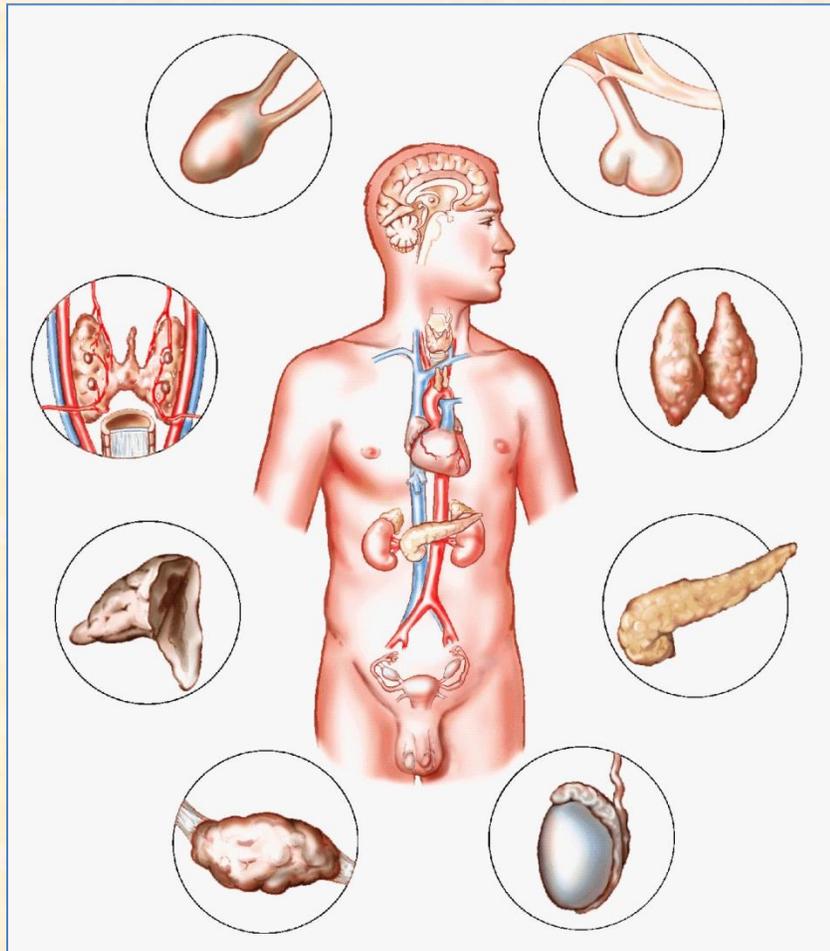


USMLE Step 1 Rapid Learning Series – Course GuideBook



RapidLearningCenter.com
Chemistry : Biology : Physics : Math

Table of Contents – Topical Summary

Series Summary

Core Unit #1 – Introduction to the USMLE Exam

In this core unit, you will review the USMLE Step 1 exam, including its format, content covered, and study tips and approaches. You will also be introduced to the structure and content of this series.

Chapter 01: Introduction to the USMLE Exam

- Exam structure
- Content covered
- Sample types of questions
- Study tips and approaches
- Structure and content of tutorials in this series

Core Unit #2 – Human Development and Behavior

In this core unit, you will review human embryology, development and aging. Human behavior and psychiatry are also reviewed, as well as biostatistics.

Chapter 02: Embryology

- Embryogenesis
- Congenital abnormalities

Chapter 03: Human Development and Aging

- Developmental milestones
- Childhood disorders
- Changes in the elderly

Chapter 04: Behavioral Science and Patient Treatment

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- Clinical trials
- Ethics
- Behavioral physiology

Chapter 05: Psychiatry

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- Personality disorders
- Psychiatric diseases
- Pharmaceutical treatment in psychiatry

Chapter 06: Biostatistics

- Study design
- Concepts of biostatistics

Core Unit #3 – Biochemistry and Biology

In this core unit, you will review core concepts of biochemistry and biology, with an in-depth review of genetics, microbiology and immunology topics relevant to the USMLE Step 1 exam.

Chapter 07: Biochemistry

- Energy metabolism
- Metabolic pathways of small molecules
- Diseases linked to biochemical disorders

Chapter 08: Cell Biology

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- Cellular responses to environmental changes

Chapter 09: Genetics

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- Immune system structure and function
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Core Unit #4 – Pathology and Pharmacology

In this core unit, you will review core concepts of pathology, histology and pharmacology.

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- Repair mechanisms
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- Pharmacology of the autonomic nervous system
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Core Unit #5 – Organ Systems

In this core unit, you will learn about the normal and abnormal function of the major organ systems. Tutorials include clinical notes on important diseases to know for the USMLE Step 1 exam.

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- Normal cardiac processes
- Abnormal cardiac processes
- Cardiovascular therapeutics

Chapter 16: The Endocrine System

- Normal endocrine processes
- Abnormal endocrine processes
- Endocrine therapeutics

Chapter 17: The Gastrointestinal System

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- GI system therapeutic principles

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- Abnormal hematopoietic processes
- Hematopoietic therapeutics

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- Pharmacological treatment of neural abnormalities

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Chapter 21: The Renal System

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- Renal system therapeutics

Chapter 22: The Reproductive System

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- Abnormal reproductive function
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Chapter 23: The Respiratory System

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- Respiratory therapeutics

Chapter 24: Multisystem Processes

- Nutrients and nutrition
- Adaptation to changing environments
- Heavy metals

Tutorial Series Features

This tutorial series is a carefully selected collection of core concept topics in human medicine that cover the essential concepts. It consists of three parts:

USMLE Step 1 Concept Tutorials – 24 essential topics

Problem-Solving Drills – 24 practice sets

Condensed Cheat Sheets – 24 super review sheets

Tutorials

- Self-contained tutorials...not an outline of information which would need to be supplemented by an instructor.
- Concept map showing inter-connections of new concepts in this tutorial and those previously introduced.
- Definition slides introduce terms as they are needed.
- Visual representation of concepts.
- Conceptual explanation of important properties and problem solving techniques.
- A concise summary is given at the conclusion of the tutorial.

Problem Solving Drills

Each tutorial has an accompanying Problem Set with 10 problems covering the material presented in the tutorial. The problem set affords the opportunity to practice what has been learned.

Condensed Cheat Sheet

Each tutorial has a one-page cheat sheet that summarizes the key concepts and vocabularies and structures presented in the tutorial. Use the cheat sheet as a study guide after completing the tutorial to re-enforce concepts and again before an exam.

Chapter by Chapter Content Guide

01: Introduction to the USMLE Exam

Chapter Summary:

The USMLE Step 1 exam covers a number of topics, including human development and behavior; biochemistry and biology; pathology and pharmacology; and organ systems. The first lecture in this series reviews the details of this exam. The tutorial also includes reviews of common anatomical terms and the physical exam, to lay the groundwork for the remaining tutorials in the series.

Tutorial Features:

Specific Tutorial Features:

- Exam structure and strategies
- Content covered
- Sample types of questions
- Study tips and approaches
- Structure and content of tutorials in this series
- Review of anatomical terminology
- The physical exam

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- The USMLE exam structure, including topics and question types
- Study tips and approaches for the Step 1 exam
- Key terminology in anatomy
- Basics of the physical exam

Chapter Review:

USMLE Step 1 Exam

- **Step 1 Exam:** assesses understanding and application of basic science concepts in medicine, with an emphasis on principles and mechanisms underlying health, disease and therapies
- Students are expected to be competent in a number of knowledge areas that can be divided into two basic categories: general principles, which comprises 40-50% of the material, and organ system, which is the other 50-60% of materials.
- All questions in the USMLE Step 1 exam are multiple-choice.
- Questions on the USMLE fall into two categories: the one best answer format, and the clinical vignette.
- Never leave an answer blank – unanswered questions are automatically counted as incorrect answers, and you are not penalized further for providing an incorrect answer.

Review of Anatomical Terminology

- The human body can be divided into the transverse, coronal and median planes. It has bilateral symmetry around the median plane.
- Directional terms describe the positions of body structures relative to other structures or locations within the body. In humans, the superior or cranial end of the body is the head, while the inferior or caudal portion is the feet. Anterior refers to the front, and posterior to the back. Lateral refers to the area away from the median plane, while medial describes a structure near the midline of the body. An intermediate structure is in between lateral and medial.
- The terms superficial and deep are relative to the surface of the body.
- Abduction is the movement of a limb away from the median plane of the body, while adduction is movement towards the median plane.
- Adjusting the angle between two body parts may either be described as flexion, which is a movement that decreases the angle between two parts, or extension, which increases the angle between two body parts.

The Physical Exam

A physical exam consists of four parts:

- **Inspection:** refers to a thorough visual examination of the external features of the patient, including body features, skin color, symmetry of appearance, gait, speech patterns, frequency and volume of breaths during respiration, unusual odors or sounds.
- **Palpation:** areas of the body are felt to determine size, firmness and/or location.
- **Percussion:** a method of tapping on a surface to determine the underlying structure, such as with the thorax and abdomen.
- **Auscultation:** the clinical term for listening to the internal sounds of the body using a stethoscope. This technique is used to examine sounds of the circulatory, respiratory and gastrointestinal tract systems.

02: Embryology

Chapter Summary:

Embryology is the study of early human development, or embryogenesis. A number of congenital abnormalities are possible during embryogenesis that significantly impact human health. This tutorial reviews embryology topics commonly addressed during the USMLE Step 1 exam, including fetal landmarks, early fetal development, developmental milestones of major organ systems, and common congenital abnormalities. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Embryogenesis
- Congenital abnormalities

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Embryogenesis has a number of common fetal development landmarks
- Congenital abnormalities may be due to exogenous or endogenous factors

Chapter Review:

Embryogenesis

Fetal Landmarks

Day 0 – sperm fertilizes egg forming zygote and beginning embryogenesis.

Week 1 – zygote implants as a blastocyst.

Week 2 – bilaminar disk forms as epiblast and hypoblast.

Week 3 – gastrulation occurs, as well as formation of the primitive streak, notochord and neural plate.

Weeks 3-8 – organogenesis occurs and the neural tube is formed. Fetus is extremely vulnerable to teratogens during this period.

Week 4 – heart starts beating and limb buds form.

Week 8 – fetus begins to resemble a baby and fetal movement is present.

Week 10 – male or female expression of genitalia is present.

Early Development

- 2nd week – rule of 2's – 2 germ layers – the epiblast and hypoblast make up the bilaminar disk.
- 3rd week – rule of 3's – 3 germ layers of the gastrula are formed – the endoderm, mesoderm and ectoderm.
- 4th week – rule of 4's – 4 limb buds form, 4 heart chambers present

Twinning

- Monozygotic twins:

- 1 zygote divides evenly to form 2 separate amniotic sacs with a single chorion and placenta
- 1 zygote divides evenly and forms 2 separate amniotic sacs, 2 chorions and 2 placentas
- Dizygotic or fraternal twins: fertilization of independent ova

Placental Development

- The *maternal component* is made up of the decidual basalis which is derived from the endometrium.
- The *fetal component* is composed of 2 layers

Umbilical Cord

- 2 umbilical arteries return deoxygenated blood back to the mother via the placenta.
- 1 umbilical vein provides oxygenated blood to the fetus from the mother via the placenta.
- The urachus carries urinary waste from the fetal bladder back to the mother via the placenta.

Development of the Interventricular Septum

Step 1 – the *muscular ventricular septum* forms leaving an opening between the left and right called the interventricular foramen.

Step 2 – the *aorticopulmonary septum* forms to divide the truncus arteriosus into the aortic and pulmonary trunks.

Step 3 – the muscular ventricular and aorticopulmonary septa join to form the *membranous interventricular septum*, which closes the interventricular foramen.

Development of the Interatrial Septum

Step 1 – the *septum primum* extends toward the endocardial cushions narrowing the *foramen primum*.

Step 2 – the septum primum further develops leaving only perforations and forming the *foramen secundum*.

Step 3 – the *septum secundum* begins to develop while the foramen secundum maintains the left-to-right shunt.

Step 4 – the septum secundum forms a permanent opening called the *foramen ovale*.

Step 5 – the foramen secundum enlarges as the upper portion of the septum primum degenerates.

Step 6 – the remaining lower portion of the septum primum forms the *valve of the foramen ovale*.

Fetal Erythropoiesis

- **Y**olk sac from 3-8 weeks
- **L**iver from 6-30 weeks
- **S**pleen from 9-28 weeks
- **B**one marrow from 28 weeks

Fetal-Postnatal Derivatives

- The umbilical vein forms the *ligamentum teres* in the falciform ligament.
- The umbilical arteries form the *medial umbilical ligaments*.
- The ductus **A**rteriosus forms the *ligamentum Arteriosum*.
- The ductus **V**enosus forms the *ligamentum Venosum*.
- The **F**oramen **O**vale forms the *Fossa Ovalis*.
- The **U**rachus or urachus forms the *medial umbilical ligament*.
- The **N**otochord forms the *Nucleus pulposus of the intervertebral disks*.

Congenital Abnormalities

Teratogens: Thalidomide, ACE inhibitors, Iodide, Vitamin A, Warfarin, anticonvulsants, and x-rays, Fetal infections, Tobacco, Cocaine, Alcohol

Fetal Alcohol Syndrome: the most common cause of congenital abnormalities in the US and includes: microcephaly, facial abnormalities, heart and lung fistulas, limb dislocations, and pre- and postnatal developmental retardation.

Cleft Lip and Cleft Palate:

- Cleft lip is a congenital anomaly that results from the failure of formation of the primary palate – fusion of the maxillary and medial nasal processes.
- Cleft palate is a congenital anomaly that results from failure of formation of the secondary palate – fusion of the lateral palatine process, nasal septum and/or the medial palatine process.

03: Human Development and Aging

Chapter Summary:

Human development and aging involves a number of developmental milestones at birth, at puberty, and in the elderly. In this tutorial, we review key milestones of development and aging, with a focus on developmental milestones, childhood disorders and common changes in the elderly. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material, as well as several sample questions with fully explained answers in the USMLE Step 1 exam style.

Tutorial Features:

Specific Tutorial Features:

- Developmental milestones
- Childhood disorders
- Changes in the elderly

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Developmental milestones provide guidelines for identifying normal and abnormal development patterns
- Childhood disorders may be due to genetic or environmental influences
- Changes in the elderly are a normal progression of changes that may be complicated by disease

Chapter Review:

Developmental Milestones

Apgar Score: Points given to every newborn infant at 1 minute and 5 minutes after birth.

- **A**ppearance: blue – 0, pink trunk – 1, pink trunk and limbs.
- **P**ulse: none – 0, < 100/min – 1, > 100/
- **G**rimace, or response to stimulation: none – 0, positive – 1, positive with pulling away.
- **A**ctivity: none – 0, mild – 1, active – 2.
- **R**espiration: none – 0, weak & irregular – 1, strong & regular – 2.

Developmental Milestones – Infant

- From birth to 3 mos, the rooting reflex is present.
- At 3 months, the infant should be able to hold its head up and smile socially.
- At 4-5 months, the infant should roll from front to back, sit when positioned, and demonstrate facial recognition.
- At 7-9 months, the infant should sit on its own, crawl, recognize voice, and have stranger anxiety.
- At 12-14 months, the up-going Babinski reflex should no longer be present.
- At 15 months, the infant should be walking, speak a few words, and demonstrate stranger anxiety.

Developmental Milestones – Toddler

- At 12-24 months, the toddler should be able to go up stairs, stack 3 blocks, and speak 2 word sentences by the age of 2.
- At 18-24 months, the toddler should be able to stack 6 blocks and realize rapprochement – relationship with others.
- At 24-36 months, the toddler should realize his or her own core gender identity.
- At 24-48 months, the toddler should demonstrate parallel play with other children.

Developmental Milestones – Preschool

- At 30-36 months, the preschooler should be able to stack 9 blocks and be toilet trained. Mnemonic: “pee at 3”.
- At 3 yrs, the preschooler should be able to ride a tricycle (mnemonic: 3 wheeler at 3 yrs), copy line or circle drawings, and speak in complete sentences.
- At 4 yrs, the preschooler should be able to hop on 1 foot, draw simple stick-figure drawings, participate in cooperative play, and brush their own teeth.

Developmental Milestones – School Age (6-11 years old)

- the ability to read
- having same-sex friends and identifying with their same-sex parent
- having an understanding of death, and the development of conscience.

Developmental Milestones – Adolescence (11 yrs of age in girls & 13 yrs of age in boys)

- abstract reasoning
- formation of personality

Tanner Stages of Sexual Development

Stage 1 – no pubic hair or changes in genitalia and breasts.

Stage 2 – soft pubic hair begins to develop, testes enlarge in boys, and breasts tissue elevation begins in girls.

Stage 3 – pubic hair fills in and becomes coarse and curly, penis grows in size and length in boys, and breast tissue begins to extend beyond the areola in girls.

Stage 4 – the penis widens as the scrotum enlarges and darkens in boys, and breast tissue continues to develop with a raised areola in girls.

Stage 5 – male and female adult sexual characteristics are present.

Childhood Disorders

Effects of Low Birth Weight: low birth weight is defined as that less than 2500 g and may be caused by prematurity or intrauterine growth retardation. Low birth weight infants are at risk for respiratory distress syndrome (RDS), infections, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), persistent fetal circulation (PFC)

Effects of Infant Deprivation: refers to the separation of the infant from its mother or caregiver, with lack of physical contact and affection for the infant.

