Preface

Dear student,

Before you lies the booklet for Theme 3 of Semester 1 of Year 1 Medicine at the University of Manchester. Slim Academy has summarized the most important study material for you, so that you can study as pleasantly as possible. We wish you the best of luck with your studies!

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Team Slim Academy

P.S. This summary has been written based on the author's own interpretation. It remains a summary and should be seen as a supplement to the required study materials — not a replacement

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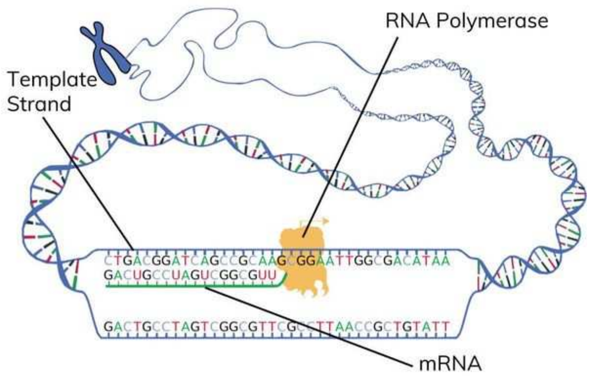
Innate immune system and Mendelian Inheritance

Each chapter is based on the respective ILO. The ILO's can be found on Canvas. Because of copyright protection we will no longer copy the ILO's in this booklet. We recommend you find yourself the ILO's and keep them next to the summary.

Chapter 1 - Transcription and Translation in Protein Synthesis

Introduction
Transcription and translation allow genetic information encoded in DNA to be converted into functional proteins. Transcription occurs in the nucleus, producing mRNA from a DNA template, while translation takes place in the cytoplasm, where the mRNA sequence is decoded by ribosomes to synthesize a polypeptide chain. Together, these processes ensure the accurate transfer of genetic information from DNA to functional proteins.

Transcription

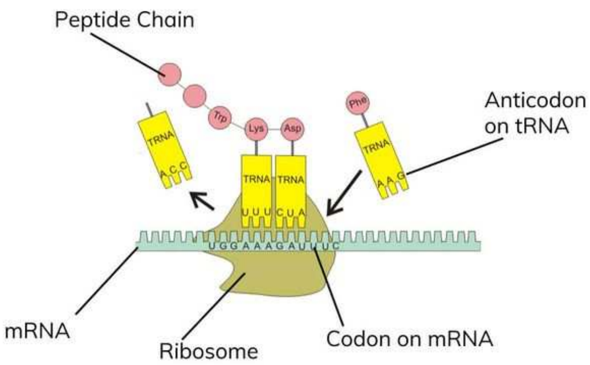


Transcription. *Source: https://senecalearning.com/*

Transcription is a cellular process whereby genetic information encoded in DNA is transcribed into messenger RNA (mRNA). This enables the genetic code to be transferred from the nucleus to the cytoplasm, where it is involved in protein synthesis. Transcription is initiated by the enzyme RNA polymerase when it binds to a specific DNA sequence known as the promoter region, which is the recognition and initiation site for transcription and determines the template strand to be used.

As RNA polymerase moves along the DNA template, it unravels the double helix structure and synthesizes a complementary RNA strand by forming RNA nucleotides with their corresponding DNA bases. The initial RNA transcript or pre-mRNA, contains both non-coding sequences (introns) and coding sequences (exons). After it reaches the termination sequence, RNA polymerase releases the pre-mRNA. Before it leaves the nucleus, the pre-mRNA goes through several processing steps: a 5' cap is added, a polyadenylated (poly-A) tail is added at the 3' end, and introns are removed through splicing. These steps signal the transition from pre-mRNA to mature mRNA. The mature mRNA is then transported through the nuclear pore into the cytoplasm to serve as a template for protein synthesis.

Translation



Translation. *Source: https://senecalearning.com/*

Translation is a process in which the nucleotide sequence of mRNA is used to synthesize a polypeptide chain, to form a functional protein. This process occurs within the cytoplasm and consists of three principal stages: initiation, elongation, and termination.

During initiation, the ribosome attaches at the start codon of the mRNA which is AUG. The initiator tRNA, recognizes the start codon and enters the ribosomal P site with the amino acid, methionine. Once the initiator tRNA is in place, additional tRNA molecules, each carrying a specific amino acid, enter the A site one by one. Their anticodons match the next codon on the mRNA, so that the correct amino acids are added in sequence. Energy from GTP helps these tRNAs bind properly and allow for the ribosome to move along the mRNA.

Throughout elongation, the ribosome translocates along the mRNA strand in a codon-by-codon manner. Corresponding tRNAs deliver their amino acids, and the ribosome catalyzes the formation of peptide bonds, thereby elongating the nascent polypeptide chain.

Termination occurs when the ribosome encounters a stop codon (UAA, UAG, or UGA) on the mRNA. Release factors then promote the breakdown of the ribosomal complex and detachment of the completed polypeptide.

Slim Summary!
• Transcription takes place in the nucleus and translation in the cytoplasm, together enabling the precise transfer of genetic information from DNA to functional proteins, which are essential for cellular structure and function.

Chapter 2 - Changes in DNA

Introduction

Humans possess 46 chromosomes: females have a 46,XX karyotype, while males have 46,XY karyotype. Each chromosome is composed of one short arm (p) and a long arm (q), separated by a centromere. Chromosomes 13, 14, 15, 21, and 22 are classified as acrocentric so they have centromeres positioned near one end. Therefore, their short arms consist predominantly of satellite DNA which refers to repetitive, non-coding sequences of DNA .

Chromosome structure is susceptible to breakage and rearrangement, which can occur within a single chromosome or between two chromosomes. The phenotypic consequences of change depends on the specific genes that are deleted, duplicated, or otherwise disrupted.

Truncating mutations

Truncating mutations result in the premature termination of protein synthesis or a complete absence of the protein. **Nonsense mutations** introduce a premature stop codon, leading to an incomplete protein product. **Frameshift mutations** arise from insertions or deletions which are not in multiples of three nucleotides which alter the reading frame and result in abnormal proteins. **Splice-site mutations** disrupt the normal pre-mRNA splicing, potentially causing the inappropriate retention of intronic sequences or the removal of essential exonic regions.

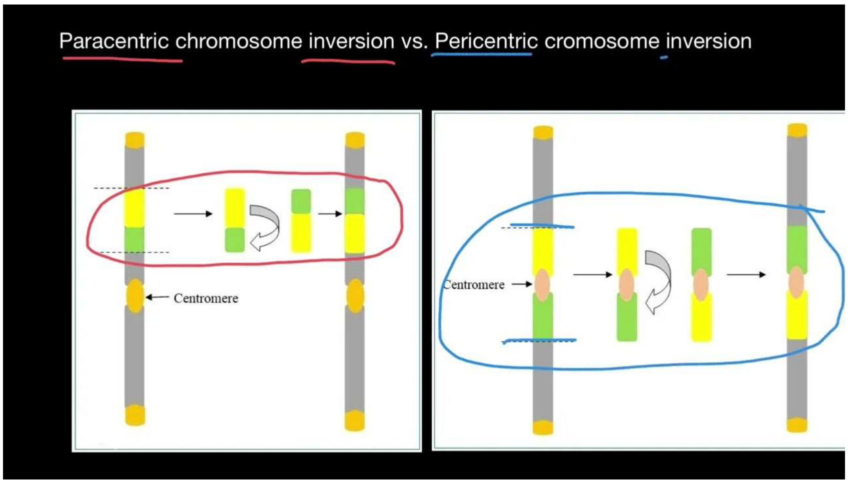
Non-truncating mutations

This type of mutation does not affect the overall length of the protein but can still cause functional impairment. **Missense mutations** substitute one amino acid for another, potentially altering protein formation, function, or stability. **Silent mutations** alter the DNA sequence without changing the encoded amino acid, and are generally considered to have minimal or no phenotypic effect. Repeat expansion disorders → such as Huntington's disease, result from excessive trinucleotide repeat expansions (e.g., CAG repeats). If it surpasses the normal threshold, it can lead to pathogenic consequences. Regulatory mutations can occur in promotors, enhancers, or other regulatory regions which can increase or decrease gene expression.

Structural chromosomal abnormalities

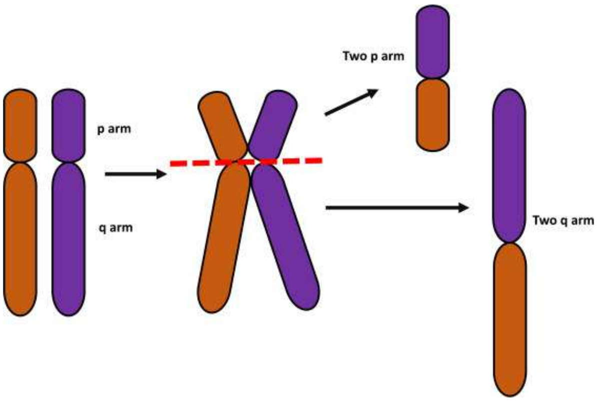
Changes in the physical structure of chromosomes, often caused by breakage and improper rejoining.

Inversions involve the reversal of a chromosomal segment. Pericentric inversions include the centromere, whereas paracentric inversions do not.



Paracentric vs. Precentric Inversion. *Source:https://www.youtube.com/watch?v=josbhCabsis*

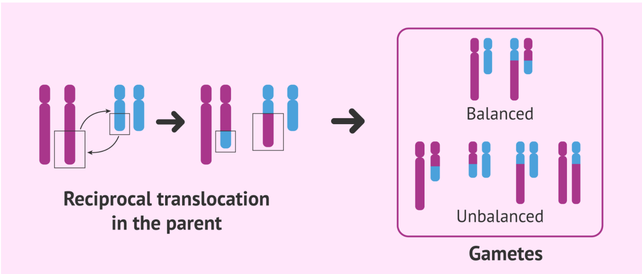
Isochromosomes arise when the centromere divides vertically instead of horizontally, producing chromosomes with two identical arms → either two short (p) arms or two long (q) arms.



