait spots (light brown skin spots), axillary or inguinal freckles, skin-fold freckling, hypopigmented macules, urticaria pigmentosa, naevus anaemicus and benign cherry angiomas, juvenile xanthogranulomas (benign orange papules)

2) Neurofibromas
   - May be in the skin or subcutaneous tissues; cutaneous neurofibromas

3) Ocular problems
   - Tumours of the optic nerve (gliomas) occur
   - Most common presentation is asymmetrical visual field defects.
   - In NF2, posterior subcapsular or juvenile cataracts can precede CNS symptoms.

4) Skeletal problems
   - Congenital pseudoarthrosis, bowing of the tibia is the most common presentation, thinning and angulation of long bones with prominence of the anterior tibia and progressive deformity can occur throughout early childhood, bowing of the forearm (less common), fractures (spontaneously or after trivial injury), asymmetrical thoracic cage with flaring or prominence of the inferior ribs, scoliosis (with or without kyphosis), osteoporosis

5) Neurological problems
   - Develop from tumours and malformations, including aqueduct stenosis
   - Skull deformity can lead to pulsating exophthalmos.
   - Severe scoliosis can deform the spine, causing cord compression and respiratory compromise
   - Pressure on peripheral and spinal nerves and the spinal cord will also have neurological sequelae
   - Epilepsy (mild).
   - Acute or progressive sensory disturbance, motor deficit and inco-ordination or sphincter disturbance, which may indicate an intracranial lesion or spinal cord compression.

6) Cardiovascular problems
   - Congenital heart disease (pulmonary stenosis and hypertension)
   - Carotid artery stenosis/occlusion and cerebral aneurysm may occur with NF1.

7) Gastrointestinal (GI) –
   - Abdominal bloating, pain, dyspepsia, haemorrhage and constipation may suggest a GI neurofibroma, anaemia and GI bleeding.

8) Psychological
   - Disfigurement and the unpredictable course of NF may cause anxiety & depression

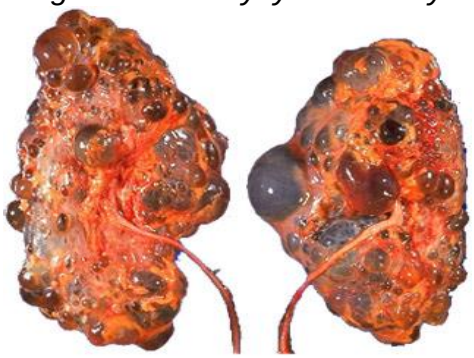
9) Endocrine
   - Precocious puberty occurs in about 3% and is associated with tumours of the optic chiasma

10) Obstetric
   - Increased risk of perinatal complications in NF1, higher stillbirth rate, IUGR
   - During pregnancy, neurofibromas may grow in size and number and there is the risk of cord compression if spinal plexiform neurofibromas expand
   - Pelvic neurofibromas may impede delivery of the baby

6. POLYCYSTIC KIDNEY (PKD)

- A large portion of the renal parenchyma is changed into cysts of variable size
- There are 2 forms namely adult PKD (autosomal dominant disease) and infantile PKD (autosomal recessive disease)
- Occurs due to mutations of genes PDK1 and PDK2 located on chromosome 16

Diagram 3.7: Polycystic Kidney



Clinical Features

- Dull ache in the lumbar regions, haematuria, passage of blood clots in urine, renal colic, hypertension, urinary tract infection and progressive chronic renal failure with polyuria and proteinuria

7. VON WILLIBRAND DISEASE

- Is an inherited bleeding disorder that affects both sexes equally

Pathophysiology

- Results from mutation of ***vWF*** gene is located on the short arm of chromosome 12
- Found on the megakaryocytes and endothelial cell
- The mutation causes quantitative or qualitative abnormality of Von Willebrand (vWB) VIIIR factor which is a plasma glucoprotein
- vWB factor is synthesized by vascular endothelium and megakaryocytes and its abnormalities include reduced synthesis of all oligomers associated with amino acid defects, which prevents formation of complexes.
- Functions of the glycoproteins include
    - Platelet adhesion to vascular sub endothelium hence its deficiency results in prolonged bleeding time, low platelet adhesion (this differentiates it from Haemophilia)
    - Carrier protein for Factor VIII that is a coagulation protein and protects it from premature destruction.

Clinical Features

- Anaemia resulting from excessive bleeding from cuts, injuries, epistaxis, gastro-intestinal tract, gums, menorrhagia and haemoarthrosis