Anaclitic Depression: refers to infants who become depressed secondary to being separated from their mother or caregiver.

Regression in Children: children may regress to younger behaviors such as bedwetting in a toilet trained child that did not previously wet the bed, or reverting to baby-talk. Such behavior can manifest during stressful situations such as punishment, physical illness, birth of a sibling, or hospitalization.

ADHD: Attention deficit hyperactivity disorder or ADHD is a disorder of children who demonstrate a shortened attention span and hyperactive behavior.

Conduct Disorder: refers to patterns of behavior that violate basic social expectations and the personal rights of others.

Oppositional Defiant Disorder: refers to ongoing patterns of defiant, uncooperative and hostile behavior against authority figures that interferes with the child's day to day function.

Tourette's Syndrome: refers to a condition in which the afflicted child demonstrates motor and vocal tics, with possible involuntary profanity. Onset is usually at less than 18 yrs of age and there is an increased incidence in children with OCD.

Separation Anxiety Disorder: refers to a psychological condition with onset at 7 – 8 yrs of age in which the child suffers excessive anxiety over fears of being separated from those they are emotionally bonded to, such as their mother and/or father.

Autism: is a disorder of childhood that is manifested by impaired communication, poor social interaction, lack of formation of relationships, and the presence of repetitive behaviors.

Asperger's Disorder: is considered to be a milder form of autism in which the child has normal intelligence and verbal skills, but still suffers from impaired social interaction, poor relationship formation, and the presence of repetitive behaviors.

Rett's Disorder: is an inherited X-linked disorder that affects only girls and is manifested by loss of developmental milestones, mental retardation, loss of normal hand movements, and stereotypical handwringing.

Childhood Disintegrative Disorder: refers to a condition in which children develop normally until 2 – 3 yrs of age, but then demonstrate a significant loss in motor skills, play skills, expressive and receptive language skills, social skills, and bladder and bowel control.

Child Abuse: refers to behaviors by anyone in contact with children that result in the mistreatment of or harm to a child. There are 4 main categories of child abuse: Physical Abuse, Sexual Abuse, Psychological Abuse, and Neglect

Changes in the Elderly

Sexual Changes

- Males become slower to get an erection, take longer to ejaculate, and have a longer refractory period.
- Females demonstrate vaginal dryness, vaginal wall thinning, and vaginal shortening.

Sleep Patterns: increase in the time it takes to fall asleep (sleep latency), increase in the number of awakenings during the night, decreased REM sleep, decreased slow-wave sleep

Common Medical Conditions in the Elderly: hypertension, heart disease, diabetes, arthritis, osteoporosis, dementia

Psychiatric Conditions Prevalent in the Elderly

- There is an increased suicide rate among the elderly with 18% of all suicides in the United States falling into this age category, while the elderly only makes up 13% of the population.
- The highest suicide rate in the US is among males from 65 – 74 yrs of age.

04: Behavioral Science and Patient Treatment

Chapter Summary:

As it applies to humans, behavioral science refers to a collective study of disciplines that examine and analyze the activities, interactions and relationships among people. Such disciplines include epidemiology, psychology, sociology, ethics and biostatistics. Particularly important is the field of epidemiology which examines the transmission and control of disease in a population, forming conclusions that serve to further improve the general health of that population. This tutorial reviews key concepts of epidemiology, clinical trials, ethics, and behavioral physiology.

Tutorial Features:

Specific Tutorial Features:

- Epidemiology
- Clinical trials
- Ethics
- Behavioral physiology

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Behavioral science refers to a collective study of disciplines that examine and analyze the activities, interactions and relationships among people.
- Clinical Trials are experimental studies involving humans conducted to gather safety and efficacy data for medical interventions.
- The four core ethical principles are autonomy, beneficence, nonmaleficence and justice.

Chapter Review:

Epidemiology

Behavioral science refers to a collective study of disciplines that examine and analyze the activities, interactions and relationships among people.

Epidemiology Studies – The Three C’s:

- **Case control studies** are both observational and retrospective studies that compare a group of people with disease to a group without disease.
- **Cohort studies** are both observational and prospective studies that compare a group of people with a given risk factor to a group without the risk factor in order to assess whether or not the risk factor increases the likelihood of disease.
- **Cross-sectional studies** are observational studies that collect data from a group of people in order to assess the frequency of a disease and its related risk factors at a specific point in time.

Epidemiology Studies – Twin Concordance and Adoption Studies

- **Twin concordance studies** which compare the frequency with which both monozygotic and dizygotic twins develop a disease.
- **Adoption studies** which examine factors in siblings raised by biologic parents compared with those raised by adoptive parents.

Disease Prevention – PDR

- 1° - **Prevent** the disease from occurring altogether.
- 2° - **Detect** the disease early to so that it might be cured.
- 3° - **Reduce** the ill-effects or disability of the disease once it is present.

Reportable Diseases: Certain infectious diseases are required to be reported to health agencies in all states. Such as **Hepatitis A, Hepatitis B, Hepatitis C, HIV, Salmonella, Shigella, Syphilis, Measles, Mumps, AIDS, Rubella, Tb, Chicken pox, Gonorrhea.**

Leading Causes of Death in U.S.

- 0–12 months - Congenital anomalies, prematurity/low birth weight, SIDS, maternal complications during pregnancy, RDS.
- 1–14 years - Trauma, cancer, congenital anomalies, homicide, heart disease.
- 15 – 24 years - Trauma, homicide, suicide, cancer, heart disease.
- 25 – 64 years - Cancer, heart disease, trauma, suicide, stroke.
- > 65 years - Heart disease, cancer, stroke, COPD, pneumonia, influenza.

Medicare and Medicaid

Medicare is a federal health insurance program that funds hospital and medical care for the elderly and disabled. Medicare Part A covers hospitalizations; Medicare Part B covers outpatient care.

Medicaid is a federal and state funded, state run program that provides medical services funding for people of limited income.

Clinical Trials

Clinical Trials: refer to experimental studies involving humans conducted to gather safety and efficacy data for medical interventions.

Phases of Clinical Trials

- **Phase 1** – a small group of healthy volunteers receive a drug and the safety, toxicity and pharmacokinetics of the drug are measured.
- **Phase 2** –a small group of patients with a disease of interest receive the drug and its optimal dosing, treatment efficacy and adverse side effects are assessed.
- **Phase 3** - a much larger number of patients are randomized into groups who receive the drug being studied, and receive either the best known treatment for the disease of interest, or a placebo, in order to assess how effective the experimental drug is in comparison to what is being received by the other groups.

Meta-Analysis: is the process by which the results of several studies testing similar hypotheses are combined to form a conclusion with more statistical power than the individual studies that are being combined.

Types of Bias

- **Selection bias** – occurs when the assignment to a study group is not random.
- **Recall bias** – occurs when previous knowledge alters recall by a study subject.
- **Sampling bias** – occurs when some members of the population are more likely to be included in the study than others and therefore the subject groups are not representative of the general population.

- **Late-look bias** – occurs when sampling is obtained too late so as some study subjects previously in the study may no longer be present.
- **Procedure bias** – occurs when not all subject groups are treated the same.

Ways to Reduce Bias: Blind Studies, Placebo responses, Crossover studies & Randomization

Ethics

The Hippocratic Oath: is a pledge historically taken by physicians when they graduate from medical school in which they swear to practice medicine in an ethical manner.

The Four Core Ethical Principles

- **Autonomy** – refers to the physician having respect for a patient as an individual and their ability to make their own decisions regarding their healthcare.
- **Beneficence** – refers to the physician acting in the best interest of the patient, which may sometimes conflict with the patient's autonomy.
- **Nonmaleficence** – refers to the physician acting so as to do no harm to the patient.
- **Justice** – refers to the physician treating all patients fairly.

Informed Consent: refers to a manner of communication between a patient and physician in which the result is that the patient agrees to undergo a certain medical intervention.

Exceptions to Informed Consent:

- The patient is incapable of making the decision or is legally incompetent.
- Consent is implied in an emergency situation.
- Therapeutic privilege occurs in a situation where disclosure of the information would pose serious harm to the patient, so the information is withheld.
- A waiver is generated in which the patient waives the right of informed consent.

Consent for Minors: Informed consent for minors must be obtained from a parent or legal guardian, except in the case that the minor is married or otherwise emancipated.

Advance Directives – Oral and Written

- **Oral advance directive** refers to a situation in which an incapacitated patient's previous oral statements guide their end of life care.
- **Written advanced directives** may take 2 forms: **Living will & Durable power of attorney**

Patient Confidentiality: refers to the respect for a patient's privacy and autonomy.

Exceptions to Patient Confidentiality

- If there is potential for significant harm to come to the patient or others.
- If there is no method available to inform others who are at risk.
- If there are steps that the physician can make that would prevent harm to the patient or others.

The Four D's of Malpractice: Duty, Dereliction, Damage & Direct.

Good Samaritan Laws: are legal acts that protect an individual from liability in situations when they act to aid others that are injured or ill.

Behavioral Physiology

Effects of Stress on the Body: Stress has a significant effect on the body causing the production of catecholamines, 17-OH corticosteroids, free fatty acids, lipids and cholesterol.

Body Mass Index (BMI): is a measurement of weight relative to height and offers an indication of the amount of total body fat.

Sleep Stages

Stage 1 – light sleep for 5% of the time with theta EEG waveform.

Stage 2 – deeper sleep for 45% of the time with sleep spindles and K complexes on EEG.

Stage 3-4 – aka 'slow-wave sleep' is the deepest non-REM sleep, occurs for 25% of the time with delta EEG waveform.

REM - dreaming occurs with loss of motor tone for 25% of the time with beta EEG waveform.

Brain Areas Involved in Sleep: Sleep is initiated by the serotonergic predominance of the raphe nucleus.

REM Sleep: rapid eye movement sleep is a normal stage of sleep stimulated by ACh which occurs approximately every 90 minutes while asleep.

Narcolepsy and Cataplexy

- **Narcolepsy** is a sleep disorder due to irregularity of sleep-wake cycles which is characterized by excessive daytime sleepiness such that those affected fall asleep at inappropriate times.
- **Cataplexy** is an associated disorder that manifests with sudden and transient loss of muscle tone, usually as a result of a strong emotional stimulus.

05: Psychiatry

Chapter Summary:

Psychiatry is the medical specialty dedicated to the study and treatment of various mental disorders. In this tutorial, we review the core concepts of psychology and psychiatric diseases, including personality disorders and common psychiatric diseases. The tutorial includes a review of commonly prescribed pharmaceutical therapeutics for the treatment of psychiatric disorders. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Psychology
- Personality disorders
- Psychiatric diseases
- Pharmaceutical treatment in psychiatry

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Psychiatry is the medical specialty dedicated to the study and treatment of various mental disorders.
- Orientation is essentially self-awareness – it refers to the patient’s ability to understand who they are, where they are, and the time period in which they are living.
- Personality is a core trait which can occasionally undergo change during disease processes.
- Personality traits are enduring patterns of perceiving, relating to, and thinking about the environment and oneself that encompasses the wide range of social and personal contexts in which personality is evident.

Chapter Review:

Psychiatric Diseases

Orientation is essentially self-awareness – it refers to the patient’s ability to understand who they are, where they are, and the time period in which they are living.

Specific types of orientation disorders include:

- **Depersonalization:** which occurs when the person’s mind does not feel connected to their body
- **Anosognosia:** which is a lack of awareness that the patient is ill, and
- **Autotopagnosia:** which is a severe loss of the ability to identify and/or locate your own body parts

Amnesia – a disruption of memory. There are 2 common types: 1) **Retrograde** is when the patient cannot recall information before the injury. 2) **Anterograde** is when the patient cannot remember life events after the injury.

Delirium – an acute state of confusion.

Dementia – With dementia, the most common change is a gradual decrease in cognition, most commonly memory loss.

Hallucination, Illusion, Delusion & Loose Association

- **Hallucinations** take place in the absence of an external stimulus.
- **Illusions** misinterpret a real, external stimulus, such as the visual appearance of an object.
- **Delusions** are false beliefs that cannot be changed in the face of facts to the contrary.
- **Loose associations** are issues with tying together associated thoughts in a coherent fashion.

Dissociative Fugue: is diagnosed when a patient has one or more episodes of amnesia, and exhibits an inability to recall the past combined with confusion about their identity that may include the assumption of a new identity.

Types of Hallucination: By nature, they affect the sensory system, and are often associated with other psychiatric disorders. These include: **Visual & auditory hallucinations, Tactile hallucinations & Olfactory hallucinations**

Schizophrenia: is diagnosed when there is are periods of psychosis and disturbed behavior combined with declined functioning over a period greater than 6 months.

- **Positive & Negative Symptoms of Schizophrenia:** Diagnosis of schizophrenia requires the presence of at least 2 symptoms. The symptoms are divided into those that are “positive” and those that are “negative”.
- **The 5 Types of Schizophrenia:** Disorganized, Catatonic, Paranoid, Undifferentiated & Residual

Bipolar Disorder: There are 6 different types of bipolar disorder, categorized based on the differing combinations of manic & depressive episodes.

Manic Episodes: occur when there is a period of abnormally elevated or irritable mood, or excessive energy levels, lasting at least 1 week.

Hypomanic Episodes: are remarkably similar to manic episodes, except there is no severe impairment of social or occupational functioning or psychotic features that require hospitalization.

Major Depression: is a mood disorder that is diagnosed when there are at least 5 of the following symptoms present for at least 2 weeks: **D**epressed mood most of the day, **E**nergy loss, **A**nhednoia (which is loss of interest), **D**eath thoughts that are recurrent, **S**leep disturbances, **W**orthlessness or excessive guilt, **A**ppetite of weight change, **M**ental concentration or decisiveness decreases & **P**sychemotor agitation.

Panic Disorder: consists of short periods of intense fear and discomfort that peaks in intensity approximately 10 minutes into the episode.

Phobias: is an intense, persistent fear of certain situation, objects or people.

Post-Traumatic Stress Disorder (PTSD): is a severe anxiety disorder in which the patient experiences recurring flashbacks or nightmares related to a traumatic event.

Other Anxiety Disorders: **Adjustment Disorder & Generalized Anxiety Disorder**

Levels of Gain: Gain is primary, secondary or tertiary.

Somatoform Disorders & Gain: mental condition where the patient experiences symptoms that mimic physical disease or injury where there are no identifiable causes.

Personality Disorders

Personality Traits & Disorders: Personality is a core trait which can occasionally undergo change during disease processes. Personality traits are enduring patterns of perceiving, relating to, and thinking about the environment and oneself that encompasses the wide range of social and personal contexts in which personality is evident.

Personality Disorders: occur when these traits become maladaptive and inflexible, impairing social and/or occupational functioning. They are often "clustered" into 3 categories that can be remembered as follows: **A: weird, B: wild & C: worried.**

- **Cluster A Personality Disorder ("Weird"):** Their behavior is considered eccentric compared to social norms, yet there is no evidence of psychosis. The 3 primary types are *paranoid, schizoid & schizotypal.*
- **Cluster B Personality Disorders ("Wild"):** These patients exhibit dramatic changes in personality often associated with mood disorders and/or substance abuse. These disorders include: antisocial, borderline, histrionic & narcissistic.
- **Cluster C Personality Disorders ("Worried"):** These patients are anxious or fearful, and often exhibit symptoms of anxiety disorders. These disorders include: *avoidant, obsessive-compulsive & dependent disorders.*

Schizo-Disorders: are actually spectrums of disorders. From least to most severe, these are: schizoid, schizotypal (which is schizoid plus odd thinking), schizophrenic and schizoaffective.

Eating Disorders: are considered to be personality disorders because of their foundation in a person's self-perception of their body weight and image. The 2 types are: **Anorexia Nervosa & Bulimia and Nervosa.**

Substance Dependence: is when an individual persists in the use of an abusive substance despite issues related to use of that substance, typically drugs or alcohol.

Substance Abuse: takes dependence one step further to become a maladaptive pattern leading to clinically significant impairment or distress.

Withdrawal: When an abusive substance is withdrawn, there is a set of associated behavioral, physiologic & cognitive state changes that take place.

Psychology

Intelligence Quotient (IQ) - can be measured using tests that include the Stanford-Binet and Wechsler tests.

Conditioning – Classical & Operant: Psychology is the study of human behaviors. Two types of conditioning are:

- Classical conditioning: in which the patient learns a specific behavior or physiological response to a specific stimulus.
- Operant conditioning: this is learning in which a specific response is elicited because the patient learns it is associated with a reward or punishment.

Conditioning – Reinforcement Schedules: Reinforcement schedules dictate how quickly a behavior is learned or lost.

Structural Theory of the Mind: According to Freud, there are 3 structures of the mind: **Id, Ego & Superego.**

Topographic Theory of the Mind: is similar to Freud's structural theory in its presumption of three layers of consciousness: **Conscious, Preconscious & Unconscious**

Ego Defenses (Immature & Mature): are automatic, unconscious reactions to psychological situations that are designed to protect a person's ego, and are divided into immature and mature responses.

- Immature defenses include acting out, dissociation, denial, regression, repression, and rationalization

- Mature ego defenses are less primitive responses, and include behaviors such as altruism, humor, sublimation and suppression.

Pharmaceutical Treatment in Psychiatry

Antipsychotics (Neuroleptics): Most antipsychotics block the D2 dopamine receptors, and are used for treating disorders such as schizophrenia, psychosis, acute mania, and Tourette's syndrome.