Isochromosome. *Source: sciencedirect.com*

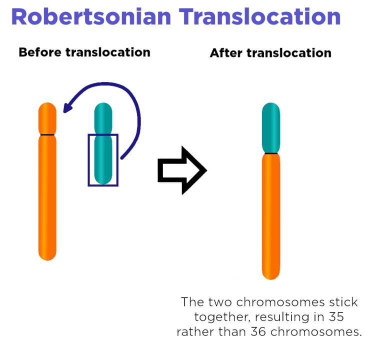
Translocations entail the exchange of chromosomal segments between chromosomes.

In balanced reciprocal translocations, segments are exchanged between non-homologous chromosomes without any net loss or gain of genetic material, resulting in a phenotypically normal carrier. However, during meiosis, the rearranged chromosomes may segregate unevenly, leading to unbalanced reciprocal translocations in gametes, which can result in miscarriage, congenital abnormalities, or developmental disorders in offspring.



Unbalanced vs. Balanced Translocation. *Source: https://www.invitra.com/*

Robertsonian translocations involve the fusion of the long arms of two acrocentric chromosomes with the loss of their short arms. Carriers of Robertsonian translocations are typically phenotypically normal but are at increased risk of producing offspring with unbalanced chromosomal complements. For example, the occurrence of Down syndrome is due to a 14:21 translocation.



Robertsonian Translocation. *Source: https://www.expii.com/*

Numerical Chromosomal Abnormalities
Arise when chromosomes fail to separate during cell division (meiosis or mitosis), resulting in aneuploidy (abnormal chromosome number) or polyploidy (additional complete chromosomal sets).

Aneuploidies involving sex chromosomes tend to have comparatively milder phenotypes.

- **Turner syndrome** (45,X) is typically associated with short stature, webbed neck, and gonadal dysgenesis;
- **Klinefelter syndrome** (47,XXY) frequently presents with tall stature, small testes, infertility, and occasionally gynecomastia.
- Individuals with triple X syndrome (47,XXX) or Jacob's syndrome (47,XYY) are usually phenotypically normal aside from increased stature;
- **Trisomy 21** (Down syndrome) is characterized by intellectual disability and distinct craniofacial features;
- **Trisomy 18** (Edwards syndrome) is associated with profound developmental delay, clenched fists, and rocker-bottom feet;
- **Trisomy 13** (Patau syndrome) manifests with midline facial anomalies, polydactyly, congenital heart and renal defects, and a high neonatal mortality rate.

Polyploidy, defined as the presence of additional complete chromosome sets. Triploidy (69 chromosomes) or tetraploidy (92 chromosomes) is incompatible with postnatal survival and commonly results in spontaneous abortion or stillbirth. The principal mechanisms underlying these conditions include nondisjunction which is the failure of chromosomes to segregate properly. Anaphase lag which is loss of a chromosome during cell division. Postzygotic mitotic errors, which may lead to mosaicism, wherein only a subset of cells contains the chromosomal abnormality.

Epigenetic Modifications
Epigenetic modifications regulate gene expression without altering the underlying DNA sequence. Acetylation of histone tails can result in a more relaxed chromatin structure, known as euchromatin, which is accessible to transcriptional machinery and facilitates gene expression.

However, excessive acetylation can result in aberrant activation of oncogenes, contributing to tumorigenesis.

Histone deacetylation compacts chromatin into heterochromatin, repressing gene expression and potentially silencing critical tumor suppressor genes, which can lead to the malignant transformation of cells.

Histone methylation exhibits context-dependent effects, either activating or repressing transcription based on the specific residues modified and the broader chromatin environment. Aberrant histone methylation patterns are frequently observed in various cancers and developmental disorders.

DNA methylation, particularly at CpG dinucleotides, leads to transcriptional silencing. Hypermethylation of promoter regions in tumor suppressor genes can result in their inactivation, whereas hypomethylation may promote oncogene activation and genomic instability.

Additional histone modifications, such as phosphorylation and ubiquitination, play essential roles in modulating protein function, including signal transduction, DNA repair, cell cycle regulation, and targeted protein degradation.

Nucleotide Substitutions
Nucleotide substitutions introduce changes at the DNA sequence level that can alter protein structure and function. Synonymous substitutions replace one nucleotide with another without affecting the encoded amino acid, and typically have minimal impact on protein function. Non-synonymous substitutions result in amino acid changes, which may disrupt protein conformation and activity. These substitutions can be classified as transitions, involving the exchange of a purine for another purine or a pyrimidine for another pyrimidine, or as transversions, which involve the substitution of a purine for a pyrimidine or vice versa. Transversions generally exert a more pronounced effect on protein function due to the greater chemical disparity between purines and pyrimidines.

Slim Summary!
• Humans have 46 chromosomes; abnormalities can be structural (mutations, inversions, translocations) or numerical (aneuploidy, polyploidy), affecting gene function and development; • Truncating mutations (nonsense, frameshift, splice-site) disrupt protein production, while non-truncating mutations (missense, silent) may alter function without changing length; • Chromosomal rearrangements include inversions, isochromosomes, and translocations, which can impact offspring even if carriers are phenotypically normal; • Epigenetic changes, such as DNA methylation and histone modifications, regulate gene expression and can contribute to disease without altering DNA sequence; • Nucleotide substitutions can be synonymous (no protein change) or non-synonymous (alter protein structure), with transitions and transversions affecting protein function differently.

Chapter 3 - Changes to protein function

Introduction
Genetic mutations are alterations in the DNA sequence, which can range from single nucleotide substitutions to larger insertions or deletions of genetic material. These changes can influence the process of protein synthesis, affecting protein structure, stability, function, and expression. While many mutations are neutral and do not result in phenotypic consequences, others can disrupt cellular homeostasis and contribute to disease pathogenesis. Mutations in DNA can manifest as point mutations, insertions, deletions, or modifications in regulatory elements that regulate gene expression.

Point Mutations
Point mutations involve the substitution of a single nucleotide base within the DNA sequence and are classified as follows:
- **Silent Mutations**: These mutations result in a codon change which does not change the encoded amino acid, thereby leaving the protein's function intact;
- **Missense Mutations**: A single nucleotide change which leads to the substitution of one amino acid for another within the protein sequence. This can impair protein folding, stability, or activity. An example of this is sickle cell anemia, whereby a glutamic acid to valine substitution in hemoglobin results in erythrocyte deformation;
- **Nonsense Mutations**: These mutations create a premature stop codon, resulting in truncated proteins that are typically nonfunctional due to incomplete polypeptide chains;
- **Frameshift Mutations**: Insertions or deletions of nucleotides which are not in multiples of three which can shift the reading frame, altering downstream amino acid sequences and producing nonfunctional proteins, as seen in certain cases of cystic fibrosis.

Regulatory Sequence Mutations
Mutations within regulatory DNA regions, such as promoters or enhancers, can disrupt the expression of genes. For example, within oncogenesis, overactivation of proto-oncogenes (oncogenic mutations) can promote unregulated cellular proliferation, while loss-of-function mutations in tumor suppressor genes can impair cellular growth control mechanisms.

Splice Site Mutations
Mutations at exon-intron boundaries can interfere with pre-mRNA splicing, leading to the incorrect inclusion or exclusion of exonic or intronic sequences. Such defects can often result in the synthesis of dysfunctional proteins and are found in various malignancies and neuromuscular disorders.

Post-Transcriptional mRNA Modifications

Following transcription, pre-mRNA undergoes several essential modifications to produce mature mRNA suitable for translation. Errors in these processes can compromise protein synthesis:

- **5′ Capping**: The addition of a methylated guanine cap at the 5′ end of the mRNA molecule is essential for mRNA transcript stability and efficient ribosome recognition during translation initiation.
- **Polyadenylation**: The attachment of a polyadenine tail at the 3′ end of the mRNA promotes translational efficiency;
- **Splicing**: Removal of introns and ligation of exons generates a mature mRNA template. This permits the generation of multiple protein isoforms into one gene, whereas splicing errors can lead to the production of multiple, non-functional proteins.

Consequences of Mutations on Protein Structure and Function

Alterations in DNA or mRNA processing can lead to a variety of deleterious effects on proteins:

- Structural Alterations: Mutations may disrupt proper protein folding, leading to instability or loss of function;
- Loss of Function: Truncations or conformational changes may render proteins incapable of performing their physiological roles, as observed with dysfunctional tumor suppressors;
- Gain of Function: Certain mutations produce proteins with constitutive activity or novel functions, a phenomenon frequently encountered in oncogenic processes;
- Dysregulation of Expression: Mutations affecting gene regulation can result in aberrant protein levels, disrupting cellular signaling and homeostasis.

Slim Summary!
• DNA Sequence Changes: mutations such as point mutations (silent, missense, nonsense), frameshifts, and regulatory or splice site mutations can alter protein structure, function, or expression, potentially leading to disease; • Post-Transcriptional Modifications – Processes like 5′ capping, polyadenylation, splicing, and RNA editing are essential for producing functional mRNA; errors can result in abnormal or nonfunctional proteins; • Protein Consequences – Mutations and RNA processing defects can cause misfolded proteins, loss or gain of function, and dysregulated expression, contributing to genetic disorders, cancers, and developmental abnormalities.

Chapter 4 - Mendelian patterns of inheritance

Introduction
This chapter describes how to interpret mendelian patterns of inheritance and define the associated risks in families.

Key concepts
Patterns of inheritance can involve dominant or recessive genes that cause disease. For every gene, each parent contributes a randomly selected allele to their offspring. This is defined as segregation. Separate genes are independently assorted, which means that separate genes for separate traits are passed to offspring independently unless the genes are linked. If genes are linked (on the same chromosome) then they are sorted as a unit. Note that when there is a percentage risk of offspring having the condition, the chance is the same for each child and does not increase or decrease for future offspring. Therefore, if there is, for example, a 50% chance of offspring having a condition, it does not necessarily mean that exactly half of the children will have the condition.

Autosomal dominant
In autosomal dominant inheritance, only one copy of the faulty allele is required to present with the condition.