TOPIC 4: AUTOSOMAL RECESSIVE DISORDERS

Objectives

At the end of the lesson the learner will be able to: -

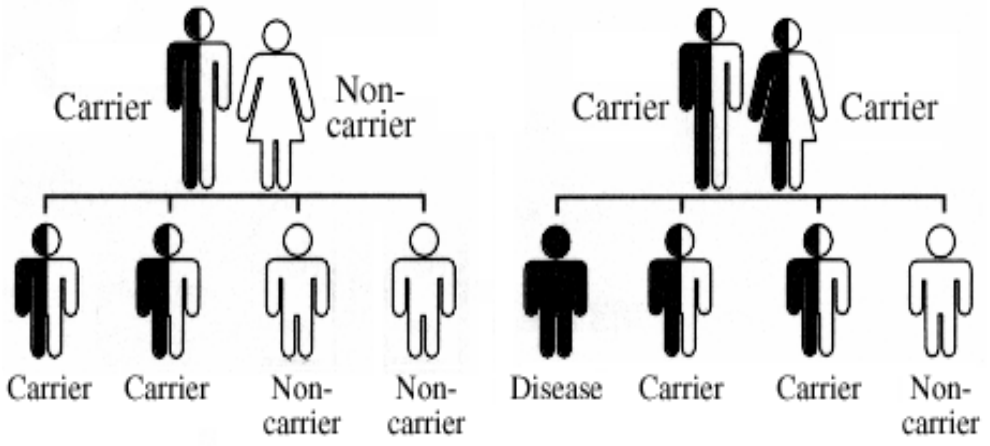
1) Explain the pathology of single gene autosomal recessive disorders

1.0. INTRODUCTION

- Require that both copies of the inherited gene carry mutations
- Mutations may be passed on by carriers
- Typically not seen in every generation of an affected family

2.0. TRANSMISSION (MODE OF INHERITANCE)

Diagram 4.1: Transmission of autosomal recessive disorders



Examples

- Albinism; Congenital deafness; Cystic Fibrosis; Sickle cell disease; Storage disorders e.g. Gaucher's disease; Thalassemia; Wilson's disease

3.0. INDIVIDUAL DISORDERS

1) ALBINISM

Introduction

- A disease in which a person has partial or complete loss of pigmentation (colouring) of the skin, eyes and hair
- Consists of a group of inherited abnormalities of melanin synthesis and are typically characterized by a congenital reduction or absence of melanin pigment
- Albinism results from defective production of melanin from tyrosine through a complex pathway of metabolic reactions

Pathogenesis

- Inheritance of a mutation of **TYR gene** located on chromosome 11q and gene for P protein

Pathophysiology

- TYR gene gives instructions for synthesis of **tyrosinase enzyme** located in the **melanocytes**
- It is used to convert the amino acid tyrosine into pigment molecules called **melanin** that gives colour to the skin, hair, and eyes
- Number of melanocytes is normal but melanin produced is reduced or absent
- P protein is a melanosomal membrane protein involved in the transport of tyrosine prior to melanin synthesis
- Two other enzymes involved in the formation of eumelanin are tyrosinase-related protein 1 (TRP1; DHICA oxidase) and tyrosinase-related protein 2 (TRP2; dopachrome tautomerase) coded on chromosome 9
- Mutation to the *TRP1* gene causes OCA 3
- Mutation to the *TRP2* gene does not produce albinism.

Pathology

- Deficiency of melanin pigment in the body

Types

	Type	**Subtype**	**Gene, affected protein**
1.	Type I –OCA 1 Occulocutaenous albinism OCA 1	OCA 1A (tyrosinase-negative OCA	Tyrosinase
		OCA 1B (yellow-mutante)	
		OCA 1A/1B heterozygote	
2.	Type II - OCA 2 (tyrosinase-positive) – most prevalent		P protein
3.	Type III- OCA 3		Tyrosinase-related protein
4.	Type IV – OA1 Ocular albinism OA1		
5.	Type V -AROA autosomal recessive ocular albinism		Tyrosinase in some cases P protein in some cases

Clinical Features

Ocular Albinism

- Hypopigmentation of the fundus with clearly visible choroidal vessels, foveal hypoplasia, hypopigmentation of the iris, strabismus, nystagmus, photophobia, absent stereoacuity and high refractive errors including hypermetropia , vision may be near normal but usually worse, reduced visual acuity

Oculocutaneous Albinism

- Snow-white skin; snow-white hair, no pigment in their eyes, iris is a pale bluish pinkish colour, while the pupil may actually be red (from light entering the pupil and reflecting off of blood vessels in the retina, the light-sensitive layer of tissue lining the back of the eyeball