Atypical Antipsychotics: block 5HT-2 & dopamine receptors, & are useful for treating both the positive and negative symptoms of schizophrenia.

Lithium: is the classic treatment for bipolar affective disorder, and is used as a mood stabilizer.

Busipirone: is an anxiolytic used to treat generalized anxiety disorder, without causing sedation or addiction.

Antidepressants - SSRIs, Hetertricyclic antidepressants (including tricyclic antidepressants, or TCAs), and MAO inhibitors.

SSRIs - are selective serotonin reuptake inhibitors used to treat depression and OCD by preventing reuptake of serotonin once released into the synapse.

TCAs - Tricyclic antidepressants block the reuptake of both norepinephrine and serotonin.

MAO Inhibitors - such as phenelzine and tranylcypromine, non-selectively inhibit MAO, thereby increasing the levels of amine neurotransmitters.

Methylphenidate (Ritalin) - Ritalin has a similar mechanism of action to amphetamines, which is increased presynaptic release of norepinephrine.

06: Biostatistics

Chapter Summary:

Biostatistics uses proper study design and data analysis for disease measurement and prevention. The USMLE Step 1 exam increasingly asks questions that require application of biostatistical concepts such as predictive values and specificity, requiring an understanding of these concepts. In this tutorial, we review need-to-know concepts including study design, clinical trials, outcome analysis, meta-analysis, and the use of biostatistics for disease prevention.

Tutorial Features:

Specific Tutorial Features:

- Study design
- Concepts of biostatistics

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Biostatistics uses proper study design and data analysis for disease measurement and prevention.
- Biostatistics is useful for PDR: prevent, detect, and reduce disability.

Chapter Review:

Study Design

Observational Studies – Case Control

- One asks, “What happened?”
- A group with a disease is compared to a group without the disease
- The study is observational and retrospective and measures the OR, (odds ratio)

Observational – Cohort Study

- One asks, “What will happen?”
- A group with a given risk factor is compared to a group without the risk factor
- The study is observational and retrospective and measures the RR, (relative risk)

Observational – Cross-Sectional

- One asks, “What is happening?”
- At particular point in time, data is collected from a group of people to determine the frequency of disease, along with related risk factors.
- The study is observational and measures disease prevalence

Observational – Twin Concordance and Adoption Studies

- In **twin concordance**, one compares the frequency of disease development for both twins, monozygotic or dizygotic; Measures heritability
- In **adoption studies**, one compares siblings raised by biological parents to those raised by adoptive parents; Measures heritability and environmental factors

Experimental Studies – Clinical Trials: involve humans and they seek to compare 2 or more treatments; There are three phases in clinical trials:

- In phase I a small number of patients, usually healthy, are used.
- In phase II a small number of patients with the disease of interest are used.

- In phase III a large number of patients are used.

Experimental Studies – Meta-Analysis

- Several studies are examined
- The data is combined and an overall conclusion is reached
- Can yield a greater statistical power, although this depends on the quality of the individual studies and/or in bias in deciding which studies to combine

Sampling and Sample Size (not in First Aid)

- Researchers cannot sample an entire population, as a consequence they must make decisions about how to select individuals for study, sampling, and how many individuals to select, sample size.
- In sampling the concern is to ensure that the selection of the population is unbiased or random.
- In selecting the sample size the concern is to ensure that the measured outcome is statistically significant.

Subject selection & exposure allocation (eg, randomization, stratification, self-selection, systematic assignment) (not in First Aid)

- **Simple random sampling, or randomization** - the subjects are chosen randomly, e.g., using random number generators.
- **Stratified random sampling or stratification** - subgroups are randomly sampled.
- **Systematic sampling** – every k^{th} person is selected.
- **Self-selection**, individuals select themselves to be part of the study.

Outcome Analysis – Prevalence vs. Incidence

- Prevalence is defined as the total cases in population at a given time divided by the total population at risk.
- Incidence is defined as the new cases in population over a given time period divided by the total population at risk during that time.

Concepts of Biostatistics

Outcome Analysis – Evaluation of Diagnostic Tests – Sensitivity

- Sensitivity measures the proportion of actual positives, who test positive.
- Sensitivity is equal to the number of true positives divided by the number of true positives plus the number of false negatives.

Outcome Analysis – Evaluation of Diagnostic Tests – Specificity

- Specificity measures the proportion of all people without a disease, who test positive.
- Specificity is equal to the number of true negatives divided by the number of true negatives plus the number of false positives.

Outcome Analysis – Evaluation of Diagnostic Tests – Positive Predictive Value

- The positive predictive value is the proportion of positive tests that are true positives.
- It is equal to the number of true positives divided by the number of true positives plus the number of false positives.
- The PPV gives the probability that a person truly has the disease given a positive test result

Outcome Analysis – Evaluation of Diagnostic Tests – Negative Predictive Value

- The negative predictive value is the proportion of negative tests that are true negatives.
- It is equal to the number of true negatives divided by the number of true negatives plus the number of false negatives.
- The NPV gives the probability that a person truly is disease-free given a negative test result.

Odds Ratio

- The odds of having a disease in an exposed group, divided by, the odds of having a disease in an unexposed group.

Relative and Attributable Risks

- The relative probability in the exposed group of getting a disease as compared to the

unexposed group.

- The attributable risk is the difference in risk between the exposed and unexposed groups.

Precision vs. Accuracy

- Precision in a test refers to (1) consistency and reproducibility, i.e. the reliability and (2) the absence of random variation
- Accuracy in test refers to the trueness or validity of the measurement.

Random vs. Systematic Error

- Random error leads to reduced precision while systematic error leads to reduced accuracy.

The Five Types of Bias

- 1) Selection bias, 2) Recall bias, 3) Sampling bias, 4) Late-look bias, and (5) Procedure bias

Ways to Reduce Bias

- (1) blind or double blind studies, (2) use of placebos, (3) crossover studies, where each subject acts as their own control, (4) randomization.

Statistical Distribution – Normal Distribution

- The data is symmetrically distributed about the mean value.

Statistical Distribution – Bimodal, Positive & Negative Skew

- A bimodal distribution has two peaks in the probability distribution function.
- In positive skew the mean is greater than the median which is greater than the mode.
- In negative skew the mean is less than the median which is less than the mode.

Types of Hypothesis – Null: A statement that you want to test. It asserts a lack of effect or of difference.

Types of Hypothesis – Alternative: It is compared with the null hypothesis & there is some difference.

Error – Type I: Also known as error of the first kind, α error, or a false positive, occurs when no effect or difference exists but it is stated that there is an effect or difference.

Error – Type II: Also known as an error of the second kind, a β error, or a false negative, occurs when an effect or difference exists but it is stated that no effect or difference occurred.

Power (1 - β): It is the probability of rejecting the null hypothesis when it is in fact false. As power increases, the chances of a Type II error decrease.

Standard Deviation & Standard Error: is defined as, σ , and is the square root of its variance. It shows how much variation there is from the mean.

Confidence Interval – (CI): gives an estimated range of values which is likely to include an unknown population parameter.

T-test: checks whether the means of two groups are statistically different from each other.

ANOVA: generalizes the t-test to 3 or more groups; it checks the difference between the means of 3 or more groups.

χ^2 : The chi-squared test is used most commonly to compare observed data with the expected data from a scientific hypothesis.

Correlation Coefficient (r): The correlation coefficient, r, ranges from -1 to +1.

Biostatistics for Disease Measurement & Prevention

Disease Prevention – PDR: Prevent, detect, and reduce disability

07: Biochemistry

Chapter Summary:

For the USMLE Step 1 exam, the biochemistry material focuses on metabolic pathways, with emphasis on critical enzymes and enzymes deficiencies that lead to disease. This tutorial provides a review of the metabolic pathways involved in energy metabolism and the related metabolic pathways of small molecules. Emphasis is on relating these pathways to diseases linked to biochemical disorders, and discussing practice questions similar to those on the Step 1 exam.

Tutorial Features:

Specific Tutorial Features:

- Overview of energy metabolism
- Key features of metabolic pathways of small molecules
- Review of diseases linked to biochemical disorders

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Energy metabolism
- Metabolic pathways of small molecules
- Diseases linked to biochemical disorders

Chapter Review:

Metabolism

Metabolism: Occurs at the mitochondria and/or the cytoplasm.

Rate-Determining Enzymes in Metabolic Processes

- Isocitrate dehydrogenase, Carbamoyl phosphate synthase I, Acetyl-CoA carboxylase, Carnitine acyltransferase I, HMG-CoA reductase, ALA synthase

Overview of HMP Shunt: The HMP shunt pathway is a process that generates NADPH & sugars.

Overview of Glycolysis: The glycolysis pathway converts glucose into pyruvate.

Overview of Gluconeogenesis: The gluconeogenesis pathway results in the generation of glucose from non-carbohydrates.

Energy Metabolism

ATP:

- (1) Aerobic metabolism of glucose, which in the heart and liver produces 32 ATP via the malate-aspartate shuttle and in the muscle produces 30 ATP via the glycerol-3-phosphate shuttle.
- (2) Anaerobic glycolysis, which produces only 2 ATP for every glucose molecule.

Activated Carriers: Serves as energy shuttles

5-Adenosyl-Methionine: SAM, the methyl donor man, is made from ATP and methionine.

Universal Electron Acceptors: the universal electron acceptors, nicotinamides, NAD^+ , NADP^+ , and flavin nucleotides, FAD^+ , participate in oxidation/reduction reactions.

Oxygen-Dependent Respiratory Burst: NADPH oxidase employs oxygen to oxidize the formed NADPH with resultant production of superoxide anion.

Hexokinase vs Glucokinase: hexokinase is found everywhere while glucokinase is found in the liver and β cells of the pancreas.

Regulation of Glycolysis

- The net glycolysis reaction is: $\text{Glucose} + 2 \text{ P}_i + 2 \text{ ADP} + 2 \text{ NAD}^+ \rightarrow 2 \text{ Pyruvate} + 2 \text{ ATP} + 2 \text{ NADH} + 2 \text{ H}^+ + 2 \text{ H}_2\text{O}$
- **Key Enzymes:** Hexokinase or glucokinase, Phosphofructokinase, Phosphoglycerate kinase, Pyruvate kinase

F2, 6BP: A metabolite that affects the activity of phosphofructokinase and fructose 1,6-bisphosphatase.

Glycolytic Enzyme Deficiency

- Due to deficiencies in pyruvate kinase, 95% of cases, phosphoglucose isomerase, 4% of cases, & other glycolytic enzymes.
- Associated with hemolytic anemia as the activity of $\text{Na}^+ \text{-K}^+ \text{-ATPase}$ decreases leading to RBC swelling and lysis.

Pyruvate Dehydrogenase Complex

- Contains three enzymes and requires five cofactors: the first four B vitamins, pyrophosphate, FAD, NAD and CoA, and lipoic acid.
- The net reaction is: $\text{pyruvate} + \text{NAD}^+ + \text{CoA} \rightarrow \text{acetyl-CoA} + \text{CO}_2 + \text{NADH}$.

Pyruvate Dehydrogenase Deficiency: causes a backup of substrate, pyruvate and alanine, to occur. And the backup results in lactic acidosis.

Pyruvate Metabolism:

- (1) Amino groups are carried by alanine from the muscle to the liver.
- (2) Oxaloacetate can have 2 functions, it can replenish the TCA cycle
- (3) To transition from glycolysis to the TCA cycle.
- (4) Be the end of anaerobic glycolysis. This is a major pathway in RBCs, kidney medullar, leukocytes, testes, cornea and lens.

Cori Cycle: The metabolic burden is shifted to the liver, as lactate, generated under anaerobic metabolism, becomes a source of glucose for muscle and RBCs.

TCA Cycle:

- In one turn of the citric acid cycle, the TCA cycle, 3 NADH, 1 FADH_2 , 2CO_2 and 1 GTP are produced per acetyl-CoA.
- Two acetyl-CoA are produced per glucose, which means two cycles are completed for each glucose molecule.

Electron Transport Chain and Oxidative Phosphorylation

- There are two routes for the NADH electrons from glycolysis to enter the mitochondria: the malate-aspartate or glycerol-3-phosphate shuttle.
- Oxidative phosphorylation can be poisoned through a number of mechanisms: Electron transport inhibitors, ATPase inhibitors & uncoupling agents.

Metabolic Pathways of Small Molecules

Gluconeogenesis:

- **Pyruvate carboxylase** is found in the mitochondria.
- **PEP carboxykinase** is found in the cytosol.
- **Fructose-1,6-bisphosphate** is found in the cytosol.
- **Glucose-6-phosphate** is found in the ER.

HMP Shunt: Produces NADPH and is required for three purposes

- Fatty acid biosynthesis, Steroid synthesis, & Glutathione reduction in RBCs

G6P Dehydrogenase Deficiency:

- In HMP shunt, which produces NADPH, the enzyme G6PD is a rate-limiting enzyme. To keep glutathione reduced, which neutralizes free radicals and peroxides, NADPH is required.

Fructose Metabolism Disorders:

- (1) Fructose intolerance is caused by a hereditary deficiency of **aldolase B**, which is recessive.
- (2) Essential fructosuria occurs when there is a defect in **fructokinase**.

Galactose Metabolism Disorders:

- Galactosemia is caused by the absence of galactose-1-phosphate uridylyltransferase and is autosomal recessive.
- **Galactokinase deficiency** causes galactosemia and galactosuria.

Lactose Deficiency: Occurs due to the loss of brush-border enzyme.

Amino Acids: only the L-form amino acids are found in protein

Ammonium Transport: transport of ammonium between muscle and liver is facilitated by alanine and glutamine.

Urea Cycle: the enzyme carbamoyl phosphate synthetase I is the rate limiting step.

NH_4^+ , CO_2 and aspartate enter the cycle, urea exits the cycle.

Amino Acid Derivatives: include phenylalanine, tryptophan, histadine, glycine, arginine and glutamate.

Phenlketonuria, Alkaptonuria & Albinism: due to the loss of brush-border enzyme.

Metabolic Fuel Use: Exercise & Fasting and starvation

Insulin: Insulin is made in the β cells of the pancreas in response to ATP from glucose metabolism acting on K^+ channels and depolarizing cells.

Glycogen Storage Diseases: There are 12 types all of which result in glycogen accumulation due to abnormal glycogen metabolism.

Glycogen Synthesis: gluocose-6-phosphate is converted to glucose-1-phosphate which is converted to UDP-glucose by the action of uridylyl transferase.

Lysosomal Storage Diseases: are caused by a deficiency in one of the many lysosomal enzymes.

Fatty Acid Metabolism Sites: occurs in the cytosol.

Ketone Bodies: form when the TCA cycle stalls, this shunts glucose and FFA to ketone bodies which are excreted in urine and the breath smells like acetone.

Essential Fatty Acids: linoleic and linolenic acid.

Porphyrias: Lead poisoning, acute intermittent porphyria, and porpphyria cutanea tarda

Heme Catabolism: converted to biliverdin which is converted to bilirubin.

Hemoglobin – CO₂ Transport: Reverse from oxygen CO₂ is transported from tissue to lungs.

Hemoglobin Modifications: Modifications to hemoglobin reduce the oxygen saturation and the oxygen content, leading to tissue hypoxia.

08: Cell Biology

Chapter Summary:

Cell biology is a core concept that underlies understanding of tissue and organ system biology. This tutorial reviews core concepts that frequently appear on the USMLE Step 1 exam. The tutorial is divided into three parts: cellular structure and function; protein structure and function; and cellular responses to environmental changes, including adaptation and cell death. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Review of cellular structure and function
- Review of protein structure and function
- Cellular responses to environmental changes

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Cellular structure and function
- Protein structure and function
- Cellular responses to environmental changes

Chapter Review:

Cellular Structure and Function

Cellular Components

Eukaryotic cells have a number of organelles and other structures, including: mitochondria, rough and smooth endoplasmic reticula, cytoplasm, nucleus, and Golgi apparatus.

Cell Cycle

- There are four phases in the cell cycle, G_1 phase, S phase, G_2 phase and M phase.
- The G_1 , S and G_2 phases are collectively known as interphase.
- M phase is the shortest, during which two coupled processes occur, mitosis, the chromosomes are divided between the two daughter cells, and cytokinesis, the cytoplasm divides in half.
- Regulation of the cell cycle is controlled by cyclins and cyclin-dependent kinases, CDKs. CDKs are constitutive and inactive.
- Permanent cells stay in G_0 and regenerate from stem cells.
- Stable, or quiescent, cells enter G_1 from G_0 upon stimulation.
- Labile cells never enter G_0 and divide rapidly.

Rough Endoplasmic Reticulum

- At the rough endoplasmic reticulum secretory proteins are synthesized and N-linked oligosaccharides are added to many proteins.
- Cells rich in rough endoplasmic reticulum include: mucus-secreting goblet cells of the small intestine and antibody-secreting plasma cells.

Smooth Endoplasmic Reticulum

- At the smooth endoplasmic reticulum a variety of metabolic processes take place including, synthesis of lipids and steroids, metabolism of carbohydrates, regulation of calcium concentration, drug detoxification, attachment of receptors on cell membrane proteins, and steroid metabolism.