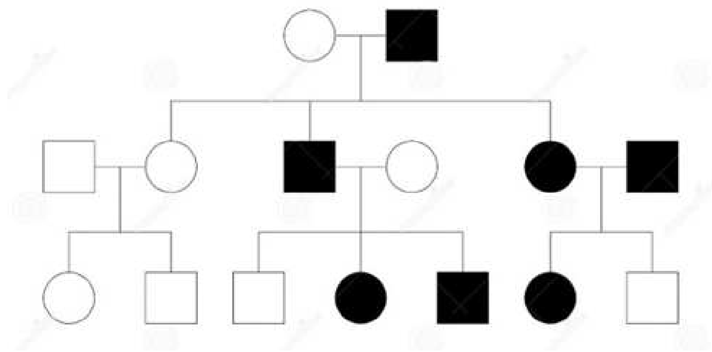
For example, if one parent has an autosomal dominant condition:

Parent Genotypes: Aa aa
Gametes: A a a a
Possible genotypes: Aa, aa (1:1)

	A	a
a	Aa	aa
a	Aa	aa

Autosomal dominant punnett square. *Source: SlimAcademy*

There is a 50% chance of each child having the condition.



Autosomal dominant pedigree diagram. *Source: dreamstime.com*

In an autosomal dominant pedigree, all affected children will have an affected parent. Males and females should be equally affected.
Examples of autosomal dominant conditions include autosomal dominant polycystic kidney disease and Huntington's disease.

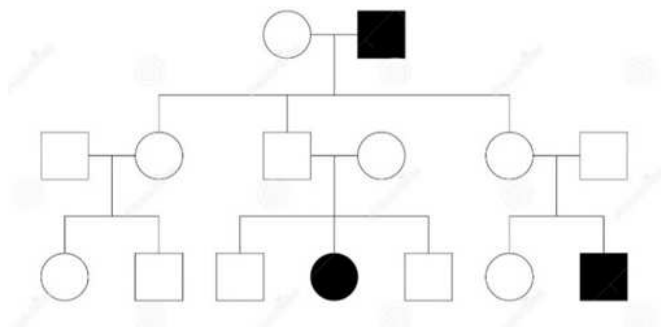
Autosomal recessive
In autosomal recessive inheritance, two copies of the faulty allele are required for the condition to present. Carriers will have one copy of the faulty allele but won't present with the condition.
For example, if both parents are carriers of the recessive faulty allele:

Parent genotypes: Bb Bb
Gametes: B b B b
Possible genotypes: BB, Bb, bb (1:2:1)

	B	b
B	BB	Bb
b	Bb	bb

Autosomal recessive punnett square. *Source: SlimAcademy*

There is a 25% chance for each child of having the condition.



Autosomal recessive pedigree diagram. *Source: dreamstime.com*

In an autosomal recessive pedigree, there are affected children with unaffected parents. Males and females should be equally affected.
Cystic fibrosis is an example of an autosomal recessive condition.

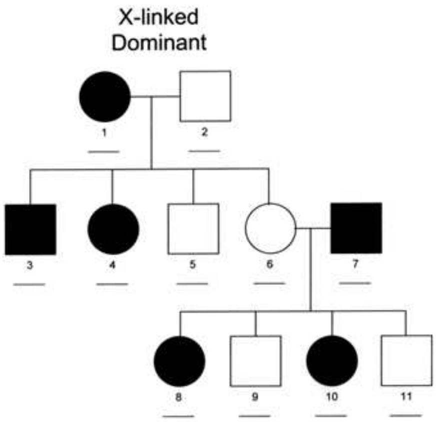
X-linked dominant
In X-linked dominant inheritance, only one affected X chromosome is required to present with the condition.
For example, if the father has the condition:

Parent genotypes: X^RY X^rX^r
Gametes: X^R Y X^r X^r
Possible genotypes: X^RX^r, X^rY (1:1)

	X^R	Y
X^r	X^RX^r	X^rY
X^r	X^RX^r	X^rY

X-linked dominant punnett square. *Source: SlimAcademy*

All daughters will have the condition, whilst no sons will have the condition. Therefore, there is no male-male transmission, because a son will always inherit the Y chromosome from his father, not the affected X chromosome. This is shown in individual 6 and 7's offspring in the pedigree diagram below, where 7 is an affected father.



X-linked dominant pedigree diagram. *Source: migrc.org*

In an X-linked dominant pedigree diagram, generally more females are affected than males. As mentioned before, there is also no male-to-male transmission because sons always inherit the Y chromosome from their father. If a male is affected, it is because they inherited the affected X chromosome from their mother.

Examples of X-linked dominant conditions are Rett syndrome and fragile X syndrome.

X-linked recessive

In X-linked recessive inheritance, women require two affected X chromosomes to present with the condition, whilst men only require one affected X chromosome as they do not have a second X chromosome to compensate. Women with one affected X chromosome are carriers of the condition but do not present with it.

For example, if the father has the condition:

Parent genotypes: X^gY X^GX^G

	X^g	Y
X^G	X^GX^g	X^GY
X^G	X^GX^g	X^GY

X-linked recessive punnett square. *Source: SlimAcademy*

There is a 0% chance of offspring presenting with the condition, but all the daughters will be carriers. Like in X-linked dominant inheritance, there is no male-to-male transmission as sons always inherit the Y chromosome from their father and not the affected X chromosome.

Then, if one of the carrier daughters has offspring:

Parent genotypes: X^GY X^GX^g

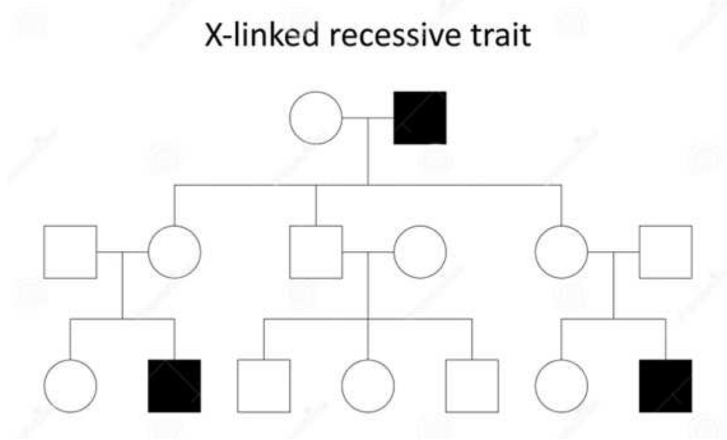
Gametes: X^G Y X^G X^g

Possible genotypes: X^GX^g, X^GX^G, X^GY, X^gY (1:1:1:1)

	X^G	Y
X^G	X^GX^G	X^GY
X^g	X^GX^g	X^gY

X-linked recessive punnett square. *Source: SlimAcademy*

Sons will have a 50% chance of having the condition. No daughters will present with the condition, but some may end up being carriers.
This is shown in the pedigree diagram below.



X-linked recessive pedigree diagram. *Source: dreamstime.com*

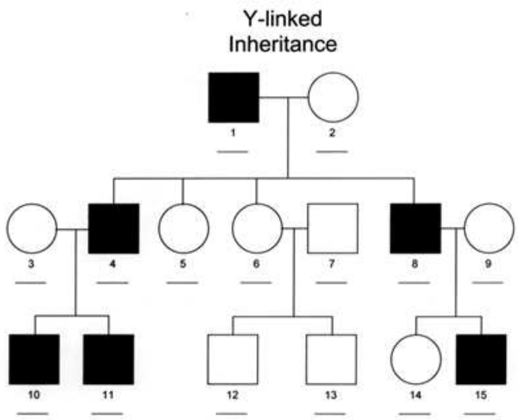
In an X-linked recessive pedigree, much more males tend to be affected than females. With an affected male, the transmission of the condition tends to skip a generation from grandfather to grandson due to the inheritance pattern explained above. There is also no male-to-male transmission which is also explained above. For a female to be affected, she must have both an affected father and an affected or carrier mother, which is quite rare. If an affected female has offspring, all her sons will also be affected, as sons always inherit their X-chromosome from their mother and both of the mother's X-chromosomes would be affected in this situation.
Examples of X-linked recessive conditions are haemophilia and Duchenne muscular dystrophy.

Y-linked
In Y-linked inheritance, only males are affected as only males possess a Y chromosome. If the father has the condition, his sons will always have the condition too as the affected Y chromosome is inherited from the father:

Parent genotypes: XY^d XX
Gametes: X Y^d X X
Possible genotypes: XY^d XX (1:1)

	X	**Y^d**
X	XX	XY^d
X	XX	XY^d

Y-linked recessive punnett square. *Source: SlimAcademy*



Y-linked pedigree diagram. *Source: migrc.org*

In a Y-linked pedigree, all sons with an affected father will have the condition. No females are affected as explained before. This is distinguishable from X-linked recessive inheritance because there is male-to-male transmission in Y-linked inheritance, but no male-to-male transmission in X-linked recessive.

Examples of Y-linked conditions are non-obstructive spermatogenic failure and webbed toes.

Slim Summary!
• Patterns of inheritance include dominant, recessive and sex chromosome linked patterns; • Cystic fibrosis is an autosomal recessive condition; • Each pattern of inheritance has identifiable features in pedigrees to distinguish the mode of inheritance.

Chapter 5 - Carrier frequencies

Introduction
This chapter defines carrier frequencies in the general population and calculates the associated risks with a focus on cystic fibrosis. Carrier frequency is the proportion of individuals in a population who carry a single copy of a specific recessive allele.

Carrier frequency of cystic fibrosis
Cystic fibrosis is an autosomal recessive condition. In the United Kingdom, over 2 million people are carriers of the faulty CFTR gene. This is approximately a 1 in 25 probability of being a carrier (carrier frequency). For offspring to inherit two faulty alleles and present with cystic fibrosis, both parents would have to be carriers of the condition. The probability of each parent being a carrier would be 1 in 25, so the probability that both are carriers would be 1 in 625:

1/25 x 1/25 = 1/625

Then, if both parents are carriers, there is a 25% or 1 in 4 probability that a child will inherit two faulty alleles and have cystic fibrosis.

1/625 x ¼ = 1/2500

Therefore, the average proportion of cystic fibrosis cases in all UK births would be expected to be 1/2500.

Slim Summary!
• Carrier frequency is the proportion of individuals in a population who carry a single copy of a specific recessive allele; • The average proportion of cystic fibrosis cases in all UK births is expected to be 1/2500, which is calculated using carrier frequency and the probability of having offspring with cystic fibrosis.

Chapter 6 - Ion transport

Introduction
This chapter outlines the mechanisms by which Na+, K+ and Cl- ions are transported across the cell membrane in relation to the function of the CFTR channel protein. All of these ions require proteins such as transporters, pumps or channels to cross cell membranes as they are polar molecules and cannot cross the phospholipid bilayer.