Complications

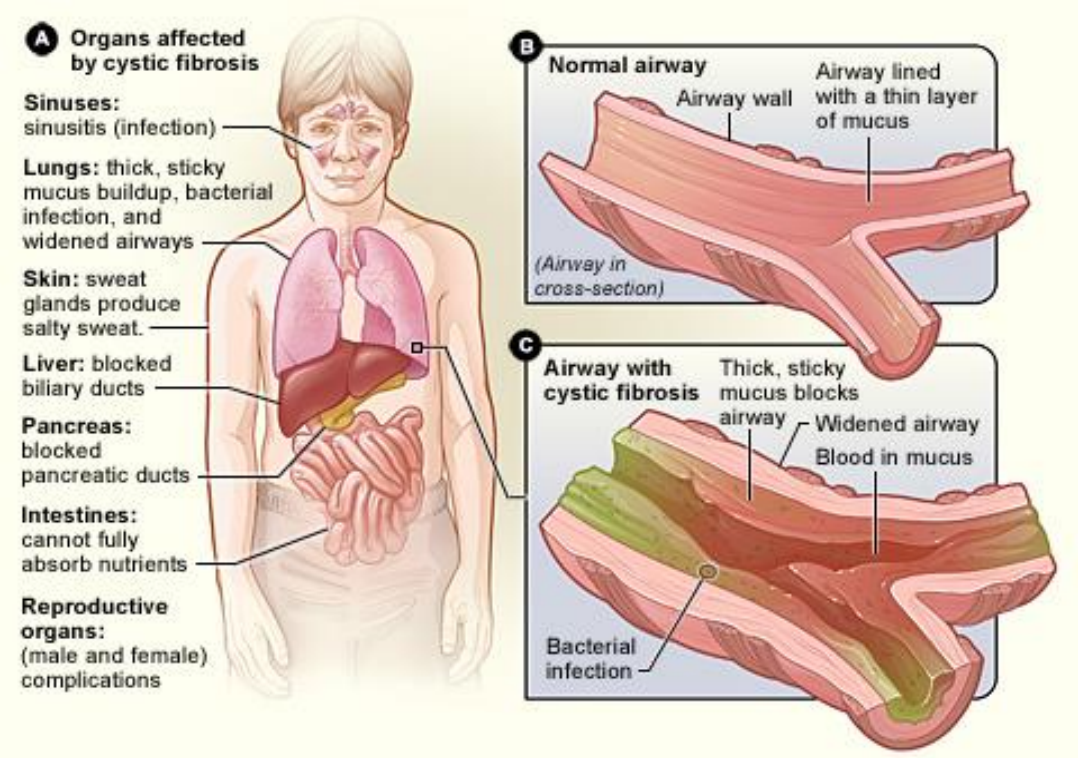
i. Non-melanoma skin cancers in keratinocytes
ii. Risk for squamous cell carcinoma
iii. Premature skin aging

2) CYSTIC FIBROSIS

Introduction

- Life threatening disease associated with production of thick, sticky mucus that builds up in the lungs, digestive tract, and other areas of the body
- The disease is marked by mucus hyper production and plugging in many organs

Diagram 4.2: Organs affected in Cystic Fibrosis



Pathogenesis

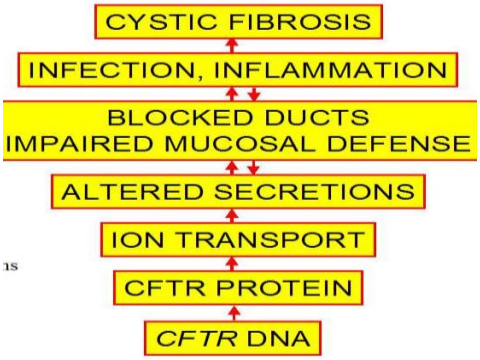
- Inheritance of mutant transmembrane conductance regulator **(*CFTR)*** gene located on chromosome 7

Pathophysiology

- Transmembrane conductance regulator **(*CFTR)*** gene encodes for a protein that functions as a chloride channel and regulates the flow of other ions across the apical surface of epithelial cells
- *CFTR* is regulated by cAMP[1] so its mutation result in abnormalities of cAMP-regulated chloride transport across epithelial cells on mucosal surfaces

[1] cyclic adenosine monophosphate

- In non-cystic fibrosis individuals, the affected chloride channels are found in the cells lining the epithelium of the respiratory and gastrointestinal tract whereas in cystic fibrosis there are no chloride ion channels and the chloride ions are trapped within the cell
- There is decreased secretion of chloride and increased reabsorption of sodium and water across epithelial cells
- This results in reduced height of epithelial lining fluid and decreased hydration of mucus results in formation of thick sticky mucus
- Secretions in the respiratory tract, pancreas, GI tract, sweat glands, and other exocrine tissues have increased viscosity, which makes them difficult to clear.



Pathology

- Abnormality of chloride channels and chloride transport system

Clinical Features

1) New-borns – delayed growth, failure to gain weight normally during childhood, no bowel movements in first 24 to 48 hours of life, salty-tasting skin
2) Bowel function - abdominal pain, abdominal distention, severe constipation, increased gas, bloating, nausea and loss of appetite, stools (mucoid, pale or clay coloured, foul smelling), weight loss
3) Lungs and sinuses - coughing or increased mucus in the sinuses or lungs, fatigue, nasal congestion caused by nasal polyps resulting in recurrent episodes of pneumonia
4) Infertility (in men)
5) Repeated inflammation of the pancreas (pancreatitis)

Complications

1) Respiratory system - recurrent chronic respiratory infection e.g. pneumonia, sinusitis, haemoptysis
2) GIT - such as gallstones, intestinal obstruction and rectal prolapse
3) Endocrine - Diabetes
4) Reproductive system - Infertility
5) Hepatobiliary system - liver failure, pancreatitis, biliary cirrhosis
6) Malnutrition
7) Musculo-skeletal system – osteoporosis and arthritis
8) Pneumothorax
9) Right-sided heart failure (cor pulmonale)

3) SICKLE CELL DISEASE (SCD)