Golgi Apparatus and Lysosomes

- The primary function of the Golgi apparatus is to process and package proteins and lipids from the ER to the plasma membrane, lysosomes, and secretory vesicles.
- The structure of the Golgi is a series of flat membrane stacks known as cisternae. Proteins enter, progress through, and are packaged and sent to their final destination.
- Lysosomes contain enzymes to aid in the digestion of food and they act as the cell's garbage disposal removing worn out organelles, viruses and bacteria. They are formed from early endosomes by the addition of hydrolytic enzymes.

Microtubules: are long cylindrical structures composed of α - and β -tubulin arranged in a helical formation.

Cilia

- There are two types of cilia, motile cilia, composed of two central microtubule doublets in addition to the nine outer doublets, a 9+2 axoneme, and non-motile, or primary, cilia, composed of a ring of nine outer microtubule doublets, called a 9+0 axoneme.
- The motor protein dynein is an ATPase; its motion causes the sliding of the microtubules in the axoneme of motile cilia, producing the bending movement needed for cilia to beat.
- In **Kartagener's syndrome** cilia are immotile due to a defect in the structure of dynein.

Cytoskeleton

- The key components include: (1) Actin and the motor protein myosin, (2) Microtubules & (3) Intermediate filaments.

Plasma Membrane: contains lipids, sterols, proteins and carbohydrates. The lipid composition is asymmetric with the negatively charged lipids found in the inner leaflet.

Mitochondria: are membrane-enclosed organelles known as the powerhouse of the cell for their role in producing cellular ATP.

Maintenance of Membrane Potential – the Na-K ATPase

- The sodium-potassium exchange pump plays a major role in establishing the membrane potential.
- The protein is an integral membrane protein and the ATP site is located on the cytoplasmic side.

Collagen: is the most abundant protein in the human body, it is extensively modified & it acts to organize and strengthen the extracellular matrix. There are 4 types.

Collagen Synthesis & Structure: the synthesis of collagen is a multistep process and there is some variation in the details between the different types of collagen.

Ehlers-Danlos Syndrome and Osteogenesis Imperfecta

- Ehlers-Danlos syndrome arises from a defect in collagen synthesis, primarily the synthesis of type III collagen.
- Osteogenesis imperfecta also arises from a defect in collagen synthesis; there are a variety of gene defects leading to different types of osteogenesis imperfecta.

Elastin: is an elastic protein found within the lungs, large arteries, elastic ligaments, vocal cords, skin, bladder, elastic cartilage and ligament flava.

Protein Structure and Function

Protein Structure: the folding of a protein begins with the amino acid sequence of the protein, which is called the primary structure.

Protein Folding: the folding pattern depends on bonds such as weak hydrogen bonds between amino acids that lie close to each other, strong ionic bonds between R groups with positive and negative charges, and disulfide bridges (which are strong covalent S-S

bonds). Types of Proteins: 1) Enzymes, 2) Structural Proteins & 3) Regulatory Proteins
Review of Enzyme Kinetics

Types of Enzyme Inhibition: Enzyme inhibitors may be competitive or noncompetitive. Competition refers to competition between the normal substrate for the enzyme, and the inhibitor in question.

Signal Transduction – Receptors: We can describe receptors as the components of a cell or organisms that interact with a drug and initiate the chain of events that lead to the drug's observed effect.

Signal Transduction – Second Messengers: tend to amplify their signal strength as they pass from one step to the next, creating what are known as signal transduction cascades.

Signal Transduction – Ion Channels: are transmembrane proteins that transmit their signal intracellularly through passage of small ions across the cell membrane via passages opened within the proteins themselves.

Cellular Responses to Environmental Changes

Maintenance of pH

- The interior of each cell contains the cytoplasm, which has a pH value typically of 7.4 +/- 0.1.
- Maintenance of pH is required to create an environment where normal processes can take place.

Inclusion Bodies: Cells may sometimes exhibit cytoplasmic or nuclear aggregates of stainable substances, such as proteins or pigments, called inclusion bodies.

Transport across the Cell Membrane: A common environmental change that cells must handle is the passage of molecules across the membrane. There are five primary mechanisms by which a compound can cross a cell membrane. **1. Filtration, 2. Passive diffusion, 3. Active transport, 4. Facilitated diffusion, 5. Endocytosis**

Filtration: occurs when small molecules cross the cell membrane through pores down a concentration gradient. By nature, molecules that are filtered must be: **1. small (MW ≤ 100), 2. Water soluble (hydrophilic). 3. non-ionized**

Passive Diffusion: is the most common mechanism by which foreign compounds cross the cell membrane. It is an energy-independent process that does not rely on cellular ATP, and is influenced primarily by the chemical characteristics of the compounds themselves.

- 3 key criteria: 1. there must be a concentration gradient across the membrane. 2. The compound must be lipid soluble. 3. the compound must be non-ionized

Degree of Ionization: One important concept is that the degree of ionization of a compound will vary by the pH of the solution it is in; thus, a compound that may be easily absorbed across the membrane in the stomach where the pH is around 1 may cross the cell membrane less easily in the blood, where the pH is around 7.4, if it becomes ionized in the higher pH.

Active Transport: By definition, active transport involves: 1. a specific membrane-bound carrier system (transporter), 2. a metabolic energy source to drive the process (most commonly ATP), 3. transport against a concentration gradient

Facilitated Diffusion: is similar to active transport because 1) there are specific transporters involved and 2) the process may be saturated or inhibited.

Endocytosis: is the process by which the cell membrane forms a pocket around a molecule to draw it into the cell in a membrane-bound vesicle that then enters the intracellular lysosomal degradation system.

Cell Injury – Reversible vs Irreversible

- **Reversible cell injury** involves: cellular swelling, nuclear chromatin clumping, and a decrease in ATP synthesis, ribosomal detachment and glycogen depletion.

- **Irreversible cell injury** involves: damage to the plasma membrane, lysosomal rupture, calcium influx leading to an increase in oxidative phosphorylation, mitochondrial permeability and nuclear pyknosis, karyolysis, karyorrhexis.
- Apoptosis:** is often referred to “programmed cell death” because it can occur naturally as part of the body’s tissue maintenance, allowing for removal of damaged cells from tissues.
- Necrosis:** is a form of cell death that is distinguishable from apoptosis in that it is not controlled and orderly like apoptosis.

09: Genetics

Chapter Summary:

Genetics is the study of gene expression, which influences genetic attributes of individuals and populations, and is a primary determinant of numerous clinical diseases. On the Step 1 exam, genetics is a high-yield topic closely related to biochemistry, cell biology and pathology. This tutorial reviews critical concepts of gene expression, population genetics and clinical genetics, with a review of the latest medically relevant laboratory techniques every student taking the Step 1 exam should be familiar with.

Tutorial Features:

Specific Tutorial Features:

- Gene expression
- Review of population & clinical genetics
- Medically relevant laboratory techniques

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Gene expression
- Population genetics
- Clinical genetics
- Laboratory techniques

Chapter Review:

Gene Expression

Chromatin Structure: in chromatin, negatively charged DNA loops twice around each positively charged histone octamer, to form a nucleosome bead, think beads-on-a-string, and the histone H1 turns the beads-on-a-string structure into a 30 nm diameter helical structure.

Heterochromatin vs. Euchromatin: the condensed form of chromatin is referred to as heterochromatin and is transcriptionally inactive while the extended form is referred to as euchromatin and is transcriptionally active.

Nucleotides

- Can be divided into two categories: Purines, A and G, which have two rings and pyrimidines, C, T, U, which have one ring.
- The G-C bond is stronger than the A-T bond, 3 hydrogen bonds versus 2 hydrogen bonds.

Features of the Genetic Code: the genetic code is unambiguous, a codon specifies only one amino acid, and redundant, more than one codon may specify the same amino acid.

DNA Replication – Eukaryotes: the eukaryotic genome has multiple origins of replication which begins at a consensus sequence of AT-rich pairs.

DNA Replication – Prokaryotes: there is a single origin of replication, which is continuous and bidirectional on the leading strand and discontinuous, Okazaki fragments, on the lagging strand.

Directionality of DNA, RNA, and Protein Synthesis: DNA & RNA are synthesized 5' to 3' and protein is synthesized N to C.

Transition and Transversion

- **Transition** a purine is substituted for a purine or a pyrimidine is substituted for a pyrimidine.
- **Transversion** a purine is substituted for a pyrimidine or vice versa.

Types of DNA Mutations

- Silent mutations the codon codes for the same amino acid.
- Missense mutations the codon codes for a different amino acid.
- A nonsense mutation results in a stop codon appearing prematurely, and can be remembered with the mnemonic **Stop the nonsense**.

DNA Repair: base excision repair, nucleotide excision repair & mismatch repair

Mechanisms of Genetic Exchange - including transformation, transduction, conjugation, crossover

Functional Organization of Genes – includes Codons, Promoters, Enhancers and Silencers

Types of RNA

- Messenger RNA carries the protein sequence info. to the ribosome
 - Transfer RNA transfers a specific amino acid to the growing polypeptide chain
 - Ribosomal RNA is the catalytic component of ribosomes.
- RNA Polymerases:** in eukaryotes RNA polymerase I makes rRNA, RNA polymerase II makes mRNA and RNA polymerase III makes tRNA.

RNA Processing: (1) Capping the 5' end by adding 7-methylguanosine, (2) polyadenylation, addition of approximately 200 adenine residues, on 3' end and (3) splicing out of the introns.

Splicing of Pre-mRNA: (1) Spliceosome is formed when the primary transcript combines with snRNPs & other proteins. (2) A lariat-shaped intermediate is formed. (3) Release of lariat, removing the intron, and joining the two exons.

Introns and Exons

- **Exons** are DNA regions that contain the genetic information for coding protein.
 - **Introns** are DNA regions within genes that are not translated into protein.
- tRNA:** contains 75-90 nucleotides has cloverleaf form, 2^o structure and the anticodon end is opposite the 3' aminoacyl end.

tRNA Wobble: The first two nucleotide positions are required for accurate base pairing, codons differing in the third, "wobble", position may code for the same tRNA/amino acid.

Protein Synthesis:

- **Initiation:** the small subunit of the ribosome, 40S, binds to the 5' end of mRNA with the help of initiation factors (IF).
- **Elongation:** During elongation an aminoacyl-tRNA able to base pair with the next codon on the mRNA arrives at the A site.
- **Termination:** It occurs when the ribosome reaches the stop codon.

Population Genetics

Hardy-Weinberg Population Genetics: States that both allele and genotype frequencies in a population remain constant from generation to generation.

Imprinting: In genomic imprinting at a single locus only one allele is active, the other has been inactivated by methylation or histone modification.

Autosomal Inheritance – Dominant & Recessive

- **Autosomal dominant inheritance** many generations of both males and females are affected and defects in structural genes are common. It is often pleiotropic, in many cases clinical presentation occurs at puberty.
- **Autosomal recessive inheritance** twenty-five percent of offspring are affected, it usually only seen in one generation and enzyme deficiencies are common.

X-Linked Inheritance – Dominant & Recessive

- **X-linked dominant inheritance** transmission is through both parents: if the father is affected, then all female offspring are diseased, and if the mother is affected, the male or female offspring may be affected.
- **X-linked recessive inheritance** sons of heterozygous mothers have a fifty percent chance of being affected.

Mitochondrial Inheritance: Is only through the mother and all offspring may show signs of disease. Due to heteroplasmy there may be variable expression in the population

Clinical Genetics

Autosomal Dominant Diseases: Marfan's, Huntington's, familial hypercholesterolemia

Autosomal Recessive Diseases: cystic fibrosis, albinism, α_1 -antitrypsin deficiency, phenylketonuria, thalassemias, sickle cell anemias, glycogen storage disease, mucopolysaccharidoses

Cystic Fibrosis: Arises from an autosomal-recessive defect in the CFTR gene on chromosome 7, most commonly deletion, of phenylalanine 508.

Fragile X Syndrome: the defect affects the methylation and expression of the FMR1 gene and it is a triplet repeat disorder.

Autosomal Trisomies: 3 autosomal trisomies are: Down syndrome, trisomy 21, Edward's syndrome, trisomy 18, & Patau's syndrome, trisomy 13

Chromosomal Inversions

- **Pericentric** involves the centromere and proceeds through meiosis.
- **Paracentric** does not involve the centromere and does not proceed through meiosis.

Cri-Du-Chat Syndrome: a congenital deletion of the short arm of chromosome 5.

22q11 Syndrome: caused by the deletion of a small piece of chromosome 22.

Laboratory Techniques

Microarrays and Blotting Techniques: the Southern blot which detects DNA, the Northern blot which detects RNA and the Western blot which detects protein.

Methods for Analyzing DNA: sequencing, restriction analysis, PCR amplification, hybridization (FISH)

Cloning Methods: plasmids and bacteriophages

ELISA: enzyme-linked immunosorbent assay, is a technique for rapidly testing antigen-antibody reactivity.

Transgenic Models: (1) The random insertion of a gene into the mouse genome. (2) Targeted insertion, knock-in, or deletion, knock-out of a gene, done through homologous recombination with mouse gene.

10: Microbiology

Chapter Summary:

Medical microbiology covers a broad range of topics, including bacteriology, virology, parasitology and microbiology. In this tutorial, we review methods of bacterial classification, then discuss the biology and pathology of bacteria, viruses, fungi and parasites. The tutorial concludes with a review of systems microbiology for a number of clinically relevant pathogens. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Microbial classification
- Bacteria and bacterial diseases
- Viruses and viral diseases
- Fungi and fungal infections
- Parasites and parasitic diseases
- Systems microbiology

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Microbial classification
- Bacteria and bacterial diseases
- Viruses and viral diseases
- Fungi and fungal infections
- Parasites and parasitic diseases
- Systems microbiology

Chapter Review:

Microbial Classification

Bacterial Structures

- Peptidoglycan - a polymer composed of sugars and amino acids.
- Inside the cell there are ribosomes, used for protein synthesis; and plasmids that contain genes for antibiotic resistance, enzymes & toxins.
- For mobility bacteria have flagellum and to mediate adherence fimbriae, protein filaments. Pili, protein filaments slightly larger than fimbriae, assist in the transfer of genetic material between bacteria.

Cell Walls & Bacteria with Unusual Cell Walls

- The cell wall of gram positive and gram negative bacteria contain many common features: a cytoplasmic membrane, peptidoglycan, capsule, pilus and flagellum.
- Two bacteria with unusual cell membranes and/or walls are mycoplasma and mycobacteria.

Gram Stain Limitations: The following bugs do not stain well: **Treponema**, **Rickettsia**, **Mycobacteria**, **Mycoplasma**, **Legionella pneumophila** and **Chlamydia**

Bacteria & Bacterial Diseases

Bacteria Growth Curve: 4 phases – lag, log phase, stationary & death.

Bacterial Genetics: Transformation, Conjugation, Transduction & Transposition

Lysogeny: The genetic code for some bacterial toxins is stored in lysogenic phages.

Bacterial Virulence Factors: *S. aureus* protein A, Group A streptococcal M protein and IgA protease.

Exotoxins: polypeptides secreted from bacteria, are produced by certain species of gram-positive and gram-negative bacteria.

Endotoxins: lipopolysaccharides are found in the outer cell membrane of most gram-negative bacteria and *Listeria*.

Special Culture Requirements: *H. influenzae*, *N. gonorrhoeae*, *pertussis*, *C. diphtheriae*, *M. tuberculosis* and *Legionella*.

Laboratory Stains: Congo red, Giemsa's, PAS (periodic acid-Schiff), Ziehl-Neelsen, India ink & Silver stain

α - and β -Hemolytic Bacteria

- α -hemolytic bacteria: *Streptococcus* & Viridan streptococci
- β -hemolytic bacteria: *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus agalactiae* & *Listeria monocytogenes*.

Bacteria that cause Food Poisoning: *Vibrio parahaemolyticus* & *V. vulnificus*, *Bacillus cereus*, *S.aureus*, *Clostridium perfringens*, *C.botulinum*, *E.coli* O157:H7 & *Salmonella*.

Identification of Gram-Positive Bacteria

Bacteria that cause Diarrhea: *Campylobacter*, *Salmonella*, *Shingella*, Enterohemorrhagic *E. coli*, Enteroinvasive *E. coli*, *Yersinia enterocolitica*, *C. difficile* and *Entamoeba histolytica*.

Legionella pneumophila: gram-negative rod that does not stain well, a silver stain should be used instead.

Pseudomonas aeruginosa: aerobic gram-negative rod which is non-lactose fermenting, oxidase positive and has a grape-like odor.

Helicobacter pylori: causes up to 90% of duodenal ulcers.

Tuberculosis: begins with infection by the bacterium *Mycobacterium tuberculosis*.

Leprosy: Hansen's disease is caused by *Mycobacterium leprae*, and there are two forms: lepromatous, which is worse, and tuberculoid which is self-limited.

Rickettsiae, Rickettsial Diseases and Vectors: are obligate intracellular parasites.

Chlamydiae and Chlamydia trachomatis Serotypes

- Chlamydiae are obligate intracellular parasites that cannot make ATP and cause mucosal infections.
- *Chlamydia trachomatis* causes reactive arthritis, conjunctivitis, nongonococcal urethritis.

Lyme Disease: *Borrelia burgdorferi* which causes Lyme disease is transmitted via the tick *Ixodes*

Syphilis: caused by the spirochete *Treponema pallidum* and is treated with penicillin G.

Antimicrobials: divided into two categories: bacteriostatic & bactericidal.