Basic transport mechanisms
Ions crossing a cell membrane down a concentration gradient can move by facilitated diffusion, where a molecule binds to a receptor on a protein channel in the membrane and causes it to open to let the ions move through. Active transport is used to transport ions against their concentration gradient and involves the use of ATP, making it an active process. An example of this is the active transport of sodium and potassium ions against their concentration gradients via the sodium-potassium pump in cell membranes. The sodium-potassium pump requires the hydrolysis of ATP to release energy. It transports three sodium ions out of cells and at the same time transports two potassium ions into cells. This is an essential process to maintain the electrochemical gradient across the cell membrane.

Ion transport and hydration of mucus
The Cystic Fibrosis Transmembrane Conductance Regulator is an ion channel which is usually present on the apical side of epithelial cell membranes. Chloride ions flow through it to cross the membrane down their concentration gradient.

To open the channel, ATP binds to the ATP binding domains and protein kinase A phosphorylates the regulatory domain. Chloride ions (Cl-) and bicarbonate ions (HCO^{3-}) are in higher concentrations inside the cell. This means that when the channel opens, they can flow out of the epithelial cells to the extracellular fluid through the channel by facilitated diffusion. Chloride ions primarily flow through the channel but the channel is still permeable to bicarbonate ions. Sodium ions (Na+) then flow out via a separate channel in order to maintain electrical neutrality. This is because the cells may become too positively charged if only negative ions leave, so positive ions leave as well.

The concentration of ions then increases in the extracellular fluid outside the epithelial cells and water potential consequently decreases. Water then flows out of the epithelial cells to the extracellular fluid via osmosis to maintain osmotic potential. The movement of water to the extracellular fluid is important to maintain the volume of extracellular fluid and hydrate the external mucus layer. Without this mechanism, the viscosity of mucus would become too high, and it would become sticky and difficult to clear.

Ion transport and sweat

Chloride ion reabsorption is also maintained by the CFTR protein, and this affects the ion concentrations of sweat. Before being released as sweat, a solution of sodium chloride and water usually moves from a gland to a duct where the ion concentrations are fine tuned. CFTR in the epithelial cells of this duct allows chloride ions to be reabsorbed into cells down their concentration gradient. Sodium ions are also reabsorbed into cells to maintain electrical neutrality, like mentioned before. If there is CFTR dysfunction, chloride ions are prevented from being reabsorbed. This would consequently cause less sodium ions to be reabsorbed, and the effect would be that the sweat released would have abnormally high concentrations of sodium ions and chloride ions.

Slim Summary!

- Ions require channels and transport proteins to cross the cell membrane as they are polar molecules;
- The CFTR protein is involved in the transport of chloride ions, which affects the hydration of mucus and also the ion concentrations in sweat.

Chapter 7-10 - Intro to the anatomy of gastrointestinal and respiratory systems

These topics will be covered in a separate anatomy booklet.

Chapter 11 - Changes in CFTR function

Introduction
Cystic fibrosis is an autosomal recessive disorder caused by CFTR gene mutations, leading to defective chloride transport, thick mucus, and multi-system complications. This chapter will discuss genetic inheritance of the CFTR gene and its classes, normal CFTR function, the effect of the mutated gene on the pulmonary and gastrointestinal system, and electrolyte balance in Cystic Fibrosis.

Cystic Fibrosis Genetics
Cystic fibrosis (CF) is a severe, progressive hereditary disorder. It is inherited in an autosomal recessive pattern, meaning an individual must receive two defective alleles, one from each parent to have the disease. The cause is mutations within the CFTR gene, located on the long arm of chromosome 7. CFTR stands for Cystic Fibrosis Transmembrane Conductance Regulator, a protein that functions as a chloride channel on the apical surface of epithelial cells. The most prevalent mutation, ΔF508, results in the deletion of a single amino acid, phenylalanine, at position 508. This alteration disrupts the protein's folding, leading to its degradation before it reaches the plasma membrane, resulting in a reduction in functional chloride channels. Additional mutations may impair protein synthesis, trafficking, gating, or stability and the outcome is insufficient CFTR activity and impaired chloride transport.

CFTR Mutation Classes
CFTR mutations are categorized based on their functional consequences:
- Class I: Virtually no CFTR protein is synthesized, typically due to premature stop codons.
- Class II: The protein is produced but misfolded and degraded before reaching the cell membrane→ ΔF508 is the typical example.
- Class III: The protein is delivered to the membrane, but the channel fails to open eg. G551D.
- Class IV: The channel opens, but chloride ion conductance is markedly reduced.
- Class V: Reduced synthesis of CFTR leads to lower protein levels.
- Class VI: The protein reaches the cell surface but is unstable and rapidly removed.

Normal CFTR Function
Normally CFTR channels facilitate the efflux of chloride ions from epithelial cells. Sodium and water then follow, preserving optimal salt and water homeostasis. This mechanism ensures that mucus remains hydrated and easily transported by the mucociliary escalator, which is responsible for clearing particulates from the airways. CFTR also modulates the activity of the epithelial sodium channel (ENaC), suppressing its function to prevent excessive absorption of sodium and water, thereby maintaining adequate airway surface liquid.

Electrolyte Balance and ENaC
Disruption of salt and water transport is a central feature of cystic fibrosis. The sodium-potassium ATPase (Na^+/K^+-ATPase) maintains intracellular ion gradients by exporting sodium and importing potassium. However, with hyperactive ENaC in the respiratory tract, there is excessive reabsorption of sodium and water into epithelial cells, further dehydrating the mucus. In contrast, in sweat glands, ENaC activity is diminished in cystic fibrosis, resulting in elevated sodium and chloride concentrations in sweat. This phenomenon underlies the characteristic salty skin of affected individuals and forms the basis of the diagnostic sweat chloride test.

Effect of CFTR Mutation on the Pulmonary System
In the context of cystic fibrosis, dysfunctional CFTR channels result in impaired chloride secretion and unchecked ENaC activity. Therefore, epithelial cells absorb excessive sodium, water follows osmotically, and the airway surface becomes dehydrated. The mucus is abnormally viscous and difficult to clear, impairing ciliary function. Under normal conditions, coordinated ciliary movement propels mucus upward to clear pathogens and debris from the lungs. In cystic fibrosis, thick, sticky mucus from defective CFTR impairs ciliary function, reducing clearance and promoting infections. This leads to mucus accumulation, chronic inflammation, airway obstruction, and may result in bacterial colonization, particularly by organisms such as Pseudomonas aeruginosa. Over time, affected individuals experience recurrent sinusitis, progressive airway destruction, hypoxemia, and ultimately bronchiectasis. The pulmonary pathology is characterized by a persistent cycle of mucus plugging, infection, and inflammation that progressively worsens.

Effect of CFTR Mutation on the Gastrointestinal Tract
The same abnormal, dehydrated mucus also obstructs pancreatic ducts, preventing digestive enzymes from reaching the intestinal lumen. As a result, malabsorption leads to failure to thrive and deficiencies in fat-soluble vitamins. Ongoing pancreatic injury may eventually result in cystic fibrosis-related diabetes mellitus. In neonates, viscous secretions can cause intestinal obstruction, referred to as meconium ileus. This obstruction can result in abdominal distension, vomiting of bile , and failure to pass meconium (first stool passed by newborns) within the first 24–48 hours of life, and may require medical or surgical intervention. In older children and adults, distal intestinal obstruction syndrome (DIOS) can occur due to thickened stool. It presents with abdominal pain, bloating, nausea, and sometimes palpable masses. Normally, the intestinal epithelium secretes fluid, but defective CFTR impairs this function, exacerbating dehydration of luminal contents.

Slim Summary!
• The ultimate effect of CFTR mutations is impaired chloride secretion, increased sodium reabsorption, and reduced water movement, which collectively result in the characteristic dehydrated mucus, recurrent pulmonary infections, gastrointestinal complications, and multisystem involvement that define cystic fibrosis.

Chapter 12 - Healthy diet

Introduction

This chapter reviews the basic components of a healthy diet and covers important functions of vitamins.

Basic components of a healthy diet include starchy carbohydrates, proteins and fats. Starchy carbohydrates are broken down to provide energy via respiration and metabolic processes. Proteins are required for growth and repair of damaged tissues and cells. Fats are not required in large quantities but are still important for another source of energy and supporting cell growth.

Vitamins are a vital part of a healthy diet, and supplements are often taken by cystic fibrosis patients due to their gut complications. **Vitamin A**, which can be formed as retinol or beta-carotene, is important for vision, immunity and cell growth. It is found in carrots, sweet potatoes and leafy greens. **Vitamin D** in the form of calciferol is taken to improve calcium and phosphate absorption and improve bone health. **Vitamin E** in the form of tocopherol acts as an antioxidant and supports immune functions. It is found in nuts, seeds, spinach and vegetable oils. **Vitamin K**, found in several green vegetables, is important for blood clotting and supporting bone health. **Vitamin C** in the form of ascorbic acid acts as an antioxidant and supports immune function. It is known to be found in citrus fruits, strawberries, bell peppers and broccoli. Vitamins A, D, E and K are all fat-soluble, whilst vitamin C is water-soluble. There are also several forms of **vitamin B** with various functions from energy production to supporting DNA synthesis. Some examples include B1 (thiamine), B2 (riboflavin), B3 (niacin), B9 (folate) and B12 (cobalamin).

Slim Summary!
• A healthy diet includes starchy carbohydrates, proteins and fats for various functions; • Several vitamins are also required for essential bodily processes, such as vitamins A, D, E, K, C and B; • Supplements of essential vitamins may be taken, especially with cystic fibrosis.

Chapter 13 - Nutrition in a cystic fibrosis patient

Introduction
This chapter reviews the nutritional management of CFTR patients which is crucial in children with cystic fibrosis (CF) due to increased energy demands and impaired nutrient absorption

Nutritional Management in Cystic Fibrosis (Birth to Puberty)
Children with cystic fibrosis require significantly increased caloric intake to support normal growth and development. Their bodies use up more energy due to persistent pulmonary infections, the increased work of breathing, and impaired nutrient absorption. Therefore, from infancy through puberty, it is essential that their diets are rich in calories and protein to facilitate appropriate weight gain and growth.