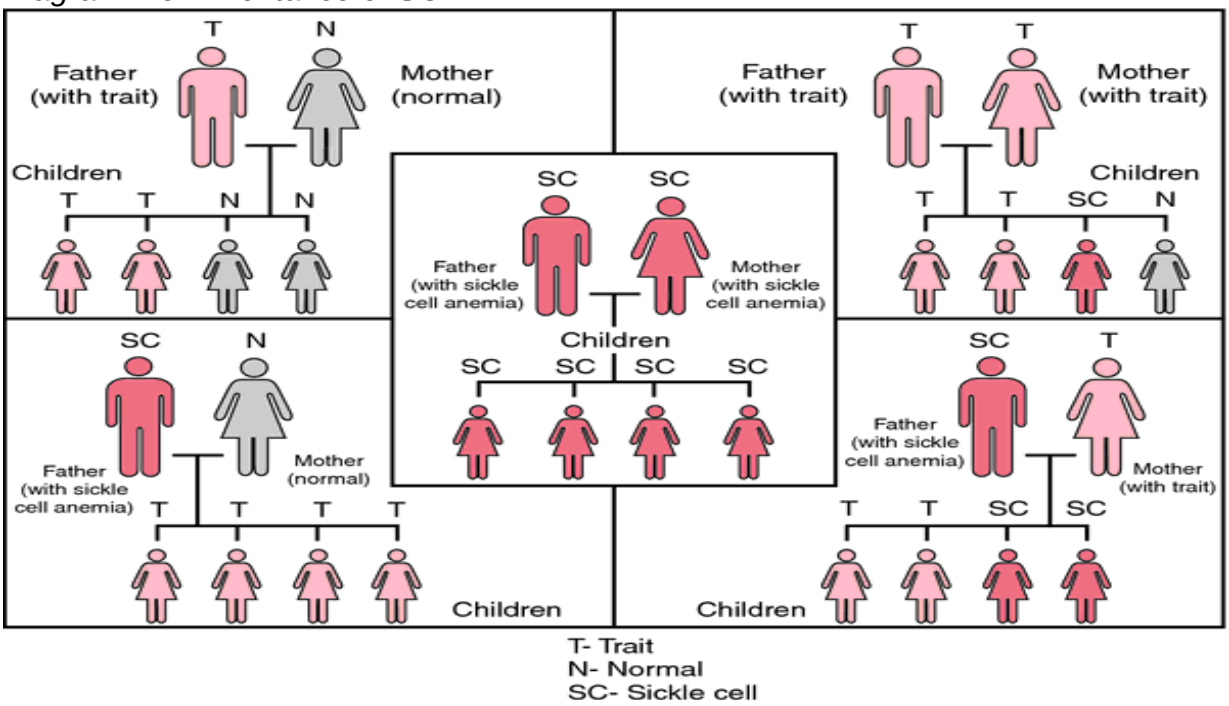
Introduction

- Sickle cell disease describes a group of inherited blood disorders associated with an abnormal haemoglobin characterized by chronic anaemia, painful events (crises), and various complications due to associated tissue and organ damage
- Characterized by red blood cells that assume an abnormal, rigid, sickle shape.
- Red blood cells with normal hemoglobin are smooth, disk-shaped, and flexible
- Normal red blood cells typically live 90-120 days, but sickle cells only survive 10-20 days
- The normal haemoglobin include HbA(2a, 2 b), HbA

Inheritance

- Inherited from parents in much the same way as blood type

Diagram 4.3: Inheritance of SCD

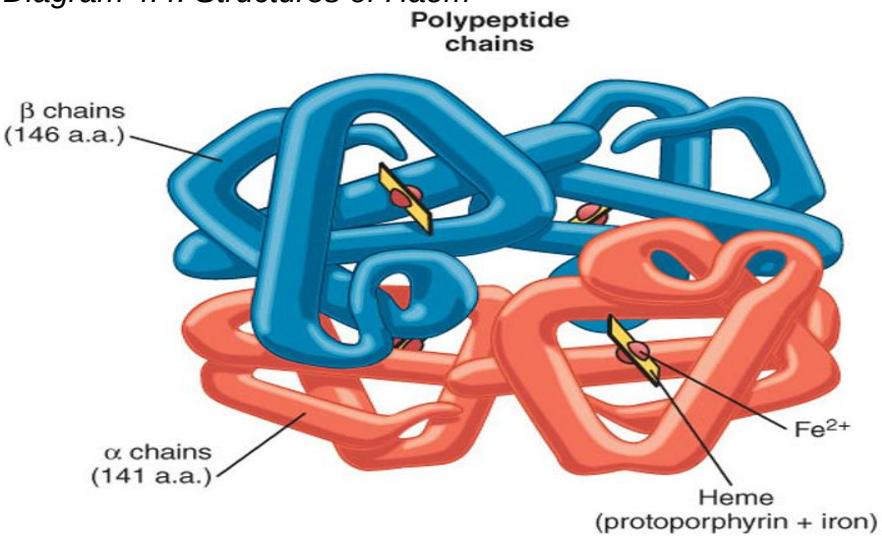


Haemoglobin

- Haemoglobin molecule has four globin subunits linked at a specific site to a haem group composed of an iron atom surrounded by a porphyrin ring.
- Consists of 2 pairs of coiled polypeptide chains and 4 prosthetic haem groups
- Four polypeptide chairs exist viz α, β, γ, δ (determined by sequences of amino acids).
- Haemoglobin comprises of the haem component (made up of pyrrole rings and contains Fe) that transports oxygen and globin, which is made up of chains of amino acids and facilitates oxygen transportation by the haem by providing a suitable environment. 100 mls of aerated blood (oxygenated) carries 19 mls of oxygen in Hb and 0.3 mls in solution of plasma