Viruses & Viral Diseases

Viral Structures: naked icosahedral viruses, enveloped icosahedral viruses, enveloped helical viruses

DNA & RNA Viral Genomes: Except for the parvoviridae virus all DNA viruses contain double-stranded DNA; Except for the reoviridae virus all RNA viruses contain single-stranded RNA

Virus Ploidy and Replication: all viruses are haploid: they contain one copy of DNA or RNA, with the exception of retroviruses which contains two identical single-stranded RNAs.

Viral Pathogens: DNA enveloped viruses, DNA nucleocapsid viruses, RNA enveloped viruses RNA nucleocapsid viruses.

DNA Virus Characteristics: they are **HHAPPPPy** viruses, **Hepadna**, **Herpes**, **Adeno**, **Pox**, **Parvo**, **Papilloma**, **Polyoma**.

Viral Genetics: In recombination there is an exchange of genes between two chromosomes.

Negative-Stranded Viruses: must transcribe the negative strand to positive using a RNA-dependent RNA polymerase.

Segmented Viruses: are all RNA viruses.

Herpes Viruses & HSV Identification: HSV-1, HSV-2, VZV, EBV, CMV & HHV-8

Picornavirus & Rhinovirus

- The picornaviruses include **poliovirus**, **echovirus**, **rhinovirus**, **coxsackievirus** and **HAV**.
- Rhinovirus is the cause of the common cold.

Rubella, Rotavirus, Rubeola & Mumps Viruses

- Rubella is a togavirus and causes German measles.
- Rotavirus is the leading global cause of infantile gastroenteritis.
- The rubeola & mumps virus is a paramyxovirus.

Influenza Viruses: orthomyxoviruses, enveloped, segmented single-stranded RNA viruses containing hemagglutinin & neuraminidase antigens.

Hepatitis Viruses & Serological Markers: **HAV, HBV, HCV, HDV & HEV**

HIV: is a retrovirus, it is an enveloped virus, containing two strands of RNA, and uses reverse transcriptase to produce DNA from the RNA.

Fungi & Fungal Infections

Fungal Spores: typically are asexual.

Candida albicans: transmitted via inhalation of spores and the infection is systemic, treated with amphotericin B, or superficial, treated with nystatin.

Systemic Mycoses: Histoplasmosis, Blastomycosis, Coccidioidomycosis & Paracoccidioidomycosis.

Cutaneous Mycoses: Tinea versicolor is caused by *Malassezia furfur*.

Opportunistic Fungal Infections: *Candida albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Mucor* and *Rhizopus*

Parasites & Parasitic Diseases

Giardia lamblia: transmitted through cysts in water and causes giardiasis the symptoms of which include bloating, flatulence and foul-smelling diarrhea.

Trichomonas vaginalis: transmitted through sexual contact and causes vaginitis the symptoms of which include foul-smelling greenish discharge, itching and burning.

Plasmodium: is a genus of parasitic protists, infection by *plasmodium* causes malaria the symptoms of which include cyclic fever, headache, anemia and splenomegaly.

Toxoplasma gondii: transmitted through cysts in meat or cat feces, the cysts can cross the placenta.

Systems Microbiology

Normal Flora: *Staphylococcus epidermidis*, *S. Epidermidis*, viridans group streptococci, *Streptococcus mutans*, *Bacteroides fragilis*, *E. coli*, *Lactobacillus*

Urinary Tract Infections: UTIs are caused by *E. coli*, *Klebsiella*, & *Staphylococcus saprophyticus*.

“ToRCHes” Infection: are transmitted in utero or during vaginal birth.

Sexually Transmitted Diseases: Gonorrhea, Primary syphilis, Genital herpes, Chlamydia, Lymphogranuloma, Trichomoniasis, AIDS, Condylomata acuminata, Hepatitis B, Chancroid, Bacterial vaginosis

Pelvic Inflammatory Disease: cervical motion tenderness and purulent cervical discharge.

11: Immunology

Chapter Summary:

Medical immunology focuses on normal and abnormal immune responses that contribute to disease. This clinically-oriented tutorial reviews the anatomy and physiology of the immune system, and then normal and abnormal immune responses, with a focus on disease of the immune system. The tutorial concludes with an overview of common therapeutics of the immune system. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Immune system structure and function
- Normal and abnormal immune responses
- Therapeutics of the immune system

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Immune system structure and function
- Normal and abnormal immune responses
- Therapeutics of the immune system

Chapter Review:

Immune System Structure and Function

Lymphoid Structures: A lymph node is an encapsulated, trabeculated lymphoid organ that has many afferent and 1 or more efferent branches.

- **Follicle** which is the site of B cell storage and proliferation.
- **Medulla** which is composed of medullary cords and sinuses acting as the filter.
- **Paracortex** which houses T cells.

Lymph Drainage

- **Arm and lateral breast** drain to the axillary lymph nodes. **Stomach** drains to the celiac lymph nodes. **Duodenum and jejunum** drain to the superior mesenteric lymph nodes. **Sigmoid colon** drains to the colic and then to the inferior mesenteric lymph nodes. **Lower rectum and anal canal above the pectinate line** drain to the internal iliac lymph nodes. **Anal canal below the pectinate line** drains to the superficial inguinal lymph nodes. **Scrotum** also drains to the superficial inguinal lymph nodes. **Testes** drain to the para-aortic lymph nodes.

Spleen Structures

- Sinusoids are composed of elongated channels with a fenestrated membrane and adjacent macrophages, functioning as a filter.
- Periarterial lymphatic sheath (PALS) in red pulp which houses T cells.
- Follicles in white pulp which house B cells.

Thymus: an encapsulated lymphoid organ where **T** cell maturation and differentiation occurs.

Passive vs Active Immunity

- **Active immunity** occurs after exposure to foreign antigens.
- **Passive immunity** occurs after being given preformed antibodies from another host.

Innate vs Adaptive Immunity

- **Innate immunity** results from receptors that are germline coded to recognize pathogens and is provided by neutrophils, macrophages, dendritic cells and complement.
- **Adaptive immunity** results from receptors recognizing pathogens and undergoing VDJ recombination during lymphocyte development.

B Cells and T Cells

- B cells make antibodies – IgG, IgA, IgM, IgE.
- T cells provide delayed cell-mediated hypersensitivity.

MHC I and II

- MHC I is encoded by HLA-A, HLA-B, and HLA-C.
- MHC II is encoded by HLA-DR, HLA-DP, and HLA-DQ.

T Cell Differentiation

- CD8+ cell differentiating to a cytotoxic T cell.
- CD4+ cell differentiating to a helper T cell, which differentiates further into Th1 and Th2 cells.

T Cell Glycoproteins

- CD8 found in cytotoxic T cells binds to MHC I on virus infected cells.
- CD4 found in helper T cells binds to MHC II on APCs.

T Cell Activation

- T cells require 2 signals for their activation process – signal 1 and signal 2

Antibodies

- Antibody Structure: **Fab fragment & Fc fragment**
- Antibody Function: **Opsonization, Neutralization & Complement activation**

Creation of Antibody Diversity and Immunoglobulin Isotypes

- Antibody diversity is produced by: **Random 'recombination', Random combination, Somatic hypermutation, Nucleotide addition to DNA**
- Immunoglobulin isotypes: **IgG, IgA, IgM, IgD & IgE**

Ig Epitopes: is the antigenic determinant, or the specific macromolecule that is recognized by the immune system. Types of epitopes: Allotype, Isotype, Idiotype

Cytokines: Refer to signaling molecules secreted by components of the immune system that facilitate cellular communication by carrying signals between cells and having an effect on them.

Cell Surface Proteins

- Helper T cells have CD4, TCR, CD3, CD28, CD40L.
- Cytotoxic T cells have CD8, TCR, CD3.
- B cells have IgM, B7, CD19, CD20, CD21, CD40, MHC II.
- Macrophages have MHC II, B7, CD40, CD14.
- NK cells have receptors for MHC I, CD16, CD56.

Complement: consists of a number of small proteins in the blood that interacts with the immune system to play a role in humoral immunity and inflammation.

Interferons: Interfere with viruses by causing uninfected cells to have antiviral qualities. Types interferon are: Alpha, Beta & Gamma

Antigen Variation: Describes a process in which an infectious agent alters its surface proteins so as not to be detected by the host immune system.

Anergy: Refers to the lack of a host immune response when the host is presented with a known antigen.

Normal and Abnormal Immune Response

Hypersensitivity

- **Type I:** Reaction is antibody mediated with immediate reaction that is anaphylactic & atopic.

- **Type II:** Reaction is antibody mediated where IgG and IgM attach to antigen on the pathogen to cause lysis by phagocytosis or complement activation.
- **Type III:** Reaction occurs when antigen-antibody complexes serve to activate complement which attracts neutrophils that release lysosomal enzymes.
- **Type IV:** Reaction is a delayed, cell mediated reaction in which sensitized T cells contact antigens and release lymphokines which lead to macrophage activation.

Immune Deficiencies from Decreased Cell Production: Bruton's agammaglobulinemia, DiGeorge syndrome (thymic aplasia), severe combined immune deficiency (SCID)

Immune Deficiencies from Decreased Cell Activation: Hyper IgM syndrome, Wiskott-Aldrich syndrome, IL-2 receptor deficiency, Job's syndrome

Immune Deficiencies from Phagocytic Cell Deficiency: Chronic granulomatous disease, Chediak-Higashi disease, Leukocyte adhesion deficiency syndrome type I

Immune Deficiencies from Idiopathic Cellular Dysfunction: Ataxia telangiectasia, Selective immunoglobulin deficiency, Common variable immunodeficiency, Chronic mucocutaneous candidiasis

Autoantibodies: Antinuclear antibodies (ANA), Anti-IgG (rheumatoid factor), Antigliadin, Anti-basement membrane, Anti-thyroglobulin and anti-microsomal, Anti-SS-A & anti-SS-B

HLA Subtypes: B27, B8, DR2, DR3, DR4 & DR5

Therapeutics of the Immune System

Types of Grafts

- Autograft – refers to tissue from self.
- Syngeneic graft – refers to tissue from an identical twin or clone.
- Allograft – refers to tissue from a nonidentical donor of the same species.
- Xenograft refers to tissue from a different species.

Transplant Rejection: Hyperacute rejection, Acute rejection, Chronic rejection, Graft-vs-host disease

Immunosuppressants

- Cyclosporine inhibits T cell production of IL-2 and its receptor by binding to cyclophilins, inhibiting calcineurin, thereby blocking the activation and differentiation of T cells.
- Tacrolimus (FK506) inhibits T cell secretion of IL-2 by blocking the FK-binding protein.
- Azathioprine is toxic to proliferating lymphocytes acting as an anti-metabolite precursor to 6-mercaptopurine, thereby interfering with the metabolism and production of nucleic acids.
- Muromonab-CD3 (OKT3) is a monoclonal antibody that binds CD3 on the surface of T cells & blocks T cell signal transduction.
- Rapamycin (Sirolimus) inhibits normal T cell proliferation as a response to IL-2 by binding to mTOR.
- Mycophenolate mofetil blocks lymphocyte production by inhibiting de novo guanine production.
- Daclizumab is a monoclonal antibody that binds to the IL-2 receptor on activated T cells.

Recombinant Cytokines: Aldesleukin (IL-2), Erythropoietin, Filgrastim and sargramostim, Alpha-interferon, Beta-interferon and Gamma interferon.

12: Pathology and Oncology

Chapter Summary:

Pathology is a foundation topic for the USMLE Step 1 exam, as topics such as inflammation and neoplasia play a role in many disease processes. The USMLE Step 1 exam frequently tests your understanding of pathological processes, requiring familiarity with this topic. In this tutorial, we first review core concepts of inflammation and the body's repair mechanisms. Next, key concepts of neoplasia are reviewed, including a review of tumor-associated genes, tumor staging and tumor markers. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Inflammation
- Repair mechanisms
- Neoplasia

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Inflammation
- Repair mechanisms
- Neoplasia

Chapter Review:

Inflammation

Apoptosis: refers to programmed cell death and is manifested by cell shrinkage, membrane blebbing, pyknosis (chromatin condensation), karyolysis (nuclear fragmentation), karyorrhexis (DNA fragmentation), and formation of apoptotic bodies which are phagocytosed.

Necrosis: refers to the enzymatic destruction of a cell due to an exogenous injury and is manifested by enzymatic digestion and protein denaturation with subsequent release of intracellular components. It occurs morphologically as: **Liquefactive** necrosis in the brain, **Coagulative** necrosis in the heart, kidney and liver, **Fat** necrosis in the pancreas, **Fibrinoid** necrosis in blood vessels, **Gangrenous** necrosis in the GI tract or limbs & **Caseous** necrosis in tuberculosis.

Inflammation: is manifested by, **Rubor** – redness, **Dolor** – pain, **Calor** – heat, **Tumor** – swelling and **Funtio laesa** – loss of function. During the inflammatory process there is: **Fluid exudation** via vasodilatation, increased vascular permeability and endothelial injury.

Leukocyte activation with emigration, chemotaxis and phagocytosis.

Acute vs. Chronic Inflammation

- **Acute inflammation** is neutrophil, eosinophil and antibody mediated.
- **Chronic inflammation** is mononuclear cell mediated distinguished by continuous destruction and repair.

- **Fibrosis** involves fibroblast emigration and proliferation with deposition of extracellular matrix.

Resolution of Inflammation: refers to the restoration of normal structure at the gross and cellular levels. Other more severe conditions that might occur are:

- **Scarring** – altered structure and function due to the deposition of collagen.
- **Fistula formation** – the formation of an abnormal connection between luminal structures.
- **Abscess formation** – the formation of a fibrotic shell surrounding pus.

Transudate vs. Exudate

- A transudate is caused by disturbances of hydrostatic and/or osmotic pressure with Na⁺ retention.
- An exudate is caused by lymphatic obstruction and inflammation.

Leukocyte Extravasation: In regions of tissue injury and inflammation, neutrophils exit blood vessels in 4 phases:

- **Rolling** – carbohydrate ligands on the surface of the leukocyte bind to selectin molecules on the endothelium, slowing the cell down.
- **Tight binding** – surface integrin molecules of the leukocyte are activated to bind tightly to receptors on endothelial cells, stopping motion.
- **Diapedesis** – the leukocyte exits the blood vessel by passing between endothelial cells.
- **Migration** – the leukocyte is stimulated to travel through the interstitium to the inflamed site via cytokines.

Free Radical Injury: may be caused by a number of processes, some of which include radiation exposure, metabolism of drugs, leukocyte reperfusion after anoxia, redox reaction, nitric oxide and transition metals.

Bactericidal Killing: may be oxygen dependent or oxygen independent.

Amyloidosis: is a condition in which amyloid proteins, which are insoluble and form in beta pleated sheets seen pathologically, are abnormally deposited in a variety of tissues giving them a waxy appearance. Types of amyloidosis are: Primary amyloid, Secondary amyloid, Senile cardiac amyloid, DM type 2 amyloid, Medullary carcinoma of the thyroid, Alzheimer's disease & Dialysis associated amyloid.

Repair Mechanisms

Factors Involved in Tissue Repair: include parenchymal cell regeneration and repair by connective tissue or fibrosis.

Parenchymal Cell Regeneration

- The ability of cells to replicate. Labile and stable cells can replicate, but permanent cells cannot.
- Factors that stimulate parenchymal cell division and migration such as growth factors, hormones and ILs.
- Phases of the cell cycle with the most critical phase being regulation of the G1 checkpoint or the G1 to S phase.
- Restoration to normal requiring preservation of the basement membrane and a relatively intact extracellular matrix (ECM).

Repair by Connective Tissue (Fibrosis): occurs when the injury is severe or persistent.

Steps required for fibrosis are:

- Neutrophil transmigration for liquefaction of injured tissue followed by macrophage transmigration to phagocytize and remove debris.
- Formation of granulation tissue.
- Production of type III collagen.

Wound Healing

- **Primary intention wound healing** in the case of a clean wound that has its margins approximated with sutures.

- **Secondary intention wound healing** in the case of dirty or infected wounds that are left open to heal on their own.

Tissue-Specific Repair

- Liver – repair after mild injury, such as hepatitis A, is possible if the normal hepatic cytoarchitecture has remained intact and there is regeneration of hepatocytes.
- Lung – type II pneumocytes replace damaged type I and II pneumocytes and produce surfactant.
- Heart – myocardial tissue is permanent tissue and damaged cells are replaced with noncontractile scar tissue.
- Brain – gliosis occurs as astrocytes proliferate in response to an injury, such as an infarction, followed by macrophages removing the debris.
- Peripheral nerves – the Schwann cell is the most significant player in this process, which also involves nerve cells and macrophages.

Neoplasia

Neoplastic Progression: Normal cells, Hyperplasia, Dysplasia, Carcinoma in situ, Invasive carcinoma and Metastatic carcinoma

Tumor Grade vs. Stage

- **Tumor grading** – an observational histologic measure of the degree of cell differentiation and number of mitoses scaled from I – IV.
- **Tumor staging** – describes the degree of localization and spread of a tumor based on size, spread to regional lymph nodes, and distant metastases.

Tumor Nomenclature

- **Carcinoma** refers to malignant tumors of the epithelium.
- **Sarcoma** refers to malignant tumors of the mesenchyme
- **Oma** after a prefix of tissue origin implies benignity.