Pancreatic Insufficiency and Impaired Fat Absorption
The majority of pediatric patients with cystic fibrosis exhibit pancreatic insufficiency, characterized by inadequate production of digestive enzymes. As a result, fat digestion and absorption are compromised, leading to symptoms such as steatorrhea, diarrhea, abdominal pain, and weight loss. To address these issues, pancreatic enzyme replacement therapy (PERT) is administered with all meals to increase nutrient absorption and reduce the risk of malnutrition.

Fat-Soluble Vitamin Supplementation
Due to chronic fat malabsorption, these patients are predisposed to deficiencies in fat-soluble vitamins A, D, E, and K. These vitamins are essential for visual health, bone strength, immune function, and coagulation.

Additional Micronutrient Requirements
Children with cystic fibrosis frequently require increased intake of micronutrients such as calcium and iron. These nutrients are vital for the prevention of anemia and for supporting optimal bone health, which is particularly important during periods of rapid growth, especially as puberty approaches.

Hydration and Electrolyte Management
Patients with cystic fibrosis lose excessive amounts of sodium and chloride through their sweat due to abnormal sweat gland function. This predisposes them to dehydration and electrolyte disturbances, particularly during febrile illnesses, hot weather, or periods of increased physical activity. Therefore, maintaining adequate hydration and ensuring sufficient salt intake are critical components of care.

Slim Summary!

- High-calorie, nutrient-rich diet is essential to support growth and compensate for energy loss from infections and malabsorption;
- Pancreatic enzyme and vitamin (A, D, E, K) supplementation prevent malnutrition and deficiencies;
- Hydration, electrolytes, and key micronutrients (calcium, iron) are critical to maintain fluid balance, bone health, and overall growth.

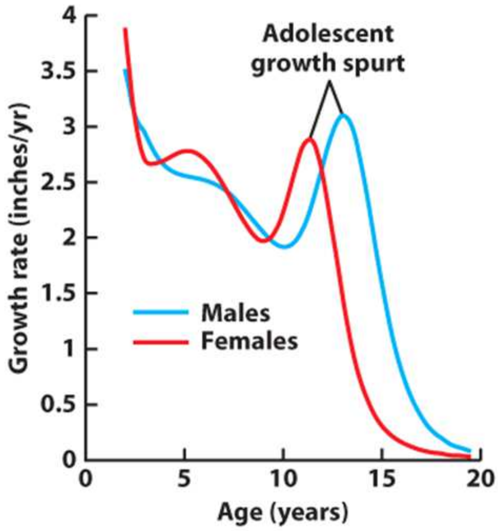
Chapter 14 - Normal patterns of growth

Introduction
This chapter describes the normal patterns of growth in infancy, childhood and pubertal development.
Infancy is the period with the most rapid physical growth. The physical growth of infants is monitored regularly at routine check-ups after birth by measuring weight, height and head circumference. Growth charts are used to monitor growth and ensure it is occurring at the expected rate.

Growth charts for infants. *Source: courses.lumenlearning.com*

From about five years of age, the rate of growth slows during childhood. Increase in weight and height still occurs but at a much slower rate than during infancy.

Then during puberty, the rate of growth rapidly increases again as a growth spurt usually occurs. The release of hormones and genetic factors determine at what age this growth spurt occurs and the normal ranges differ between girls and boys. For girls, the growth spurt typically occurs between the ages of 9.5 to 14.5, whereas for boys it occurs between ages 12 to 17. If there are concerns about growth during pubertal development, then health professionals may use growth charts during appointments to check that a patient’s growth is within the normal range.



Graph showing the growth rate during infancy, childhood and puberty. *Source: sutori.com*

Slim Summary!
• The most rapid rate of growth occurs during infancy; • Growth rate slows in childhood; • During puberty, a growth spurt should occur and the timing of this is influenced by hormones, genetics and gender.

Chapter 15 - Tests for cystic fibrosis

Introduction
This chapter discusses screening and diagnosis of cystic fibrosis and focuses on early detection of CFTR dysfunction to enable timely intervention.

Newborn Screening: Heel Prick Test
Cystic fibrosis screening typically starts immediately after birth with a heel prick blood sample. The neonatal blood is analyzed for immunoreactive trypsinogen (IRT). Elevated IRT levels suggest pancreatic impairment, as viscous secretions obstruct pancreatic ducts, resulting in trypsinogen leakage into the bloodstream. Although this assay detects the majority of cases, it is not completely specific: factors such as physiological stress, hypoglycemia, or certain gastrointestinal pathologies may also elevate IRT in infants without cystic fibrosis. Laboratories frequently utilize enzyme-linked immunosorbent assay (ELISA) for this purpose: one antibody binds IRT, while a second antibody produces a colorimetric change if IRT is present.

CFTR Mutation Analysis
If IRT is elevated, a more detailed evaluation is pursued. Molecular testing for prevalent CFTR gene mutations is performed on the infant's blood. Identification of a pathogenic variant confirms the diagnosis of cystic fibrosis. Genetic analysis is also valuable for prognostication and for informing targeted therapeutic strategies. This approach is particularly pertinent when there is a known family history of CFTR mutations.

Sweat Chloride Test
The quantitative pilocarpine iontophoresis sweat chloride test remains the gold standard for confirming cystic fibrosis. Pilocarpine is used to induce localized sweating, after which the chloride concentration in the sweat is measured. Individuals with defective CFTR channels exhibit elevated sweat chloride concentrations due to impaired chloride reabsorption. A sweat chloride value of 60 mmol/L or greater is diagnostic for cystic fibrosis. Values between 30 and 59 mmol/L are considered indeterminate, while levels below 30 mmol/L are regarded as normal. This assessment directly reflects CFTR functional integrity in epithelial tissues.

Imaging: Chest X-Ray
Chest radiography provides visualization of structural pulmonary changes. Findings may include nasal polyposis, mucosal thickening of the paranasal sinuses, or radiographic evidence indicative of mucus accumulation within the airways and sinuses, all of which are characteristic of cystic fibrosis. Imaging supports laboratory results and allows assessment of the extent of pulmonary involvement.

Slim Summary!
• Newborn screening using heel prick tests measures immunoreactive trypsinogen (IRT) to detect early pancreatic involvement; • Genetic testing identifies CFTR mutations for definitive diagnosis and guides treatment decisions; • Sweat chloride testing confirms CFTR dysfunction, with values ≥60 mmol/L diagnostic for cystic fibrosis; • Chest imaging evaluates structural lung and sinus changes to assess disease severity.

Chapter 16 - Microorganisms in Cystic Fibrosis

Introduction
This chapter discusses several key pathogens prevalent in cystic fibrosis, which causes persistent inflammation and progressive lung damage. Understanding these pathogens and their mechanisms is vital for effective management.

Gram Classification and Antibiotic Susceptibility
Bacteria are broadly categorized into Gram-positive and Gram-negative groups based on their response to Gram staining. This classification is clinically significant, as it informs antimicrobial selection. Gram-negative organisms possess a thin peptidoglycan layer and an additional outer membrane, which contributes to their inherent resistance to numerous antibiotics. Conversely, Gram-positive bacteria feature a thick peptidoglycan cell wall and lack an outer membrane, generally rendering them more susceptible to antibiotics targeting cell wall synthesis.

Principal Pathogens in Cystic Fibrosis
Pseudomonas aeruginosa
Pseudomonas aeruginosa, a Gram-negative bacteria, which is the most common pathogen in cystic fibrosis (CF). It is present in environments such as water sources and healthcare facilities and requires minimal nutrients for survival. The organism thrives at physiological temperature. In CF it colonizes the pulmonary system, forming adhesive biofilms that result in chronic persistence. These biofilms serve as protective barriers, enabling the bacteria to adhere to respiratory epithelium, persist within the viscous mucus characteristic of CF, and evade most antimicrobial agents. P. aeruginosa additionally produces a polysaccharide capsule and various toxins, impairing a patient's immune system. Chronic colonization leads to sustained inflammation, progressive airway damage, and a decline in pulmonary function. By late adolescence, approximately 80% of individuals with CF are chronically infected with P. aeruginosa. Initial management typically involves combination therapy with antipseudomonal beta-lactams (such as penicillins or cephalosporins) and aminoglycosides.

Staphylococcus aureus
Staphylococcus aureus is a Gram-positive bacteria characterized by a peptidoglycan wall. It possesses several virulence factors, including catalase (which neutralizes reactive oxygen species), coagulase (which induces plasma clotting), and immune-evasive surface proteins. S. aureus is also capable of biofilm formation. In pediatric CF populations, it is a leading pathogen, detected in approximately half of young children with the disease. Its prevalence diminishes with age. However, methicillin-resistant S. aureus (MRSA) can emerge in older patients, provoking acute pulmonary exacerbations.

Burkholderia cepacia Complex
The Burkholderia cepacia complex encompasses a group of Gram-negative bacteria that, while less frequently encountered, are associated with severe clinical outcomes in CF. These organisms can precipitate rapid pulmonary decline and are challenging to identify and treat. Despite their lower incidence, their multidrug resistance and virulence render them a significant concern.

Other Opportunistic Pathogens

CF airways are susceptible to colonization by a variety of additional organisms, including Haemophilus influenzae (commonly isolated from the respiratory tract), Mycobacterium abscessus (a non-tuberculous mycobacterium), Achromobacter xylosoxidans, and Stenotrophomonas maltophilia, among others. The microbial composition within CF lungs is dynamic and evolves with age and disease progression.

Temporal Evolution of Infection in CF

Individuals with CF experience a dynamic shift in airway microbiology over time. In early childhood, Gram-positive S. aureus predominates. With advancing age, Gram-negative P. aeruginosa becomes increasingly prevalent and often establishes chronic infection. Additional pathogens, including MRSA, H. influenzae, and S. maltophilia, may also be present. While many infections are amenable to detection and treatment, certain organisms such as Burkholderia complex present substantial therapeutic challenges and are associated with increased morbidity.

Pulmonary Consequences of Infection

Chronic Inflammation

Persistent bacterial colonization in the CF lung results in ongoing activation of the host immune response. Viscous mucus impedes the clearance of both pathogens and immune effectors, perpetuating chronic inflammation, particularly in response to P. aeruginosa. This sustained inflammatory state contributes to airway remodeling, facilitates subsequent infections, and leads to a progressive decline in lung function, which is routinely monitored via spirometry.