- Normal Hb[2] consists of a pair of alpha (α) chains and another pair of either beta (β) chains or gamma (γ) chains or delta (δ) chains
- Distribution of Hb types in a normal red blood cell - HbA (adult) which accounts for, 96-98%, HbF (foetal) - 0-10% and HbA_2 that is 1.5 – 3%
- Haemoglobin molecule undergoes structural changes during oxygen uptake & release
- In a deoxygenated state the beta chains rotate apart facilitating the functional properties of haemoglobin
- Important features of the oxygen transport system are:
  1) Hb has a high affinity for oxygen in the lungs and a low affinity for oxygen in tissues.
  2) Myoglobin has a higher affinity for oxygen than Hb at low oxygen concentrations
  3) Haemoglobin transports carbon dioxide back to the lungs where it is expelled.
  4) Haemoglobin releases its oxygen preferentially to exercising muscle rather than to resting muscle

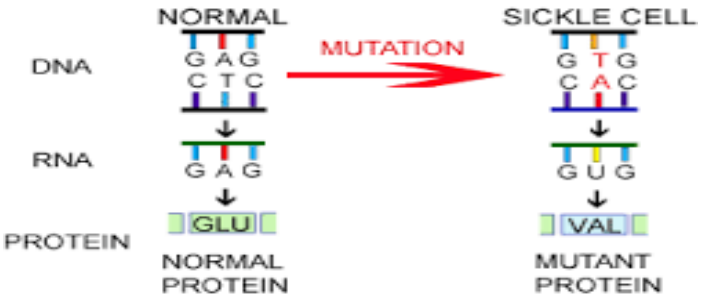
Diagram 4.4: Structures of Haem



HbA (2α and 2β); HbA_2 (2α and 2δ) and HbF(2α and 2γ)

Pathogenesis

- Sickle cell disease is an inherited, autosomal recessive, condition caused by point mutation in the β-globin gene on chromosome 11 (single nucleotide change (GAT to GTT)
- The mutation causes the sixth amino acid to be changed from glutamic acid to valine



[2] Haemoglobin

- Symptoms usually do not develop until the age of 6-12 months because of high levels of circulating fetal hemoglobin
- After infancy, erythrocytes of patients with sickle cell anemia contain approximately 90% hemoglobin S (HbS), 2-10% hemoglobin F (HbF), and a normal amount of minor fraction of adult hemoglobin (HbA2). Adult hemoglobin (HbA), which usually gains prominence at the age of 3 months, is absent