Tumor Differences

- **Benign tumors** are slow growing, well differentiated, well demarcated, noninvasive and do not metastasize.
- **Malignant tumors** grow more rapidly and erratically, are poorly differentiated, not well demarcated, invasive and do metastasize.

Diseases Associated with Neoplasms: Ulcerative colitis, Paget's disease, AIDS, Barrett's esophagus, Cirrhosis of the liver and Down Syndrome.

Oncogenes: is a gene which, when it gains function, creates neoplastic cells and only one allele need be damaged. Some examples of oncogenes and their associated tumors are: abl, c-myc – Burkitt's lymphoma, erb-B2, ras, L-myc & N-myc.

Tumor Suppressor Genes: is a gene that acts to protect a cell from becoming neoplastic, but with loss of its function, neoplastic cells may be created. Examples are BRCA1, BRCA2, APC, DCC, DPC & p16.

Tumor Markers: are substances found in blood, urine or tissue which are indicative of the presence of cancer. Examples are PSA, CEA, Alpha-fetoprotein, Beta-hCG, CA-125 & CA-19-9.

Oncogenic Viruses: is a virus that can cause cancer. Some examples of oncogenic viruses are: HTLV-1, HBV, HCV, EBV, HPV & HHV-8.

Psammoma Bodies: are microscopic, spherical collections of laminated and concentric calcium which are seen in: Papillary adenocarcinoma of the thyroid, Serous papillary cystadenocarcinoma of the ovary, Meningioma & Malignant mesothelioma.

Metastasis to Brain: 50% of brain tumors are due to secondary metastases which tend to localize at the gray/white matter junction. The most common primary tumors that metastasize to the brain are: **Lung, Breast, Skin (melanoma), Kidney & GI.**

Metastasis to Liver: are far more common than primary tumors of the liver. The most common primary tumors that metastasize to the liver in order of occurrence are: **Colon > Stomach > Pancreas > Breast > Lung.**

Metastasis to Bone: are also far more common than primary tumors of bone. The following primary tumors metastasize to bone: **P**rostate, **T**hyroid, **B**reast, **L**ung & **K**idney.
Cancer Epidemiology: second leading cause of death in the US.

13: Histology

Chapter Summary:

Histology is the microscopic study of cells and tissues, requiring knowledge of laboratory techniques to identify types of cells and tissues in normal and diseased tissue. Similar to pathology, histology is a foundation concept for the USMLE Step 1 exam, where solid grounding in histology supports your ability to easily interpret questions on the exam. This tutorial begins with a review of common histology laboratory techniques, including tissue stains and microscopic techniques. Next, we review tissue and organ system histology, with an emphasis on identifying important structures in healthy and diseased tissue.

Tutorial Features:

Specific Tutorial Features:

- Histology laboratory techniques
- Tissue histology
- Organ system histology

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
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- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Histology laboratory techniques
- Tissue histology
- Organ system histology

Chapter Review:

Histology Laboratory Techniques

Fixation: the process whereby tissue is removed from an organism and preserved to prevent degradation.

Embedding: It involves infiltrating the fixed tissue with a medium, such as paraffin or plastic resin, to create a firm structure that can be sliced, a process called sectioning.

Light microscopy: the basic reaction of stains follows the principle of the attraction of opposites. The acidic components of cells stain with a basic stain, and are called basophilic, while the basic components of cells stain with an acidic stain, and are called acidophilic.

Hematoxylin & eosin (H&E): good stain for visualizing general structure.

- **Hematoxylin** is basophilic, staining nuclei blue.
- **Eosin** is acidophilic, staining the cytoplasm pink.

To visualize **connective tissue**, a combination of three stains is used to visualize 1) nucleus 2) cytoplasm 3) matrix. Examples of commonly used stains are **Masson's**

trichrome or Mallory's triple C.T. stain.

Periodic Acid Schiff's (PAS) detects glycogen in tissue, and will stain structures containing a high proportion of carbohydrate macromolecules, such as glycogen, glycoproteins, and proteoglycan.

Silver impregnation is used to trace nerves, and to stain golgi and reticular fibers.

Wright stain is a histologic stain that facilitates the identification of blood cell types. It is primarily used to stain peripheral blood smears and bone marrow aspirates. Wright stain uses azure blue stains to stain WBC granules basophilic or neutrophilic, and is used with eosin for RBS and eosinophilic.

Tissue Histology

Fibrous Tissue: traditionally classified as epithelial, connective, muscle, nervous

Epithelial:

- **Simple epithelium** – one cell thick, where every cell is in contact with the basement membrane
 - **Squamous** - cells have a flat, smooth surface that provides a smooth, low-friction surface - nuclei tend to be flattened & elliptical due to flattened shape of the cell
 - **Cuboidal** - Each cell has a spherical nucleus in the center of the cell
 - **Columnar** - elongated such that they are taller than they are wide, with elongated nuclei that are usually located near the base of the cells - may or may contain microvilli or cilia.
 - **Pseudostratified** - simple columnar epithelial cells with nuclei at varying heights, giving the impression of stratification when in fact there is a single layer of cells.
- **Stratified epithelium** - multilayered, and is found in body linings where chemical and/or mechanical injury is common, such skin – may be further specialized to be keratinized or transitional

Connective tissue: supports and binds other tissues in the body

- Loose connective tissue, adipose tissue, dense fibrous connective tissue, elastic connective tissue, cartilage, blood and osseous tissue (bone)
- **Loose connective tissue:**
 - Collagenous fibers: made up of collagen fibrils that are coils of collagen molecules
 - Elastic fibers: made of elastin that permits stretch
 - Reticular fibers: very thin collagen fibers that join connective tissue to other tissues
- **Cells within connective tissue include:** fibroblasts, macrophages, mast cells

Muscle tissue: contractile tissue of the body

- **Skeletal muscle:** comprised of striated muscle that is typically attached to bone by bundles of collagen fibers (tendons)- basic functional unit is the sarcomere
- **Cardiac muscle:** also comprised of striated muscle, found in the myocardium of the heart - cardiac muscle cells (myocytes) are multinucleated.
- **Smooth muscle:** involuntary, non-striated muscle tissue that may be either single-unit or multiunit.

- **Blood vessels:** Arteries have thickest tunica media (includes layer of smooth muscle for regulating vascular tone) – veins have thinner tunica media, and capillaries are a single layer of squamous epithelium (no smooth muscle component)

Nervous tissue: composed of neurons (transmit neural impulses) and glia (supportive function)

Peripheral nerves: comprised of three layers: epineurium, perineurium, endoneurium (from outside in)

14: Pharmacology

Chapter Summary:

Pharmacology is a core topic of the USMLE Step 1 exam that is tested across multiple organ systems and diseases. In this tutorial, we review essential concepts of pharmacology, including pharmacodynamics, pharmacokinetics, toxicity and drug reactions. The tutorial also includes a review of drugs of the autonomic nervous system, as this topic is frequently addressed on the Step 1 exam. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Pharmacodynamics
- Pharmacokinetics
- Pharmacology of the autonomic nervous system
- Toxicity and drug reactions

Series Features:

- Concept map showing inter-connections of concepts
- Sample USMLE Step 1 exam questions with full answers
- Examples given throughout to illustrate how the concepts apply
- A concise summary is given at the conclusion of the tutorial

Key Concepts:

- Pharmacodynamics
- Pharmacokinetics
- Pharmacology of the autonomic nervous system
- Toxicity and drug reactions

Chapter Review:

Pharmacodynamics

Pharmacodynamics: the study of the relationship between drug concentration in the body, and the physiological response to that concentration of drug

- The dose of the drug is directly linked to the magnitude of the body's response to that drug.
- Drugs act through receptors.

Enzyme inhibitors may be competitive or noncompetitive

Competitive inhibitors will be:

- Similar to the natural substrate
- May be displaced by increasing concentrations of substrate
- Bind the active site of the enzymes
- Have no effect on V_{max}
- Increase K_m

Noncompetitive inhibitors:

- Do not resemble the substrate, are not displaced by increasing substrate concentration, and do not bind the active site
- Will decrease, not increase, V_{max}
- Have no discernible effect on K_m

Receptors: the components of a cell or organism that interact with a drug and initiate the chain of events that lead to the drug's observed effect.

- Determine the relationship between the dose or concentration of a drug and its pharmacological effect
- Determine the drug's selectivity, and
- Are responsible for both agonist and antagonist activity of drugs

Coupling: the process that links the drug occupancy of receptors to the pharmacological response. The efficacy of coupling is determined by:

- The initial conformational change in the receptor, which is strongly influenced by the structure of the ligand, a phenomenon known as the structure-activity relationship (SAR)
- The biochemical events that transduce receptor occupancy into cellular response

Agonists: initiate changes in cell function, producing effects of various types. Their potency depends upon their:

- **Affinity:** the tendency to bind to receptors
- **Efficacy:** the ability to initiate changes once bound

Pharmacokinetics

- **Pharmacokinetics** is the study of the movement of drugs in the body
- Volume of distribution, clearance and half-life mathematically describe the movement of a drug in the body
- Zero-order elimination that remains at a constant rate irrespective of the amount of drug in the body
- First-order kinetics occurs when the rate of elimination is proportional to the drug concentration, such that a constant fraction of a drug is eliminated per unit time
- Biotransformation of the metabolic conversion of endogenous and xenobiotic chemicals to more polar, water-soluble compounds, to aid excretion from the body

Drug Naming Conventions

- azole: antifungals, such as ketoconazole
- cillin: penicillins, such as methicillin
- cycline: class of antibiotics, including tetracycline
- navir: protease inhibitors, such as saquinavir
- olol: β -antagonists, such as atenolol and propranolol
- oxin: cardiac glycosides, including digoxin and digitoxin
- pril: used for ACE inhibitors, such as captopril and enalapril
- ane: inhaled general anesthetics – such as halothane
- azepam: benzodiazepine sedatives – such as diazepam
- caine: local anesthetics – including lidocaine and procaine
- barbital: barbiturates – such as phenobarbital
- terol: β_2 agonists, such as albuterol
- zosin: α_1 antagonists, such as prazosin
- azine: phenothiazines (neuroleptic), such as chlorpromazine
- operidol: butyrophenones (neuroleptic), such as haloperidol
- ipramine: tricyclic antidepressants (TCAs), such as imipramine
- tryptiline: tricyclic antidepressants (TCAs), such as amitriptyline
- afil: drugs for erectile dysfunction, including sildenafil
- tidine: H₂ antagonists, such as cimetidine
- tropin: pituitary hormones, such as somatotropin

Pharmacology of the Autonomic Nervous System

Central nervous systems (CNS): Nerve cord, spinal cord and the brain

Peripheral nervous system (PNS): All the sensory neurons and the nerves that connect them to the central nervous system

- **Autonomic system:** conveys all outputs from the central nervous system to the rest of the body
- **Somatic system:** Single motor neuron connects the CNS to the skeletal muscle fiber

Classification of Autonomic Neurons: can be further divided in two ways, based on either the:

- Structural features of the fibers
- Neurotransmitters released by the fibers

Types of Cholinergic Receptors: two kinds of cholinergic receptors named after the alkaloids originally used in their identification:

Muscarinic: receptors are G-Protein Coupled Receptors that mediate the effects of acetylcholine at postganglionic parasympathetic synapses primarily the heart, smooth muscle and glands

Nicotinic: receptors are directly coupled to cation channels and mediate fast excitatory synaptic transmission at the neuromuscular junction, autonomic ganglia, and at various sites in the CNS

Cholinergic Agonists: can be divided into direct and indirect acting cholinergic agonists:

- **Direct:** bind to and activate muscarinic or nicotinic receptors
- **Indirect:** work primarily through the inhibition of acetylcholinesterase

Direct Acting Cholinergic Agonists: Two groups based upon their chemical structures:

Esters of choline: including acetylcholine, bethanechol, carbachol and methacholine

Alkaloids: including nicotine, muscarine, pilocarpine and lobeline

Direct Acting Cholinergic Agonists – Mechanisms of Action: Direct acting muscarinic agonists exert their effects via two mechanisms

- Activate muscarinic receptors on the effector cells to alter organ function directly
- Interacts with receptors in the nerve terminals to inhibit the release of their neurotransmitter

Indirect Acting Cholinergic Agonists: Two main forms of cholinesterase:

- Acetylcholinesterase (AChE), which is membrane bound
- Butyrylcholinesterase (BChE), which is relatively non-selective

Indirect Acting Cholinergic Agonists:

- Carbamates: reversible inhibitors
- Organophosphates: irreversible inhibitors

Toxicity and Drug Reactions

The symptoms of lead poisoning can be remembered using LEAAAD:

- LL: Lead Lines on gingivae and on epiphyses of long bones (seen during X-rays)
- EE: Encephalopathy and Erythrocyte basophilic stippling
- AA: Abdominal colic and sideroblastic anemia
- D: wrist and foot drop

Iron toxicity tends to be due to over-consumption of iron containing food and dietary supplements.

Symptoms can be distinguished based on the length of exposure:

- Acute: gastric bleeding
- Chronic: metabolic acidosis, scarring leading to GI obstruction
- The symptoms of alcohol toxicity vary by the type of alcohol. For all three alcohols, the active enzyme in the first step of metabolism is alcohol dehydrogenase.
- Toxicity is a common side effect when one drug either induces or inhibits the activity of a CYP450 enzyme that also acts on another drug. The most common CYP450 inducers are quinidine, barbiturates, phenytoin, rifampin, griseosulvin, carbamezapine and St. John's wort.
- Herbal agents may have pharmacological actions that can be toxic either alone or in specific combinations with other herbs and/or pharmaceuticals agents.

Echinacea: used to treat the common cold, it may cause GI distress, drowsiness and headache.

Melatonin: used for jet lag and insomnia, it may also cause sedation, hypoprolactemia and suppression of midcycle LH.

St. John's Wort: believed to treat depression, this natural product is associated with GI distress, P450 induction, and serotonin syndrome when used in conjunction with SSRIs.

Kava: although it is used to treat chronic anxiety, its use has been linked to hepatotoxicity, phototoxicity and dermatotoxicity.

Ephedra: known to have actions similar to epinephrine; side effects include CNS and cardiovascular stimulation, arrhythmia, stroke and seizure at high doses.

15: The Cardiovascular System

Chapter Summary:

The cardiovascular system is a critical topic for the USMLE Step 1 exam. This tutorial reviews the core concepts of the cardiovascular system, including normal anatomy and physiology, as well as commonly encountered cardiovascular diseases and major therapeutics. Areas of focus include the heart and vasculature. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Normal cardiac processes
- Abnormal cardiac processes
- Cardiovascular therapeutics

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Normal cardiac processes
- Abnormal cardiac processes
- Cardiovascular therapeutics

Chapter Review:

Normal Cardiac Processes

Cardiac Sheath: the fibrous tissue that surrounds the **Internal jugular vein, Common carotid artery and Vagus Nerve.**

Coronary Arteries: The right and left coronary arteries arise from the right and left sinuses respectively.

Cardiac Output and Variables in Cardiac Output: The cardiac output can be obtained as follows: $CO = \text{stroke volume} \times \text{heart rate}$.

Preload and Afterload: The preload is the ventricular EDV and the afterload is the mean arterial pressure.

Starling Curve: The intrinsic relationship between the end diastolic volume and the stroke volume is known as the Frank Starling Law of the Heart. A plot of the stroke volume against the preload is known as the Starling Curve.

Ejection Fraction: The ejection fraction (EF) is an index of ventricular contractility. It is calculated using the following formula: $EF = SV/EDV = (EDV - ESV) / EDV$

Resistance, Pressure and Flow: $\Delta P = Q \times R$ whereby; ΔP is the pressure gradient, Q is the flow and R is the resistance.

- The cardiac cycle is described as one complete sequence of contraction and relaxation and can be divided into 5 phases.
- Sounds: As the valves open and close and the chambers of the heart empty and fill, there are distinct sounds that can be heard.
- Waves: An electrocardiogram of the cardiac cycle shows the following waves.

Cardiac Myocyte Physiology: When calcium enters the cardiac muscle cells during the plateau phase of the action potential and stimulates the release of calcium from the cardiac muscle SR, the muscle contracts.

Ventricular Action Potential: This type of action potential is typically seen in atrial and ventricular myocytes and Purkinje fibers. There are 5 phases.

Pacemaker Action Potential: is seen in the SAN and AVN.

Electrocardiogram: An ECG demonstrates the changes in membrane potential that occur during the cardiac cycle. In a typical ECG plot we would find: P wave, PR interval, QRS complex, QT interval, T wave, ST segment and U wave.

Control of Mean Arterial Pressure: The mean arterial blood pressure (MAP) is regulated by a number of factors.

- **Cardiac Receptors: Baroreceptors & Chemoreceptors:**

- Cardiac receptors are found in the aortic arch and the carotid sinus.
- The baroreceptors are stretch receptors in the walls of the heart and blood vessels.
- Peripheral chemoreceptors found in the carotid and aortic bodies respond to a low oxygen and pH and high CO₂ content in the blood.

Circulation Through Organs: The liver gets the largest share of the systemic output, the kidneys have the highest blood flow per gram of tissue and the heart has the largest arteriovenous O₂ difference.

Autoregulation: The various organs of the body are capable of maintaining the blood pressure through autoregulation.

Abnormal Cardiac Processes

Heart Murmurs: Auscultation is helpful in the management of many heart diseases. Such as **Mitral/tricuspid regurgitation, Aortic stenosis, Ventricular Septal Defect (VSD), Mitral prolapse, Aortic regurgitation, Mitral Stenosis and Patent Ductus Arteriosus (PDA).**

Torsades des Pointes: is the name given to ventricular tachycardia that is characterized by shifting sinusoidal waveforms on ECG.