Neutrophil Dysfunction

Neutrophils, as principal effectors of innate immunity, are recruited to the infected airways but become entrapped within the mucus. In their attempt to eradicate pathogens, neutrophils release proteolytic enzymes and reactive oxygen species, which inadvertently degrade pulmonary tissue and contribute to structural airway changes. Furthermore, neutrophils exhibit prolonged survival in the CF lung, exacerbating inflammation and tissue injury.

Biofilm Formation and Encapsulation

Biofilms significantly contribute to the exacerbation of pulmonary infections in CF. These structures enable bacteria to persist within the thickened mucus, resist antibiotic treatment, and evade host immune responses. Additionally, some bacteria produce a hydrophilic polysaccharide capsule, which evades immune recognition, inhibits complement activation, and enhances adherence to respiratory tissues. Capsule production also promotes biofilm development, further complicating efforts to eradicate infection with antimicrobial agents.

Slim Summary!

- CF infections involve Gram-positive (*S. aureus*) and Gram-negative (*P. aeruginosa*, *B. cepacia*) bacteria, with Gram-negatives generally more antibiotic-resistant;
- Bacteria form biofilms and capsules, protecting from immune responses/antibiotics;
- Infection patterns change with age: *S. aureus* dominates in childhood, *P. aeruginosa* in adolescence, with other opportunistic pathogens present;
- Chronic infection drives inflammation, neutrophil dysfunction, and lung tissue damage;
- Early detection and targeted therapy are essential, but biofilms and resistant bacteria complicate treatment.

Chapter 17 - Barriers of the innate immune system

Introduction
This chapter describes the barrier functions of the innate immune system including physical, physiological, chemical and biological barriers.

Physical barriers
Mechanical barriers include the skin and mucus membranes. The skin is layered with the top layer being keratinised stratified squamous epithelium which makes it a tough physical barrier to prevent pathogens from getting through. The skin also naturally sheds to remove dead cells and adherent pathogens. Mucus membranes, which are found in the respiratory, urinary and gastrointestinal tracts, are weaker than the cutaneous layer of skin and require maintenance if tears arise. Glands and goblet cells within the membranes produce mucus and sometimes other secretions such as tears, saliva and bile. These often have anti-microbial properties such as enzymes or specialised cells. In the respiratory tract, mucus is transported via the **mucociliary escalator** from the alveoli to the top of the trachea for it to be cleared via the mouth. This prevents the build-up of harmful bacteria and pathogens in the lungs and respiratory tract. Another kind of physical barrier found in the body is a sphincter, which is a muscle that closes an opening to prevent outside interference, such as the anal sphincter and external urethral sphincter.

Physiological barriers
Physiological barriers are active responses requiring the alteration of normal body function to dislodge harmful material. These responses can be triggered by physical irritation, dust, pH changes or physical disruption of the stomach lining. Some examples of this are coughing, sneezing, vomiting and diarrhoea.

Chemical barriers
Chemical barriers include environments with a very low pH to be less inviting to pathogens. An example of this is the acidic environment of stomach acid, which has a pH less than 3. Other areas of the body have a low pH as well to prevent unwanted pathogens. For example, the skin has a pH of 5.5, and the vagina has a pH of 4.4. There are also antimicrobial substances found in secretions from cells and glands which act as chemical barriers. Enzymes such as lysozymes in tears and saliva break down bacterial cell walls. IgA antibodies are found in tears, saliva, the small intestine and breast milk and these antibodies tag and inhibit bacteria. Proteins called defensins are also released and these make holes and channels in the membranes of fungi and bacteria to destroy them.

Biological barriers
Colonies of specific species of bacteria are naturally present throughout the body, for example in the gut microbiome, and these are often referred to as “good” bacteria. If the presence of different species of bacteria is well-balanced then this can help prevent infection from pathogens. Probiotics are often taken as supplements to promote a healthy and balanced gut microbiome. There are also several species of bacteria which are part of the normal flora of the skin and the healthy mouth mainly contains species of gram-positive bacteria.

Slim Summary!
• Physical barriers include the skin and mucus membranes; • Physiological barriers allow harmful material to be dislodged; • Chemical barriers include acidic environments and enzymes; • The natural 'good bacteria' found in colonies throughout the body form biological barriers.

Chapter 18 - Role of the innate immune system in infection

Introduction
This chapter discusses the inflammatory response, key cell types in early infection.
The innate immune system responds immediately upon pathogen entry, typically within the first 12 hours. In contrast to the adaptive immune system, which provides specific, long-lasting responses and immunological memory, the innate immune system is rapid, broad, and non-specific. It employs a combination of physical barriers, chemical defenses, and various specialized cells and molecules to contain and control infections.

Inflammatory Response
Upon tissue injury or infection, the innate immune system initiates an inflammatory response. This process increases blood flow, recruits immune cells to the affected site, and results in localized heat and swelling. These physiological changes facilitate containment of the infection and enhance the effectiveness of immune cell activity.

Key Cell Types in Early Infection

- Macrophages reside in tissues, phagocytose pathogens, and secrete cytokines such as TNF-α, IL-1, and IL-6 to recruit additional immune cells. They play roles in both acute and chronic immune responses;
- Neutrophils are the most prevalent leukocytes and are rapidly recruited to infection sites, where they engulf pathogens, create reactive oxygen species, and release proteolytic enzymes. Neutrophils also form neutrophil extracellular traps (NETs) to immobilize microorganisms;
- Dendritic Cells capture antigens and present them to T lymphocytes, to help bridge innate and adaptive immunity. They secrete IL-12 to promote Th1 differentiation and regulate autoimmunity;
- Natural Killer (NK) Cells identify and eliminate virus-infected or malignant cells through cytotoxic mechanisms;
- Mast Cells release histamine and cytokines such as IL-4 and IL-5, which amplify inflammation and recruit additional immune effectors;
- Eosinophils specialize in defense against certain pathogens, releasing cytotoxic proteins such as major basic protein (MBP) and eosinophil cationic protein (ECP), thereby modulating tissue responses and immunity;
- Basophils contribute to allergic responses and augment inflammatory processes.

Cytokines and Pyrokines
Cytokines are critical mediators of immune communication, orchestrating inflammation, hematopoiesis, and coordination of immune responses. Key examples include:

- Tumor Necrosis Factor-alpha (TNF-α): Induces inflammation and recruits immune cells;
- Interleukins (ILs): Activate lymphocytes, induce fever, and regulate immune responses;
- Interferons (IFNs): Inhibit viral replication and activate NK cells;
- Pyrokines, such as IL-1β and IL-18, are specific cytokines that induce fever, thereby contributing to the host defense against infection.

Additional Innate Immune Components
Complement System: This cascade of proteins opsonizes pathogens, enhances antibody function, and mediates direct lysis of microbial membranes.

Pattern Recognition Receptors (PRRs): Receptors such as Toll-like receptors (TLRs) detect pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs), initiating prompt innate immune responses.

Slim Summary!

- Physical, chemical, and biological barriers prevent pathogen entry;
- Inflammation recruits immune cells and enhances pathogen clearance;
- Key cells include macrophages, neutrophils, dendritic cells, NK cells, mast cells, eosinophils, and basophils;
- Cytokines and pyrokines coordinate immune responses and induce fever;
- Complement proteins and pattern recognition receptors detect and eliminate pathogens.

Chapter 19 - Multidisciplinary management of cystic fibrosis

Introduction

This chapter describes the multidisciplinary management of patients with cystic fibrosis and various treatment options. Due to the variety of symptoms that cystic fibrosis patients can experience, several types of care and treatment are provided. Clinical nurse specialists would be central in providing regular care as regular visits to clinics would be required to monitor the condition. Several specialists would also be involved in the complex care of these patients, as symptoms affect many systems in the body. Psychologists and social workers may also be involved in providing emotional, social and financial support.

Lung therapies

Airway clearance is a regular treatment which is required for cystic fibrosis. It can involve chest physiotherapy and breathing exercises (taught by a physiotherapist) to loosen and expel mucus, along with devices such as oscillation vests. Medications such as mucolytics and bronchodilators are also taken to break down mucus and open the airway further. This would be done on a daily basis, as mucus would regularly build up in the respiratory tract. A lung transplant may be required in extreme cases of end-stage lung disease. A respiratory consultant would be the one overseeing the respiratory health of a cystic fibrosis patient.

Antibiotics and medications/therapies

Antibiotics may be taken chronically to prevent the risk of infections (prophylaxis), and during exacerbations of cystic fibrosis the dosage may increase. Anti-inflammatory medications are also taken to combat the symptoms of infection. For some patients, therapeutic strategies which can modulate ion transport may be available and these will be discussed in Chapter 23. Pharmacists would be involved in managing prescribed medications.

Nutritional management and gut

Managing diet is important for cystic fibrosis patients with malabsorption and a dietician would oversee the management of nutritional needs. A high calorie, fat and protein diet with vitamin supplements and liberal use of salt is ideal. Supplements of digestive enzymes would also be taken for enzyme replacement. For those with diabetes related to cystic fibrosis, insulin may also be taken. Corrective surgery is also available to treat meconium ileus in newborns, which is when there is the accumulation of faeces and obstruction in the intestines.

Slim Summary!

- Due to the variety of symptoms that cystic fibrosis patients can experience, several types of specialist care and treatment are required;
- Daily therapies include chest physiotherapy, bronchodilators and mucolytics;
- Nutritional management overseen by a dietician is important to meet nutritional needs even with malabsorption.

Chapter 20 - Antibiotic targets

Introduction
This chapter describes the essential cellular processes that are inhibited by the antibiotics used to treat bacterial infections arising in cystic fibrosis. The different classes of antibiotics target specific cellular processes in their mechanisms of action.

Cell wall synthesis
Beta-lactams target cell wall synthesis of bacteria. They inhibit the synthesis of peptidoglycans, which leads to a weakened bacterial cell wall and cell lysis. Some examples of beta-lactams include penicillins, cephalosporins and carbapenems. These can be effective against *Pseudomonas aeruginosa*, which commonly causes lung infections in adults with cystic fibrosis. *Glycopeptides* also target cell wall synthesis by preventing the cross-linking of peptidoglycan chains. Some examples include vancomycin and bacitracin.