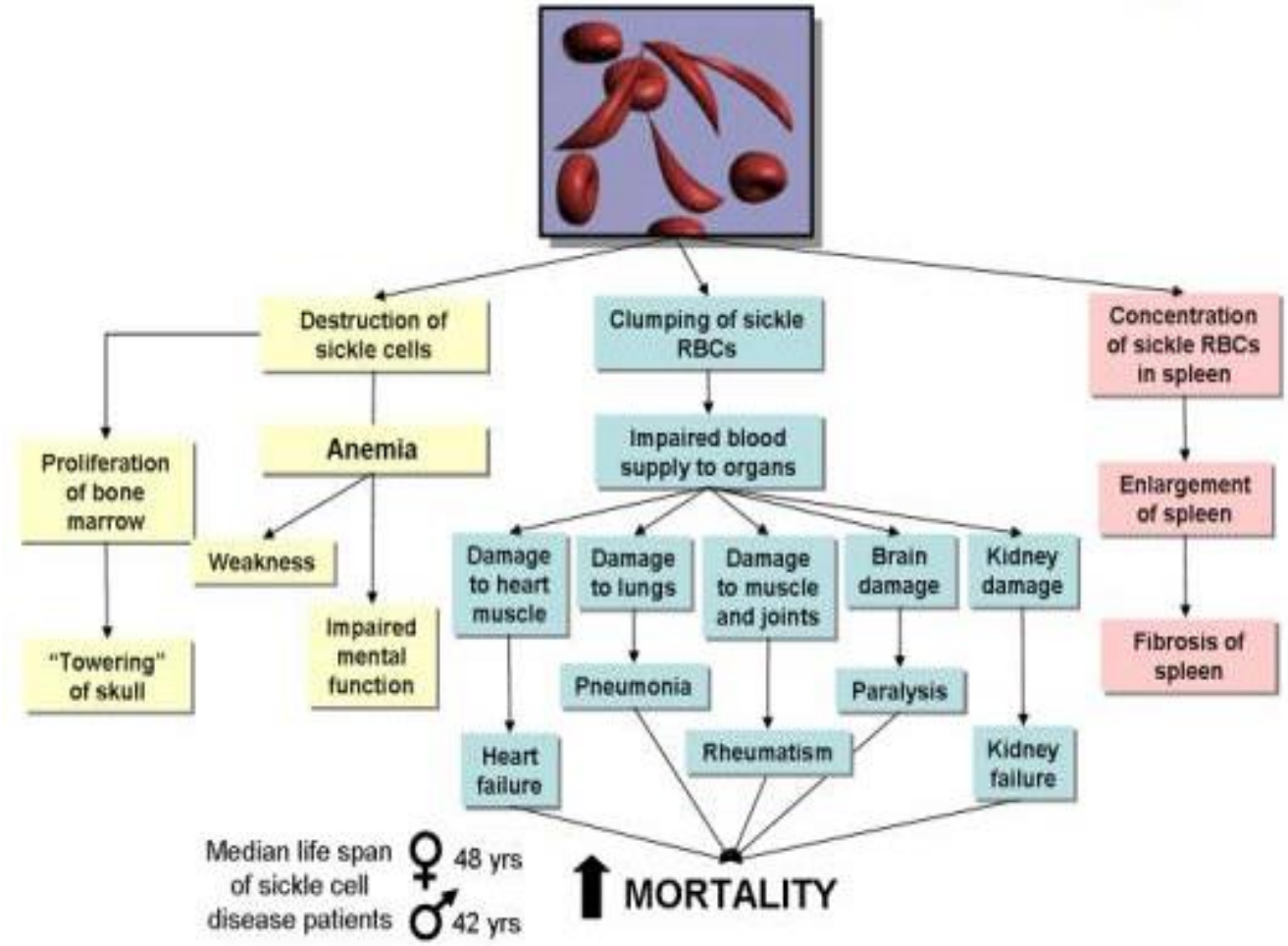
Pathophysiology

- Normal RBCs are quite elastic, which allows the cells to deform to pass through capillaries
- Loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease
- The resultant haemoglobin (called HbS) has abnormal physiochemical properties, and is prone to polymerization with other haemoglobin molecules under conditions of low oxygen tension
- The normally freely flowing cytosol of red cells become viscous making the red cell much less deformable and impairing its ability to traverse tight capillary beds
- As HbS continues to polymerize the entire RBC is deformed giving the characteristic sickle shape
- Under deoxy conditions, HbS undergoes marked decrease in solubility, increased viscosity, and polymer formation which distorts red blood cells into a sickle shape and decreases their elasticity
- Low-oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decreases the cell's elasticity
- The cells fail to return to normal shape when normal oxygen tension is restored and these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia
- Low oxygen tension in the spleen accelerates sickling & destruction of red blood cells
- The bone marrow attempts to compensate by creating new red cells, it does not match the rate of destruction resulting in haemolysis and subsequently anaemia

Mechanisms of Haemolysis

- Extravascular haemolysis accounts for 2/3 of the destruction of red cells and mediated by IgG antibodies and carried out by the macrophages (phagocytosis)
- Intravascular haemolysis accounts for 1/3 of cases of red cell destruction and usually fuelled by increased mechanical fragmentation and changes in proteins in the cell membranes