Wolff-Parkinson – White Syndrome: In this syndrome, there was an accessory atrioventricular connection is present.

Atrial Flutter: Atrial activity may be very fine and difficult to detect on the ECG or quite coarse and often mistaken for atrial flutter.

AV Block: describes a group of disorders associated with conduction disturbances within the AV junctional tissue. 1st degree AV block, 2nd degree AV Mobitz Type I block, 2nd degree AV Mobitz Type II block, 3rd Degree AV Block.

Ventricular Fibrillation: is characterized by a completely erratic rhythm with no identifiable waves.

Congenital Heart Disease: can result in various heart disease in adulthood. Congenital Heart Disease can be of two types: Right to Left Shunts (early cyanosis) or "blue babies" and Left-to-right shunts.

Tetralogy of Fallot: is the most common form of cyanotic congenital heart disease.

Transportation of Great Vessels: the pulmonary and system circulations exist in parallel rather than in the normal series relationship.

Coarctation of the Aorta: two types: **Infantile type & Adult type.**

Hypertension: is defined as blood pressure that is greater than 140/90 for more than 3 different readings.

Hyperlipidemia Signs: can be signaled by various other conditions including: **atheromas, xanthomas, tendinous xanthoma and Corneal arcus or arcus senilis.**

Arteriosclerosis: There are 3 types: **Monckeberg, Arteriolosclerosis & Atherosclerosis.**

Aortic Dissection: is a longitudinal intraluminal tear forming a false lumen.

Atherosclerosis: is a disease of the elastic arteries and large and medium sized muscular arteries.

Ischemic Heart Disease: is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium.

Infarcts: that are areas of necrosis resulting from an occlusion of the blood vessels, may be red or pale.

MI Evolution: The classical symptoms of myocardial infarction include diaphoresis, nausea, vomiting, severe retrosternal pain, pain in the left arm or jaw, shortness of breath, fatigue, adrenergic symptoms.

Cardiomyopathies: There are 3 types: **Dilated Cardiomyopathy, Hypertrophic Cardiomyopathy & Restrictive/obliterative Cardiomyopathy.**

Congestive Heart Failure: Left ventricular failure (LV), Right ventricular CHF and Isolated RV CHF.

Embolisms: There are different types of emboli: fat, air, thrombus, bacterial, amniotic fluid and tumors.

Deep Vein Thrombosis: can lead to a pulmonary embolism and is predisposed by a combination of factors known as Virchow's triad including stasis, hypercoagulation and endothelial damage.

Cardiac Tamponade: is the compression of heart by fluid in the pericardium leading to a decreased CO.

Pericarditis: is an acute inflammation of the pericardium that may also be associated with myocarditis.

Cardiovascular Therapeutics

Antihypertensive Drugs - Diuretics: There are a number of groups of diuretics that have their effects at different parts of the excretory process. Such as Loop diuretics, Thiazide diuretics, Potassium-sparing diuretics and Aldosterone antagonists.

Antihypertensive Drugs - Sympathomimetics: The sympathomimetics includes drugs that produce either direct or indirect stimulation of adrenergic receptors and have various actions depending upon the specific receptors involved.

Antihypertensive Drugs - Vasodilators: Vasodilators produce dilatation of the blood vessels and include ACE inhibitors, nitrates as well as direct acting vasodilators.

Antihypertensive Drugs - ACE Inhibitors: ACE inhibitors exert their effects by blocking angiotensin converting enzyme (ACE) and hence prevent the conversion of angiotensin I to angiotensin II.

Antihypertensive Drugs - Angiotensin II Receptor Inhibitors: Commonly known as ARBs, this group of drugs also blocks the effects of angiotensin II.

Calcium Channel Blockers (Hypertension): cause vasodilatation, with the extent of the hypotensive effect depending upon the type of calcium channel blocker used.

Treatment of Malignant Hypertension

Antianginal Therapy:

- **Lipid-Lowering Agents:** HMG CoA Inhibitors, Niacin, Fibrates, Bile acid-binding resins and cholesterol absorption inhibitors.
- **Cardiac Glycosides:** Digitalis
- **Sodium Channel Blockers:** By blocking voltage sensitive sodium channels, class I drugs reduce excitability of the non-nodal regions of the heart where the inward sodium current is important for propagation of the action potential.
- **Beta Blockers**
- **Potassium Channel Blockers**
- **Calcium Channel Blockers (Antiarrhythmics)**

16: The Endocrine System

Chapter Summary:

The endocrine system is a network of glands that synthesize, store, and release specific secretions directly into the bloodstream. Although the endocrine glands are spread throughout the body, they act in a coordinated fashion to respond to changes in the external and internal environments, and coordinate multiple activities that maintain homeostasis. This tutorial reviews the normal anatomy and physiology of major organs of the endocrine system, followed by common diseases and therapeutics of this system. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Normal endocrine processes
- Abnormal endocrine processes
- Endocrine therapeutics

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
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Key Concepts:

- Normal endocrine processes
- Abnormal endocrine processes
- Endocrine therapeutics

Chapter Review:

Normal Endocrine Processes

Adrenal Cortex and Medulla

- The adrenal gland can be divided into the adrenal cortex derived from mesoderm and the adrenal medulla derived from the neural crest. The cortex can be further divided into the zona glomerulosa, zona fasciculata, and the zona reticularis.
- The medulla is made up of chromaffin cells that are innervated by preganglionic sympathetic fibers and release catecholamines such as epinephrine.

Adrenal Gland Drainage: Both the adrenal glands drain into the inferior vena cava, the right one through the right adrenal vein and the left one through the left adrenal vein.

Pituitary Gland:

- The posterior pituitary releases neurohypophysial hormones including vasopressin and oxytocin that are made in the hypothalamus and transported to the pituitary from where they are released.
- The function of the anterior pituitary is under regulation by the hypothalamus and anterior pituitary hormone release is under feedback regulation by peripheral hormone levels.
- The hormones released by the anterior pituitary contain an
 - α -subunit that is common to TSH, LH, FSH and hCG and
 - β -subunit that is specific to each hormone.

Endocrine Cells of the Pancreas: The pancreatic cells function as a glucose sensor and release hormones to regulate the blood glucose levels.

- α cells release glucagon, a hormone that antagonizes the effect of insulin by stimulating the hepatic release of glucose.
- β -cells release insulin that is under nutrient, neural and hormonal regulation.
- δ -cells release somatostatin.

Regulation of Prolactin: Prolactin increases dopamine synthesis and secretion from the hypothalamus.

Hypothalamic-Pituitary Hormone Regulation: the hypothalamus and pituitary regulate the release of hormones via various feedback mechanisms. The common ones: Thyroid Hormones, Prolactin, Adrenocorticotrophic hormone, Growth hormone, Somatostatin and Gonadotrophin. **Adrenal Steroids:** the adrenal gland synthesizes a number of steroids including:

- mineralocorticoids from the glomerulosa
- glucocorticoids from the fasciculate
- androgens from the reticularis
- estrogens from the periphery

Congenital Bilateral Adrenal Hyperplasias (A, B and C): are characterized by an enlargement of the adrenal glands due to an increase in ACTH stimulation because of the decreased levels of cortisol. refers to a group of disorders, which result from deficiencies or complete absence of enzymes involved in adrenal steroidogenesis. Three types are Type A, Type B and Type C.

PTH: Parathyroid hormone is secreted by the chief cells of the parathyroid.

Vitamin D: increases bone resorption, renal Ca^{2+} reabsorption, and intestinal Ca^{2+} absorption.

Calcium, Phosphate and Alkaline Phosphatase Levels: an imbalance in any or all of these levels can cause different conditions.

Calcitonin: decreases bone resorption and lowers plasma Ca levels.

Steroid/Thyroid Hormone Mechanism: exert their effects in a similar way. The hormone binds to a receptor on nucleus or cytoplasm. This results in the transformation to expose the DNA binding domain.

Thyroid Hormones: The thyroid gland is regulated by the hypothalamic-pituitary-thyroid axis. Dietary iodine is required for thyroid hormone synthesis.

Insulin-Dependent Organs: Various organs are dependent upon insulin for their normal functioning.

Cortisol: is released by the adrenal fasciculata bound to corticosteroid binding globulin.

Signaling Pathways of Endocrine Hormones: Hormones, cytokines, interleukins, and growth factors use a variety of signaling mechanisms to facilitate cellular adaptive responses.

Abnormal Endocrine Processes

Cushing's Syndrome: Excessive production of endogenous cortisol manifests clinically as Cushing syndrome. It is divided into two categories.

- The first is caused by inappropriately high secretion of ACTH, usually from a pituitary microadenoma.
- The second category of Cushing syndrome results from excess cortisol produced by the adrenal cortex independent of regulation by the pituitary or hypothalamus.

Hyperaldosteronism: The causes of hyperaldosteronism can be primary or secondary.

Addison's Disease: Deficiency of adrenal production of glucocorticoids and mineralocorticoids results in adrenocortical insufficiency. Addison's disease may be primary or secondary.

Tumors of the Adrenal Medulla: Pheochromocytoma & Neuroblastoma

Sheehan's Syndrome: Postpartum pituitary necrosis is preceded by obstetric hemorrhage leading to severe circulatory collapse.

Hypothyroidism & Hyperthyroidism

- Hypothyroidism is confirmed by a increase in TSH levels.

- Hyperthyroidism is characterized by an increased total T4, free T4 uptake, T3 uptake and a decreased TSH.

Hashimoto's Thyroiditis: is an autoimmune disease that involves the production of antibodies against thyroglobulin and the destruction of the thyroid glands hormone secreting capacity.

Subacute Thyroiditis: is acute and usually a painful thyroid enlargement with dysphagia.

Toxic Multinodular Goiter: In addition to features of goiter, the clinical presentation of toxic MNG includes subclinical hyperthyroidism or mild thyrotoxicosis.

Thyroid Cancer: most are microscopic and indolent. Larger ones require treatment such as **Papillary carcinoma, Follicular carcinoma, Medullary thyroid carcinoma, Anaplastic thyroid carcinoma and Other thyroid malignancies.**

Cretinism: is a congenital hypothyroidism resulting in pot bellied, puffy face children with protruding umbilicus and protuberant tongue.

Agromegaly: is caused by an excess of growth hormone in adults resulting in a large tongue with deep furrows, deep voice, large hands and feet, coarse facial features and impaired glucose tolerance.

Hyperparathyroidism: may be primary or secondary.

Hypoparathyroidism: Patients will be positive for Chvostek sign and Trousseau phenomenon.

Hypercalcemia: serum calcium level > 10.5 mg/dL (> 2.6 mmol/L) serum ionized calcium > 5.3 mg/dL (> 1.32 mmol/L).

Pituitary Adenoma: a prolactinoma is the most common pituitary adenoma, causing amenorrhoea, galactorrhea, low libido, infertility.

Diabetes Mellitus: is characterized by polydypsia, polyphagia, weight loss, DKA (type1), hyperosmolar coma (type2) and unopposed secretion of GH and epinephrine.

Type I vs. Type II Diabetes

- Type I diabetes is caused by pancreatic islet b-cell destruction, which is immune mediated in more than 90% of the cases and idiopathic in the remainder.
- Type 2 diabetes is also known as non insulin dependant diabetes mellitus.

Diabetes Ketoacidosis: is said to occur when there is hyperglycemia (>250mg/dL), acidosis with blood pH <7.3, sodium bicarbonate <15mEq/L and the serum tests positive for ketones.

Diabetes Insipidus: A deficiency of anti-diuretic hormone (ADH) causes central diabetes insipidus with polyuria and polydypsia.

Carcinoid Syndrome: is caused by tumor secretion of hormonal mediators.

Zollinger-Ellison Syndrome: is the name given to a gastrin secreting tumor of either the duodenum or pancreas that causes recurrent ulcers.

Endocrine Therapeutics

Drugs to Treat Diabetes: depend upon the type of diabetes.

- Type 1 diabetes is best managed by a low sugar diet and insulin replacement.
- Type II diabetes requires dietary modification and exercise for weight loss followed by the use of oral hypoglycemic, such as **sulfonyureas, Biguanides, Glitazones and α -glucosidase inhibitors.**

Orlistat: alters fat metabolism by inhibiting pancreatic lipases and is useful in the long term management of obesity in patients such as those with type 2 DM.

Sibutramine: is a sympathomimetic serotonin and norepinephrine reuptake inhibitor that is useful for both short and long term obesity management.

Polythiouracil & Methimazole: are the only two drugs available to manage hyperthyroidism.

Hypothalamic/Pituitary Drugs: may be extracted or engineered in the body and have a number of clinical uses: **GH, Somatostatin, Oxytocin and ADH.**

Levothyroxine and Tri-iodothyronine: are widely available as tablets that are clinically useful as thyroxin replacement to manage hypothyroidism and myxedema.

Glucocorticoids: exert their effect through decreased production of leukotrienes and prostaglandins by inhibiting phospholipase A2 and expression of COX-2.

17: The Gastrointestinal System

Chapter Summary:

The gastrointestinal system is comprised of abdominal layers and retroperitoneal structures. GI system circulation occurs from the Celiac Trunk is comprised of the common hepatic, splenic and left gastric arteries. Collateral Circulation may sustain abdominal organ viability during an obstructed aorta. Portosystemic Anastomoses occur between the portal and systemic venous circulations. This tutorial reviews the normal anatomy and physiology of major organs of the GI system, followed by common diseases and therapeutics of this system. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- GI system anatomy
- GI system pathology
- GI system therapeutic principles

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
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Key Concepts:

- GI system anatomy
- GI system pathology
- GI system therapeutic principles

Chapter Review:

GI System Anatomy

The **GI tract** develops into the foregut, midgut and hindgut and the system is comprised of abdominal layers and retroperitoneal structures. GI system circulation occurs from the Celiac Trunk is comprised of the common hepatic, splenic and left gastric arteries. Collateral Circulation may sustain abdominal organ viability during an obstructed aorta. Portosystemic Anastomoses occur between the portal and systemic venous circulations.

Liver Structure: Anatomy at the cellular level in the liver align plates of hepatocytes with their apical surfaces, basolateral surfaces to hepatic sinusoids, and hepatic sinusoids.

Biliary Structures: Gall bladder, cystic duct, common bile duct, Ampulla of Vater, and Sphincter of Oddi.

GI Ligaments: Include the falciform, hepatoduodenal, gastrohepatic, gastrocolic, gastrosplenic and splenorenal ligaments.

Esophageal Anatomy: The muscle of the esophageal wall varies along the level of the esophagus.

Anatomy of the Digestive Tract: Layers of the gut wall from inside to outside are mucosa, muscularis externa and serosa/adventitia.

Enteric Nerve Plexuses Related to the Gut: Myenteric or Auerbach's plexus and the submucosal or Meissner's plexus.

Anatomy of **femoral region** from lateral to medial mnemonic- NAVEL, femoral triangle and femoral sheath. The **inguinal canal** is a tubular passage that extends from the internal or deep inguinal ring to the external or superficial inguinal ring and contains the spermatic cord in men.

Peyer's Patches and Brunner's Glands:

- **Peyer's patches:** Unencapsulated lymphoid tissue.
- **Brunner's glands:** Serves to neutralize acidic contents from entering the stomach.

Salivary Secretion: Stimulated by both sympathetic and parasympathetic sources.

GI Hormones: Cholecystokinin, gastric inhibitory peptide (GIP), gastrin, motilin, nitric oxide, secretin, somatostatin, vasoactive intestinal polypeptide (VIP).

Gastric Acid Secretion involves factors such as histamine, ACh, gastrin, PGI₂ and PGE₂ are capable of stimulating gastric acid secretion. Alpha amylase, lipase, phospholipase A, colipase, trypsin, chymotrypsin, elastase, carboxypeptidases and trypsinogen are all **pancreatic enzymes**.

Carbohydrate Digestion and Absorption:

- **Carbohydrate digestion:** Salivary amylase, pancreatic amylase and oligosaccharide hydrolases.
- **Carbohydrate absorption:** Only monosaccharides such as glucose, galactose and fructose are absorbed by enterocytes.

Bile and Bilirubin: Bile is made up of bilirubin, bile salts, phospholipids, cholesterol, water and ions. It is the primary mode of excretion for cholesterol.

GI System Pathology

Hernias: Protrusions of peritoneum through abnormal openings resulting from areas of wall weakness.

Achalasia: Results in a failure to relax the lower esophageal sphincter.

Esophageal Pathologies: Gastroesophageal reflux disease (GERD), esophageal varices, Mallory-Weiss syndrome, Boerhaave's syndrome, esophageal strictures, esophagitis and Plummer-Vinson syndrome. **Barrett's Esophagus** can be remembered by "BARREtt's = Becomes Adenocarcinoma, Results from Reflux".

Esophageal cancer is a squamous cell carcinoma occurs in upper 2/3 of esophagus, while adenocarcinoma occurs in the lower 1/3 of esophagus.

Tracheoesophageal Fistula (TEF) is a congenital abnormality that results in an abnormal connection between the lumens of the trachea and esophagus.

Congenital Pyloric Stenosis: Hypertrophy of the pyloric sphincter muscle.