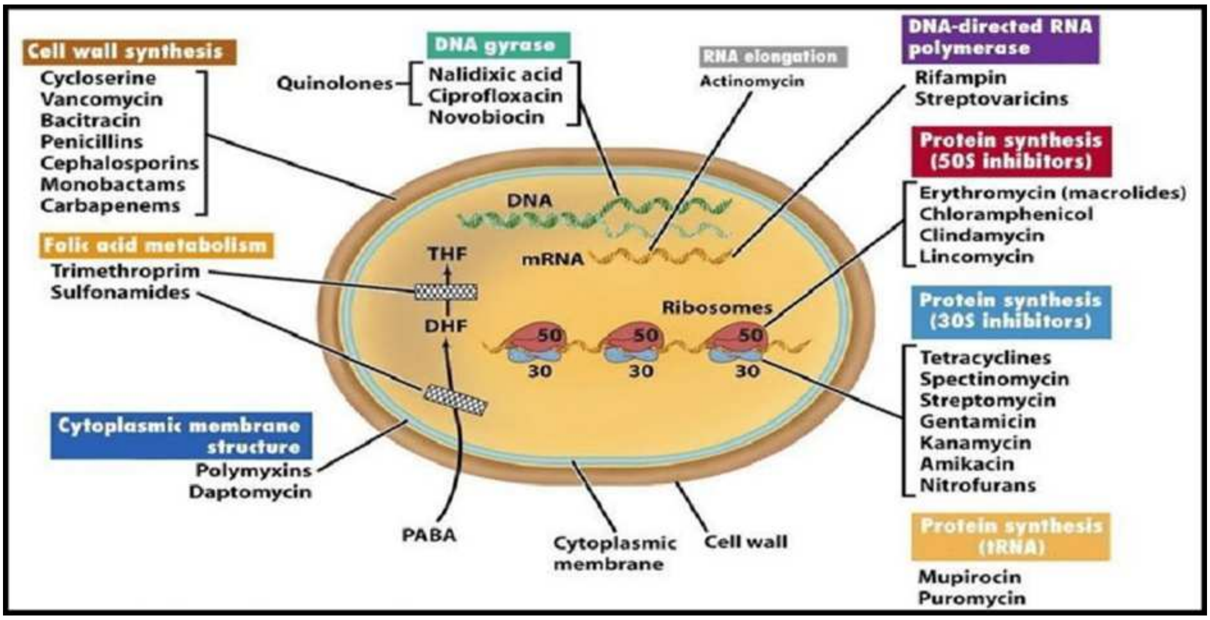
Cytoplasmic membrane structures
Polymyxins increase the permeability of the cytoplasmic membranes of bacteria by targeting cytoplasmic membrane structures. This causes intracellular contents to leak and leads to bacterial cells being destroyed.

Protein synthesis
Some antibiotics bind to ribosomal subunits to block protein synthesis and prevent bacterial growth and biofilm formation. **Aminoglycosides** bind to the 30S ribosomal subunit, whilst **macrolides** bind to the 50S subunit. Macrolides are especially effective against *Pseudomonas aeruginosa* as they limit its biofilm formation. Other antibiotics such as mupirocin and puromycin target tRNA, so they also affect protein synthesis of bacteria.

DNA synthesis
Fluoroquinolones such as ciprofloxacin target DNA replication by inhibiting specific enzymes. They inhibit DNA gyrase and topoisomerase IV, which are both enzymes required for DNA replication in bacteria. Therefore, this prevents bacterial DNA replication and cell division so that the infection is controlled and does not spread.

RNA synthesis
Some antibiotics target mRNA, which is required for protein synthesis, so this mechanism also prevents bacterial cell growth and replication. Actinomycin targets RNA elongation, whilst rifampin and streptovaricins target RNA polymerase.

Folic acid synthesis
Folic acid is essential for nucleotide synthesis in DNA synthesis and replication. **Sulfonamides** such as sulfamethoxazole and trimethoprims target folic acid synthesis. This causes nucleotide synthesis to be reduced and DNA replication is reduced so that the bacterial cells cannot divide, thereby preventing the spread of infection.



Targets of antibiotics. *Source: researchgate.net*

Slim Summary!

- Different classes of antibiotics target specific cellular mechanisms in bacteria to prevent the growth and spread of bacteria;
- Mechanisms targeted include: protein synthesis, DNA replication, cell wall synthesis, folic acid synthesis and cytoplasmic membrane structure.

Chapter 21 - Prescribing antibiotics

Introduction
This chapter outlines the strategy for prescribing antibiotics, focusing on the concept of 'antibiotic custodianship' and personalised prescription.

Antibiotic custodianship
Antibiotics should not be excessively prescribed and when taken it should be emphasised to patients that they take the full course of antibiotics even if their symptoms improve earlier. This is to prevent the development of resistant strains of bacteria, which could cause antibiotics to be less effective in the future. Health professionals have a duty to judiciously and effectively prescribe antibiotics to reduce the development of antibiotic resistance as much as possible. A targeted selection of antibiotics should be used with a narrow spectrum and combination therapy may be used with multiple antibiotics if there are known resistant strains.

Personalised prescription
Antibiotics should be prescribed specific to the pathogen but also adjusted to the patient's history and their previous experience with antibiotics. Some may have allergies or adverse reactions, so these are important to consider. New methods of administering antibiotics have also become available. Inhaled antibiotics allow a higher dosage directly to the lungs for lung or respiratory tract infections and a new phage therapy has also emerged, which involves the use of viruses to deliver antibiotics to specific areas of the body.

Slim Summary!
• Antibiotics should be prescribed judiciously and effectively and clear instructions should be delivered to patients to prevent the development of resistant strains of bacteria; • Prescriptions should be personalized to patients depending on past medical history and lifestyle.

Chapter 22 - Genetic counselling

Introduction
This chapter discusses the efficacy of genetic counselling in effective risk assessment, interpretation of genetic data, and determining carrier status to inform patients regarding the probability of disease transmission to offspring to facilitate proactive planning.

Genetic counselling
Genetic counseling provides individuals and families with an understanding of the impact of genetics on health and psychological well-being. Genetic counselors evaluate detailed family medical histories to identify inheritance patterns indicative of increased risk to specific genetic disorders. This information enables both healthcare providers and families to implement early detection strategies and make informed decisions regarding disease prevention and management.

Beyond risk assessment, genetic counselors play a role in interpreting the significance of genetic conditions. They offer explanations regarding inheritance mechanisms, the implications of genetic test results, and the potential implications for an individual's future health. Counselors ensure that patients and families have a clear understanding of their situation by translating complex genetic data into accessible terminology. Additionally, genetic counselors are trained to address the psychological and emotional challenges associated with receiving genetic information, providing support and, when necessary, facilitating referrals to other specialized professionals.

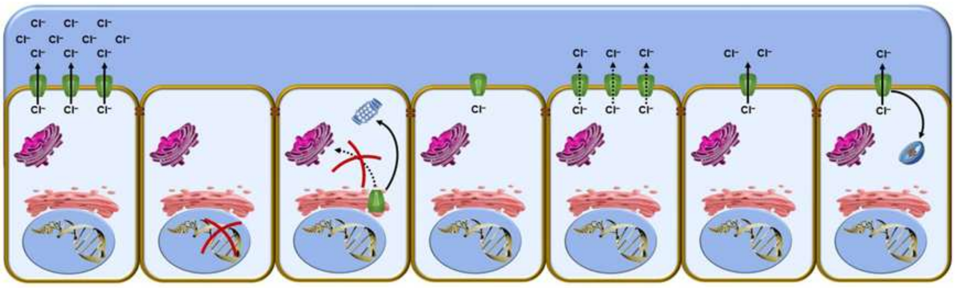
In the context of cystic fibrosis, genetic counseling is integral to clinical care. Counselors construct detailed pedigrees to ascertain any familial history of cystic fibrosis and to determine carrier status with respect to CFTR gene mutations. When an elevated risk is identified, carrier testing for prospective parents or other family members is recommended. Determining carrier status informs reproductive decision-making, clarifies the probability of disease transmission to offspring, and enables proactive planning for potential medical interventions.

Slim Summary!
• Genetic counseling assesses family history and genetic test results to evaluate disease risk and guide informed medical and reproductive decisions; • Counselors provide education and emotional support, helping individuals understand genetic conditions such as cystic fibrosis and their implications.

Chapter 23 - Genomic data and treatment

Introduction
This chapter describes how genomic data have impacted on treatment regimens and life expectancy of affected individuals focusing on cystic fibrosis. Research into the genome and gene therapy has allowed some therapeutic strategies to become available.

Investigations into genomic data
Several methods have been used to identify mutations responsible for causing CFTR dysfunction. Chromosomal tests, such as karyotyping and fluorescence in situ hybridisation (FISH), and directly sequencing DNA allow gene changes to be identified. A genetic marker, for example, RFLP, is used to detect polymorphism or alteration at a specific site. Using these methods, patients' DNA can be screened for mutations. The F508del mutation accounts for about 90% of cystic fibrosis cases, but there are several other mutations that cause it, and they can be classified by their specific effects on CFTR.



wt-CFTR	I	II	III	IV	V	VI
Defect types	**No protein**	**No traffic**	**No function**	**Less function**	**Less protein**	**Less stable**
Mutation examples	G542X R553X W1282X	G85E ΔI507 **ΔF508** N1303K	V520F S549R G551D	R117H R334W S1235R	A455E 1680-886A>G 2657+5G>A	**rΔF508** Q1412X
Required approaches	Rescue protein synthesis	Correct protein folding	Restore channel conductance	Restore channel conductance	Maturation / Correct misplicing	Promote protein stability

Classes of CFTR mutations. *Source: https://www.frontiersin.org*

CFTR modulators
Therapeutic strategies include CFTR modulators, which are small molecules identified from screening that restore chloride ion transport in cells which carry the mutant protein. There are two types of modulators: potentiators, which increase the channel opening probability, and correctors, which stabilise the mutant protein to prevent its degradation and increase the quantity of CFTR. The triple combination modulator therapy is the most effective. This involves the oral administration of two correctors, for example Elexacaftor and Tezacaftor, and one potentiator, for example Ivacaftor. This therapy is effective and directly targets CFTR, but it is expensive, so it is not readily available in many countries. Therefore, many strategies will focus on alleviating the symptoms of CFTR dysfunction rather than targeting CFTR itself. These small molecule therapies are also not effective for nonsense and splicing mutations, which account for about 10% of cystic fibrosis cases.