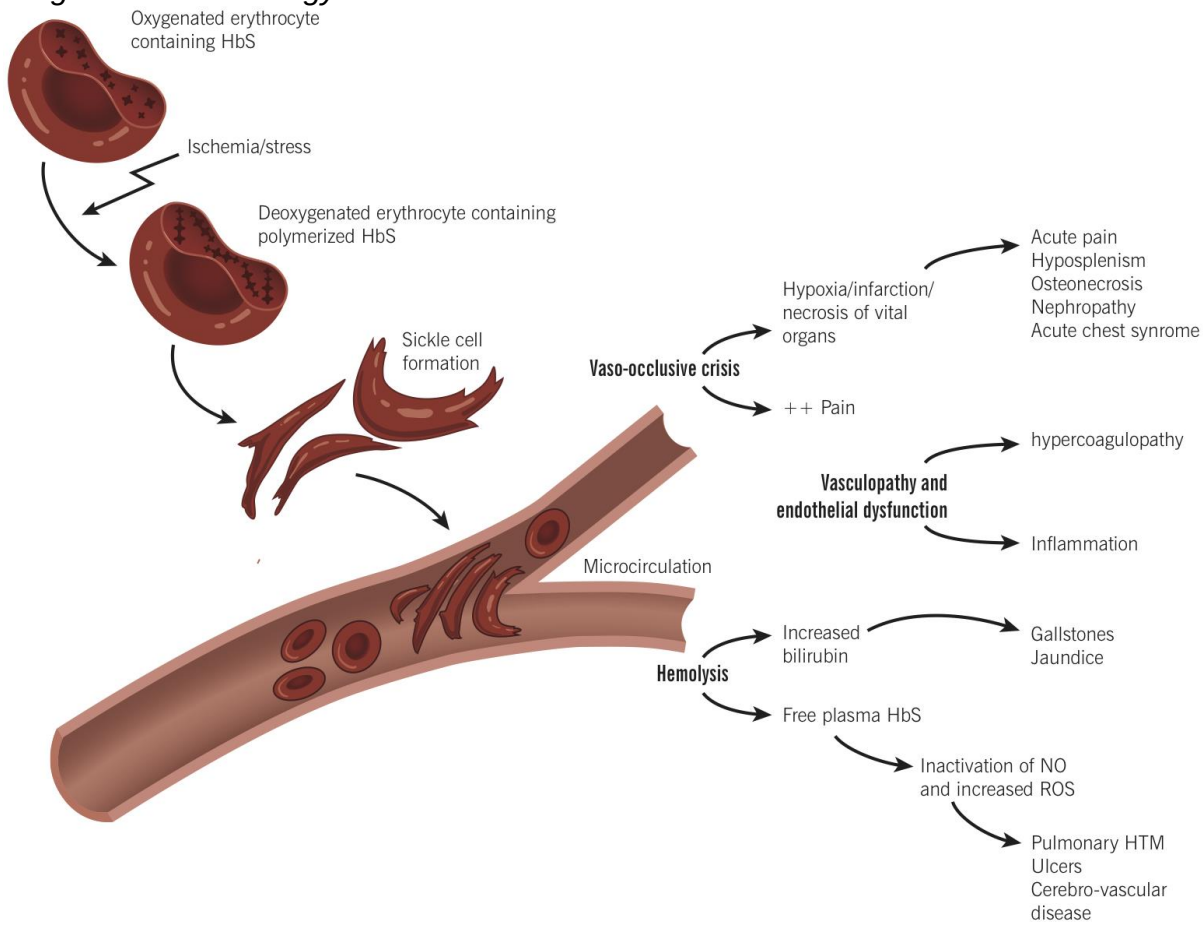
Diagram 4.5: Consequences of Sickling



Pathology

- The changes in RBCs result in a disease with the following cardinal signs i.e. hemolytic anemia, painful vaso-occlusive crisis and multiple organ damage from micro infarcts, including heart, skeleton, spleen, and central nervous system
- When the alpha chains move apart to give up oxygen the amino acid substitution leads to locking of the adjacent ends of alpha chains with the abnormal beta chains
- The Hb molecules become stuck in rows distorting the red cells forming sickle shapes in deoxygenated blood
- This facilitates destruction of red blood cells
- Hbs gives up oxygen more readily than HbA hence provides good tolerance to exercise at low Hb levels
- Intravascular sickling of red blood cells leads to multiorgan dysfunction

Diagram 4.6: Pathology of Red Blood Cells



Clinical Features

1) Severe anaemia – due to haemolysis and sequestration
   - Sickle cells are mechanically weak and are prone to intravascular hemolysis
   - More important mechanism leading to decreased red cell survival time is the extravascular hemolysis that occurs when inflexible cells are trapped in the spleen and phagocytosed by the reticuloendothelial systemBone marrow tries to compensate by increasing RBC production but it cannot match the rate of destruction.
   - Complications of increased hemolysis include **cholelithiasis** due to excessive bilirubin production

2) Vaso-occlusive complications – blockage of blood vessels leading to ischaemia
   - Due to the deformed shape, HbS induces RBC membrane damage leading to calcium influx into the cell
   - Calcium influx leads to crosslinking of the membrane proteins and activating channels that allow for the efflux of potassium and water from the cell
   - This leads to RBC dehydration exacerbating the sickling
   - Vaso-occlusive crisis results from the sickle red cells obstructing and reducing blood flow to the vital organs leading to ischemia, necrosis and pain
   - Repeated episodes lead to **bone infarction and necrosis**; and **bone marrow degeneration** occurs overtime

- Long bones are affected most commonly, but pain episodes can affect any bone marrow-containing structure, including the ribs, sternum, vertebral bodies, and skull
- **Pulmonary fat embolism** can be a life threatening complication of bone marrow infarction in patients with SCD and precipitate Acute Chest Syndrome (ACS)
- Hemoglobin released from hemolyzed cells readily binds to and depletes NO, leading to vascular smooth muscle cell contraction and enhanced platelet aggregation
- Occlusions lead to further hypoxia within the tissue, setting up conditions for a vicious cycle in which further sickling and hypoxia occur.

3) Jaundice (chronic hyperbilirubinemia)

4) Infections
   i) **Encapsulated bacterial infections**
      - Splenic sequestration of sickle cells leads to splenic congestion, as manifested by splenomegaly, and reduced immune function
      - The spleen is important for macrophage phagocytosis of encapsulated bacteria, thus patients with SCD are prone to **bacteremia** with pathogens like *Streptococcus pneumoniae (S. pneumoniae), Haemophilus Influenzae (H. Influenzae)* and *Neisseria meningitidis (N. Meningitidis)*
      - These pathogens, normally causing localized disease, may cause life-threatening sepsis in patients with sickle cell disease.Furthermore, patients with SCD develop **pneumonias**, predominantly from atypical organisms, such as, *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella*. Respiratory viruses are also common causes of pulmonary infection, while *S. pneumoniae* and *H. influenza type b* are uncommon
      - **Osteomyelitis and septic arthritis** can affect minority of patients with SCD due to both, bone damage and poor splenic function. Leading pathogens include *Salmonella*, *S. Aureus* and other gram negative bacteria

   ii) **Autosplenectomy**
      - Continued splenic dysfunction eventually leads to infarction and loss of splenic function, which is referred to as **autosplenectomy** or **functional asplenia**

   iii) Dysfunctional complement system has been proposed to contribute to the infectious complications in SCD

5) Crises
   i) Infarctive/vaso-oclusive/thrombotic
      - Results from blockage of small blood vessels causing ischemia and infarction
      - Hypoxia and infarction associated with pain in the affected region (pain crises)
      - Triggered by infection, dehydration, and acidosis
      - Common sites of involvement are bones (hand and foot syndrome a dactylitis of bones of the hands or feet, osteomyelitis), lungs, brain, liver, spleen and penis.