Gene therapy
Gene therapy to alter the mutated genes in cystic fibrosis patients is still in trials. If it is successful, it would potentially greatly improve life expectancy and reduce the severity of symptoms. This would also reduce the burden on health professionals caring for patients with cystic fibrosis, as these patients require a large variety of specialist care on a regular basis. It would allow all mutation classes of CFTR to be targeted, as some classes such as Class I have a near/complete absence of CFTR.

Slim Summary!
• Genomic data and research has allowed several mutations which cause CFTR dysfunction to be identified; • Several new treatments are being used and are also in trials as a result, such as CFTR modulators and gene therapy.

Chapter 24 - Experience of long-term conditions

Introduction

A cystic fibrosis diagnosis affects not only the patient but also the entire family, altering expectations and daily life. The emotional, social, and practical demands of managing a chronic illness can place significant strain on family functioning and well-being.

Long-term conditions

A diagnosis of cystic fibrosis has significant implications not only for the individual affected, but also for the entire family. Diagnosis frequently results in heightened levels of stress, anxiety, and a form of anticipatory grief as family members adjust to a reality different from what they had previously envisioned. Established daily routines are disrupted as families adapt to a new regimen involving complex treatment protocols, frequent medical appointments, hospital visits, and the requisite planning associated with ongoing care.

The capacity of a family to manage these demands is influenced by their circumstances. Access to social support networks, adequate financial resources, and comprehensive healthcare services facilitates adherence to prescribed treatment regimens and mitigates stress. Conversely, limited support, financial constraints, or barriers to healthcare access can exacerbate the psychological and logistical burden on the family.

The disruption caused by chronic illness extends to multiple domains of daily life, including education, employment, and social engagement. Children and adolescents with cystic fibrosis may experience frequent absences from school for medical appointments, potentially resulting in academic and social setbacks.

Slim Summary!

- The psychosocial impact extends to the family of the patient, all of whom may experience emotional and social challenges as a result;
- Health literacy and the presence of a cohesive support system are critical determinants of effective coping and overall family adaptation;
- familial understanding and support are essential in maintaining routines and promoting psychological well-being amidst ongoing uncertainty.

Chapter 25 - Stages of cognitive and psychosocial development

Introduction
This chapter discusses Erikson's psychosocial theory and Piaget's cognitive development theory which are two foundational frameworks that explain how individuals grow socially, emotionally, and intellectually across the lifespan. They highlight the key challenges and cognitive milestones that shape personality, identity, and understanding of the world.

Erikson's Psychosocial Theory
Erik Erikson's psychosocial theory delineates eight distinct developmental stages, each characterized by a central psychosocial conflict that significantly influences personality formation.

Infancy (Trust vs. Mistrust, 0–1 year): During this initial stage, infants depend on caregivers for security and nurturing. Consistent, responsive caregiving fosters a foundational sense of trust in the environment, whereas unpredictable or neglectful care results in mistrust and apprehension towards others.

Early Childhood (Autonomy vs. Shame and Doubt, 1–3 years): At this juncture, children seek to assert independence through self-directed activities. Supportive guidance enables the development of autonomy and self-confidence. Conversely, overly restrictive or critical responses may instill feelings of shame and self-doubt.

Preschool (Initiative vs. Guilt, 3–5 years): Children in this phase exhibit heightened curiosity and initiative, frequently engaging in imaginative play and exploration. Encouragement from adults cultivates a sense of initiative, whereas excessive criticism or discouragement may lead to persistent feelings of guilt regarding their actions.

School Age (Industry vs. Inferiority, 6–12 years): The primary focus shifts to academic and social competence. Successful experiences in mastering new skills and collaborating with peers foster a sense of industry and capability. Repeated failures or social exclusion can engender feelings of inferiority.

Adolescence (Identity vs. Role Confusion, 12–18 years): Adolescents engage in the task of identity formation, exploring various roles and personal values. Resolution of this psychosocial crisis results in a coherent sense of self→ unresolved conflicts may result in role confusion and uncertainty regarding one's place in society.

Young Adulthood (Intimacy vs. Isolation, 18–40 years): Individuals seek to establish meaningful, enduring interpersonal relationships. Achieving intimacy leads to emotional fulfillment, while the inability to form close bonds may result in social isolation and emotional distress.

Older Adulthood (Integrity vs. Despair, 65+ years): In later life, individuals reflect upon their accomplishments and life trajectory. A sense of integrity arises from satisfaction with one's life course, whereas pervasive regret may culminate in despair.

Piaget's Theory of Cognitive Development
Jean Piaget's theory of cognitive development outlines the qualitative changes in cognitive processes as children mature.

Sensorimotor Stage (0–2 years): Infants comprehend the world primarily through sensory experiences and motor activities. Over time, they develop object permanence, recognizing that objects continue to exist even when out of sight.

Preoperational Stage (2–7 years): Children in this stage exhibit rapid language development and engage in symbolic play. Their thinking is characterized by egocentrism and animism, and they have difficulty adopting perspectives other than their own.

Concrete Operational Stage (7–11 years): Logical reasoning emerges, but remains limited to tangible, concrete objects and events. Children at this stage grasp concepts such as conservation and reversibility, understanding that properties remain constant despite changes in form.

Formal Operational Stage (11 years and older): Abstract and hypothetical thinking becomes possible. Adolescents develop the ability to consider multiple perspectives, engage in systematic problem-solving, and reason about complex, abstract concepts such as justice and morality.

Slim Summary!
• Erikson emphasizes the resolution of psychosocial conflicts at each life stage as essential for healthy personality development, while Piaget focuses on the progressive evolution of cognitive abilities from infancy through adolescence.

Chapter 26 - Types of study in clinical research

Introduction
This chapter describes and compares the different types of study designs used in clinical research.

Clinical research
Most intervention studies will use a standard **PICO** framework within the study design they are using. This framework identifies key elements of a research question and is useful to decide the best type of study design to use. There are also other added elements to consider such as time and context depending on the study.

P-Population of interest
I-Intervention
C-Control/Comparator
O-Outcome

There are several types of study designs used in clinical research, and some have a higher risk of bias than others. **Bias** is a systematic error or deviation from the truth. It may cause the answer to a research question to be incorrect and may cause specific data to be overestimated or underestimated. There are different types of bias. **Selection bias** is when individuals or groups in a study differ systematically from the population of interest. **Attrition bias** is when there are systematic differences between study groups in the number or type of missing participants. **Performance bias** is when care provided or behaviour to study groups differs systematically. **Recall bias** is when there are differences in accuracy or completeness of recall of past events between study groups.

Confounding is a phenomenon which is sometimes classed as bias. It is when there is a distortion in association between two variables due to additional factors that are independently associated with both variables. This is important to consider when evaluating causal relationships and it may cause the strength of a causal relationship to be overestimated or underestimated.

The types of study designs can be arranged into a **hierarchy of evidence** where studies with a low risk of bias are at the top of the pyramid and studies with a high risk of bias are at the bottom of the pyramid. This does not necessarily mean that a study design at the top of the pyramid is always the best to use, however, as in some situations it is not practical to do a randomised controlled trial.

Hierarchy of evidence. *Source: https://libguides.methodistcollege.edu*

Systematic Review
Systematic reviews collate data and evidence from several trials and studies fitting a pre-specified eligibility criteria. Meta-analysis may be used to combine numerical data from multiple studies and this allows the review to be large-scale and include a lot of data. This can make the study more precise and increase the generalisability due to the large scale.

Randomised controlled trial
A randomised controlled trial evaluates the effectiveness of interventions. Participants are allocated into two groups at random and each group receives either the new treatment or the control. The participants are monitored over a specific time period, and their outcomes are compared. This type of study has a low risk of selection bias if it is well-conducted. However, its disadvantages are that it is expensive, time-consuming, sometimes unethical and there is risk of performance or attrition bias. Variations of randomised controlled trials include crossover trials, where the control and treatment group swap treatments after a certain time period, and cluster trials, where groups of people are randomised instead of individuals.

Cohort study
This type of study explores relationships between factors and a certain disease or outcome. The groups of participants are recruited over time and monitored to record their outcomes. It may utilise existing records or registries and therefore answer multiple questions simultaneously. However, it can be expensive and time-consuming and there is also a risk of selection or attrition bias and confounding.

Case-control study
This type of study also explores the relationships between factors and a certain disease or outcome but it is on a smaller scale than a cohort study. Participants are sampled with or without the outcome of interest to form a case group with the outcome of interest and a control group without it. Data is collected on the participants' past behaviour by asking questions or using records. It is usually more efficient as there is a smaller number of participants. However, there is a risk of selection or recall bias and confounding.

Case series
This is a descriptive study about the characteristics of a small group of participants with a condition or taking a treatment. It uses case reports or case studies, which relate to a single participant. This type of study is very small scale and does not include a control for direct comparison so would not be as reliable. It may still be useful to use, however, when combined with other studies in a systematic review.

Non-randomised controlled study
This is an observational study to estimate the effect of an intervention which is similar to a randomised controlled trial but without randomisation. The allocation of the treatment or control may be the clinician's decision, patient preference or by convenience. This does create a high risk of selection bias and confounding.

Cross-sectional study
This is an observational study which looks at data relating to a single point in time. It may involve participants filling out a questionnaire and this would make it a high risk for recall bias.

Quasi-experimental studies
These studies measure the changes in participants before and after an intervention. They are non-randomised studies so this creates a high risk of selection bias and confounding.

Diagnostic Accuracy study
This type of study evaluates how well a diagnostic test identifies a condition compared to the current gold standard test for it. It compares the numbers of successfully identified positive cases of the disease for each test.

Slim Summary!

- Bias is a systematic error or deviation from the correct answer to a research question and the likelihood of bias varies with study designs;
- Systematic reviews and meta analyses provide a large-scale yet precise method to answer research questions but may not always be practical;
- Selecting the type of study design involves considering several factors, for example the factors in the PICO framework and also practicality.

Afterword

Phew, you did it! You've finished reading your summary. 🎉
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We wish you lots of success with your studies and your exams!

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