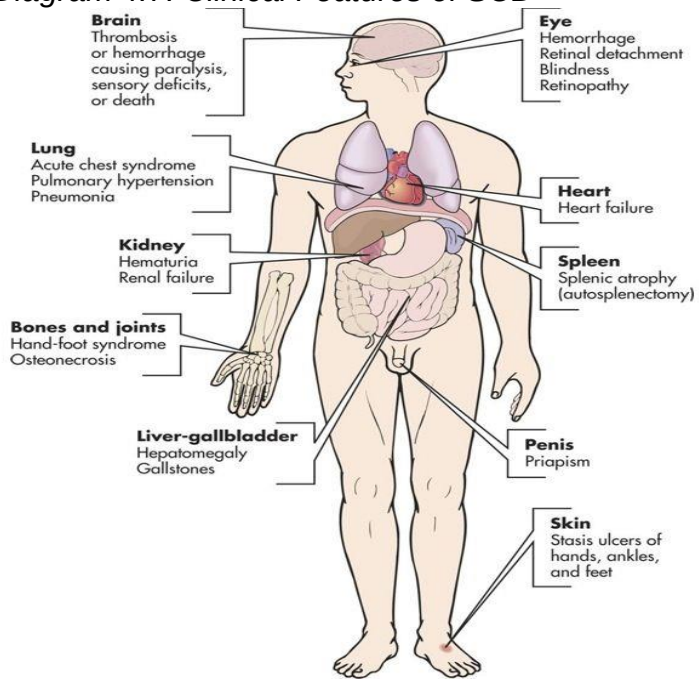
   ii) Acute chest syndrome
      - Occurs when the lungs are deprived of oxygen during a crisis
      - It can be very painful, dangerous, and even life threatening

iii) Haemolytic crisis
- Results from accelerated rate of haemolysis usually peopled by infection and can also be part of the infective crises

iv) Anaplastic crisis
- Occurs due to bone marrow failure causing severe anaemia with associated infections
- There is reduced bone marrow erythropoiesis
- Reticulocytes disappear from the peripheral blood causing sudden and rapid worsening of anaemia

v) Sequestration crisis
- Occurs in young children with an intact spleen
- There is sudden massive pooling of blood in the spleen resulting is severe anaemia and circulatory collapse

Diagram 4.7: Clinical Features of SCD

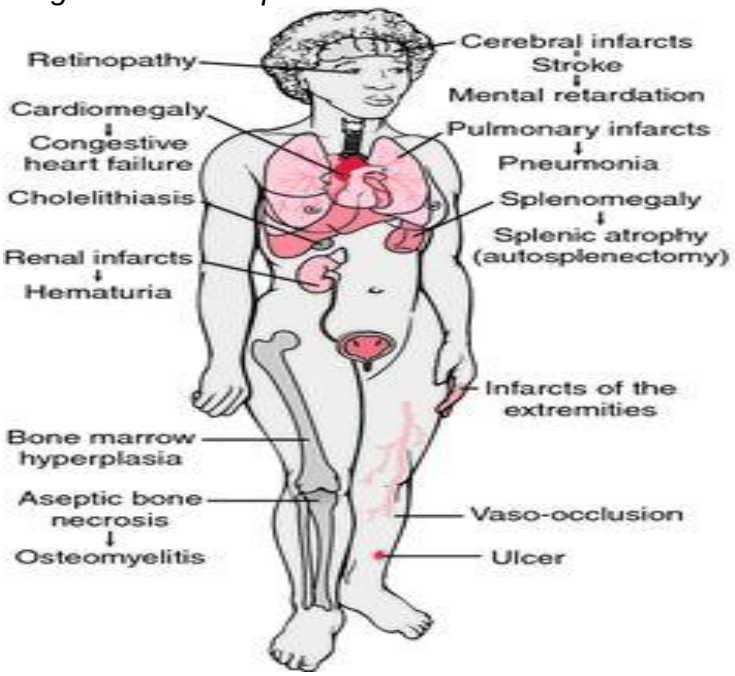


Complications

i. Recurrent SCD crises
ii. Acute infections
iii. Haematological (Haemolytic anaemia)
iv. Cardiopulmonary – cardiac failure, ischaemic heart disease, pneumonia,
v. Renal – renal failure, nephrotic syndrome
vi. Obstetric/gynaecologic, , priapism, delayed development of secondary sexual characteristics,
vii. Skeletal – dactylitis, osteomyelitis
viii. Skin – infections, abscess, ulcers
ix. Reticulo-endothelial system – reduced immunity
x. Central nervous system – stroke, haemorrhage, convulsions

xi. Hepatobiliary system – jaundice, liver failure, liver abscess, gall stones

Diagram 4.8: Complications of SCD



4) THALASSEMIA

Introduction

- An inherited disorder associated with abnormal haemoglobin and anaemia
- Humans have different haemoglobins at various stages of development
- Normal adults have a major component of HbA (90%), minor HbA_2 (2–3%) and HbF
- Main haemoglobin in foetal life is HbF, traces of which are found in normal adults

Pathophysiology

- Result from inherited defects in the synthesis of the globin chains of haemoglobin
- Result from mutations that involve either the α or β globin genes
- In β –thalassemia there is reduced synthesis of β globin chains resulting in diminished synthesis of HbA
- There are three varieties of β thalassemia namely – *β thalassemia major, intermedia and minor*.
- α Thalassemia is characterized by reduced or absent α-globin chains

Clinical Features

- Pallor, irritability, growth retardation, abdominal swelling – splenomegaly and hepatomegaly, jaundice and facial and skeletal changes