Malabsorption Syndromes: Celiac sprue, tropical sprue, whipple's disease, pancreatic insufficiency and disaccharide deficiency. **Celiac Sprue** is an autoimmune disease with antibodies forming to gliadin or wheat leading to malabsorption, diarrhea and steatorrhea.

Appendicitis: Inflammation of the appendix, usually secondary to its proximal obstruction.

Hirschsprung's Disease: A lack of Auerbach's and Meissner's plexuses in rectum due to the embryologic failure of neural crest cell migration.

Other Intestinal Disorders: Duodenal atresia, meconium ileus, necrotizing enterocolitis, ischemic colitis, adhesions and angiodysplasia.

Colonic Polyps: 90 % of colonic polyps are small and benign hamartomas, but can become large and cancerous over time.

Colorectal Cancer: Familial adenomatous polyposis (FAP), HNPCC or Lynch syndrome, and Peutz-Jeghers syndrome.

Carcinoid Tumor: Neuroendocrine and frequently produce serotonin or 5-HT.

Cirrhosis and Portal Hypertension: Diffuse fibrosis of the liver.

Reye's Syndrome: Rare childhood disease resulting from viral infection treated with aspirin. Hepatic steatosis, alcoholic hepatitis and alcoholic cirrhosis are all forms of **alcoholic liver disease**.

Gallstones and Cholecystitis: Form when bile acids and lecithin cannot solubilize and result in fallbladder inflammation.

Acute Pancreatitis occurs when there is autodigestion of the pancreas by its own enzymes.

Pancreatic Adenocarcinoma: Extremely aggressive form of cancer with grave prognosis, with increased incidence in Jewish and African-American males.

GI System Therapeutic Principles

H2 Blockers: Cimetidine, ranitidine, famotidine, and nizatidine are used to treat peptic ulcer disease, gastritis and GERD.

Misoprostol and Muscarinic Antagonists:

- **Misoprostol:** PGE1 analog.
- **Muscarinic Antagonists:** Pirenzepine and propantheline block M1 receptors ECL cells.

Infliximab and Sulfasalazine:

- **Infliximab:** Monoclonal antibody to TNF.
- **Sulfasalazine:** Combination of antibacterial sulfapyridine and anti-inflammatory mesalamine.

Odansetron: 5-HT3 antagonist.

Prokinetic Agents: Cisapride and Metaclopramide.

18: Hematology

Chapter Summary:

Hematology is the medical discipline encompassing the study of blood, blood-forming organs and blood-related diseases. This tutorial reviews hematopoiesis and blood cell function, including the physiology of mature white and red blood cells. Next, we review hematopoietic diseases and related therapeutics that are commonly addressed on the USMLE Step 1 exam. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Normal hematopoietic processes
- Abnormal hematopoietic processes
- Hematopoietic therapeutics

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Normal hematopoietic processes
- Abnormal hematopoietic processes
- Hematopoietic therapeutics

Chapter Review:

Normal Hematopoietic Processes

Blood Cell Differentiation: Blood cells differentiate from pluripotent hematopoietic stem cells.

- In the first step they differentiate into proerythroblasts, myeloblasts, monoblasts, megakaryoblasts and lymphoblasts.

Erythrocytes: are anucleate and biconcave, they have a large surface area to volume ratio which facilitates gas exchange.

Leukocytes – including Basophils, Eosinophils, Neutrophils, Monocytes

- There are two types of leukocytes, granulocytes and mononuclear cells.
- The granulocytes include **basophils, eosinophils, and neutrophils**.
- The mononuclear cells include **monocytes and leukocytes**.

Mast Cells: mediate allergic responses, play a role in wound healing and defense against pathogens.

Macrophages: are produced from the differentiation of monocytes, they are phagocytes, engulfing and digesting, bacteria and cell debris.

Dendritic Cells: The primary function is to act as antigen-presenting cells.

Lymphocytes: are round cells with a dark-staining nucleus and polyribosomes large enough to be seen under a light microscope.

B Lymphocytes: B Cells are an important part of the humoral and the adaptive immune response; they produce antibodies against antigens and are antigen-presenting cells that may further develop into memory B cells or Plasma B cells.

Plasma Cells: are B cells that having been exposed to antigen produce large amounts of antibodies which bind to microbes making them targets for phagocytosis and activation of the complement system.

T Lymphocytes: play a central role in cell-mediated immunity. They can be distinguished from the other lymphocytes by the presence of T cell receptors on their surface and further differentiate into helper T cells, MHC II, CD4, cytotoxic T cells, MHC I, CD8 and suppressor T cells.

Coagulation Cascade: is a series of reactions where the completion of one step catalyzes the next step, the coagulation factors are usually serine proteases but there are some exceptions. There are two different starting points the intrinsic pathway and the extrinsic pathway

Coagulation Factor Inhibitors & Fibrinolysis:

Convergence of Coagulation, Complement and Kinin Pathways:

Thrombogenesis: The formation of a platelet plug is a temporary repair.

Abnormal Hematopoietic Processes

Blood Groups: The four major blood groups are:

- A, which has the A antigen on the surface of red blood cells and the B antibody in plasma.
- B, which has the B antigen on the surface of red blood cells and the A antibody in plasma.
- AB, which has both A and B antigens on the surface of red blood cells and no antibodies in plasma.
- O, which has neither A nor B antigens on the surface of red blood cells but both A and B antibodies in plasma.

RBC Forms: Red blood cells can adopt a variety of forms depending on genetic defect and disease. The shapes are **Biconcave, Spherocytes, Elliptocyte, Macro-ovalocyte, Helmet cell/schistocyte, Sickle cell, Bite cell, Teardrop cell, Acanthocyte, and Target cell.**

Anemia: Hypochromic anemia, (microcitic, MCV less than 80), Megloblastic anemias, (macrocytic, MCV over 100) and Normocytic normochromic anemias.

Lab Values in Anemia: iron deficiency anemia lab results, chronic disease lab results, pregnancy/OCP use lab results, and hemochromatosis lab results.

Aplastic Anemia: Patient with aplastic anemia have pancytopenia, which is severe anemia, neutropenia, and thrombocytopenia.

Sickel Cell Anemia: arises from a single point mutation in the beta chain, at the sixth position valine replaces glutamic acid.

α - and β -Thalassemia

- Thalassemia is an autosomal recessive blood disease where reduced synthesis of one of the globin chains is observed.
- In α -thalassemia, the α -chain is underproduced.
- In β -thalassemia, depending on the mutation the β -chain may have reduced functionality, may be partially produced or may not be produced at all.

Autoimmune Annesia: a type of hemolytic anemia, the red blood cells are attacked and destroyed by the immune system.

Hereditary Spherocytosis: a hemolytic anemia and an autosomal dominant form of spherocytosis, the RBCs are more prone to hemolysis being spherocytes.

Paroxysmal Nocturnal Hemoglobinuria: a complement-induced hemolytic anemia, a defect in the attachment of proteins to the outside of the cell occurs.

Microangiopathic Anemia: a hemolytic anemia, intravascular hemolysis is observed when RBCs travel through small, damaged, vessels.

DIC: Disseminated intravascular coagulation, an activation of the coagulation cascade, occurs in response to a number of diseases.

Bleeding Disorders – Platelet Abnormalities: ITP, TTP, DIC, Aplastic anemia and Drugs.

Bleeding Disorders – Coagulation Factor Defects: Coagulopathies include: **(1) Hemophilia A, (B) Hemophilia B, (C) von Willebrand's disease.**

Hemorrhagic Disorders: Thrombocytopenia, hemophilia A or B, von Willebrand's disease, DIC, vitamin K deficiency, Bernard-Soulier disease, and Glanzmann's thrombasthenia.

Reed-Sternberg Cells: are multinucleated or binucleated giant cells seen in Hodgkin's disease.

Hodgkin's Lymphoma: Characteristics are the presence of Reed-Sternberg cells, an orderly spread of the disease from one lymph node to another, constitutional "B" signs/symptoms including low-grade fever, night sweats and weight loss and mediastinal lymphadenopathy. There are several types of Hodgkin's Lymphoma: Nodular sclerosing, Mixed cellularity, Lymphocyte predominant and Lymphocyte depleted.

Non-Hodgkin's Lymphoma: are associated with HIV and immunosuppression, they involve multiple, peripheral nodes, the spread is non-contiguous and extranodal involvement is common. There are many types of non-Hodgkin's lymphoma: Small lymphocytic lymphoma, Follicular lymphoma, Diffuse large cell lymphoma, Mantle cell lymphoma, Lymphoblastic lymphoma, and Burkitt's lymphoma.

Multiple Myeloma: is a cancer of monoclonal plasma cells. Large quantities of IgG, 55% of cases, or IgA, 25% of cases, are produced.

Chromosomal Translocations

- A t(9;22) translocation, **Philadelphia** chromosome, is associated with **CML**.
- A t(8;14) translocation is associated with Burkitt's lymphoma.
- A t(14;18) translocation is associated with follicular lymphoma.
- A t(15;17) translocation is associated with the M3 type of AML.
- A (11;22) translocation is associated with Ewing's sarcoma.
- A (11;14) translocation is associated with mantle cell lymphoma.

Leukemias: There is an increase in the number of circulating leukocytes. The rapid rise of immature blood cells crowds the marrow and it is unable to produce RBCs, leading to anemia, and mature WBCs, leading to infections, and platelets, leading to hemorrhage. Except for hairy cell leukemia and T-cell prolymphocytic leukemia leukemia's can be assigned to one of four categories: ALL, acute lymphoblastic leukemia, AML, acute myelogenous leukemia, CLL, chronic lymphoblastic leukemia and CML, chronic myelogenous leukemia,

Auer Bodies: are needle-shaped cytoplasmic inclusions composed of fused lysosomes, they contain peroxidase, lysosomal enzymes, and large crystalline inclusions.

Histiocytosis X: involves an abnormal increase in the number of histiocytes.

Hematopoietic Therapeutics

Heparin: works by catalyzing the activation of antithrombin III which inactivates thrombin and factor Xa.

Lepirudin and Bivalirudin: are derivatives of hirudin, they inhibit thrombin and can be used when heparins are contra-indicated because of heparin-induced thrombocytopenia.

Warfarin: also commonly known under the brand name Coumadin, is a vitamin K antagonist, as such it interferes with the synthesis of vitamin K-dependent clotting factors, II, VII, IX, and X and protein C and S.

Heparin vs. Warfarin

Thrombolytics: which dissolve clots, include streptokinase, urokinase, tPA and APSAC, anistreplase. They assist in the conversion of plasminogen to plasmin; their action may be direct or indirect.

Aspirin: is an irreversible inhibitor; it acts as an acetylating agent inhibiting cyclooxygenase, suppressing production of prostaglandins and thromboxanes.

Clopidogrel & Ticlopidine: irreversibly block ADP receptors, inhibiting platelet aggregation, and prevent glycoprotein III/IIIa expression, inhibiting fibrinogen binding.

Abciximab: is a monoclonal antibody; it prevents platelet aggregation by binding to the glycoprotein receptor IIb/IIIa on activated platelets.

Site of Action of Cancer Drugs: Cancer drugs may act in many different locations as enumerated herein: Drugs affecting nucleotide synthesis, Drugs affecting DNA and Drugs

working on proteins, Drugs that are cell cycle specific are methotrexate, 5-FU, 6-MP, etoposide, bleomycin, vinca alkaloids and paclitaxel. Drugs that are non-cell cycle specific are alkylating agents and antibiotics

Drugs Affecting DNA Synthesis: 4 categories are: Inhibitors of nucleotide synthesis, DNA polymerase inhibitors, DNA template damaging agents and DNA topoisomerase inhibitors.

Drugs Affecting Nucleotide Synthesis: include methotrexate, 5-FU, 6-MP, hydroxyurea

Drugs Affecting Proteins: include tamoxifen, raloxifene, trastuzumab, imatinib, vincristine and vinblastin, and paclitaxel.

19: Neurology

Chapter Summary:

Neurology is the medical specialty treating disorders of the nervous system. This tutorial reviews anatomy and physiology of the central and peripheral nervous systems (the autonomic nervous system is reviewed in Tutorial 14: Pharmacology). Topics include development of the nervous system; function of primary brain regions; spinal cord anatomy and physiology; and reflexes. The tutorial also reviews abnormal neural processes and neural disease, along with commonly prescribed therapeutics. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Normal neural processes
- Abnormal neural processes
- Pharmacological treatment of neural abnormalities

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Normal neural processes
- Abnormal neural processes
- Pharmacological treatment of neural abnormalities

Chapter Review:

Normal Neural Processes

Regional Specification of the Developing Brain

- Telencephalon - cerebral hemispheres and lateral ventricles
- Diencephalon - thalami and 3rd ventricle
- Mesencephalon - midbrain and aqueduct
- Metencephalon - pons and aqueduct, cerebellum and 4th ventricle
- Myelencephalon - medulla

The Blood-Brain Barrier: (BBB) is a physical barrier which occurs along capillaries that separates blood from CSF and limits microscopic particles from passing into the CSF.

Hypothalamic Functions: *Thirst, Adenohypophysis, Neurohypophysis, Hunger* (lateral) & satiety (medial hypothalamus), *Autonomic regulation* & circadian rhythms, *Temperature regulation* & *Sexual desire* & emotions.

Posterior Pituitary (Neurohypophysis): It is composed of hypothalamic axonal projections from the supraoptic and paraventricular nuclei delivering ADH and oxytocin respectively from these nuclei.

Thalamus: acts as a relay station, receiving sensory information from the body and sending it to the cerebral cortex. Specific relay centers are: **Lateral geniculate nucleus (LGN)**, **Medial geniculate nucleus (MGN)**, **Ventral posterior nucleus (VPL)**, **Ventral posterior nucleus (VPM)**, **Ventral anterior nucleus (VA)** and **ventral lateral nucleus (VL)**.

Cerebral Cortical Functions: The cerebral cortex serves multiple functions, which are dependent upon location. **Principal motor area, Principal sensory area, Principal visual cortex, Auditory cortex and Motor speech.**

Frontal Lobe Functions: The frontal lobe of the brain controls “executive function” such as concentration, planning, abstraction, language, judgment, inhibition, orientation, mood and motor regulation.

Hommunculus: is a graphic representation of the human body that illustrates some human function, in this case motor function.

Spinal Tract Anatomy & Functions: Dorsal columns, Spinothalamic tract and Lateral corticospinal tract.

Spinal Muscle Control: Muscle spindles are anatomically parallel to muscle fibers acting to control and monitor muscle length.

Clinical Reflexes: During a neurological physical examination, several reflexes are tested to assess nerve circuits and aid in localizing possible neurological lesions. For example: **Triceps reflex, Biceps reflex, Patella reflex, Achilles reflex & Babinski reflex.**

Primitive Reflexes: are normally present in infants up to 12 – 18 months, and may reappear in those older who have frontal lobe lesions. Some primitive reflexes are, **Moro reflex, Rooting reflex, Palmar reflex & Babinski reflex.**

Abnormal Neural Processes

Neural Tube Defects: are associated with low folic acid intake during pregnancy and may be detected by elevated alpha-feto protein (AFP) in amniotic fluid and maternal serum. Examples are: **Spina bifida occulta, Meningocele and Meningomyelocele.**

Forebrain Anomalies:

- *Anencephaly* – occurs when the cephalic end of the neural tube fails to close with resulting absence of the majority of the brain and skull.
- *Holoprosencephaly* – occurs when the forebrain fails to develop into two separate hemispheres resulting in cyclopia.

Motor Neuron Signs

Spinal Cord Lesions: Various diseases of the spinal cord localize in different areas, resulting in different symptoms and signs. Such are: **Poliomyelitis and Werdnig-Hoffman disease, Multiple sclerosis, ALS, Vitamin B12 neuropathy and Friedreich’s ataxia.**

Syringomyelia: enlargement of the spinal canal damages the crossing fibers of the spinothalamic tract resulting in bilateral loss of pain and temperature sensation, but with maintenance of touch.

Tabes Dorsalis: refers to the condition where tertiary syphilis causes degeneration of the dorsal columns and dorsal roots resulting in impaired proprioception and locomotor ataxia.

Brown-Sequard Syndrome: is the result of hemisection of the spinal cord.

Horner’s Syndrome: is a condition that results from damage to the sympathetic nervous system supplying the face, possibly from a lesion causing mass effect on the cervical sympathetic chain such as a Pancoast tumor, by syringomyelia, or by Brown-Sequard syndrome. The Classic triad of symptoms are: **Ptosis, Anhydrosis and Miosis.**

Brain Lesions: Lesions in various parts of the brain produce varying conditions depending on the location of the lesion in the brain. Such areas are Broca’s area, Wernicke’s area, Frontal lobe, Basal ganglia, Hippocampus and Cerebellar hemisphere.

Visual Field Defects: **Anopia, Bitemporal hemianopia, Homonymous hemianopia, Upper quadrant hemianopia, Lower quadrant hemianopia and Central scotoma**

Internuclear Ophthalmoplegia: is caused by a lesion (frequently MS) of the medial longitudinal fasciculus (MLF).

Disorders of Movement – Chorea, Athetosis, Hemiballismus

Aphasia: *Motor/expressive aphasia & Sensory/receptive aphasia.*

Degenerative Diseases – Cerebral Cortex: *Alzheimer’s disease, Pick’s disease, Creutzfeldt-Jakob disease & Lewy body dementia.*

Degenerative Diseases – Basal Ganglia & Brain Stem: *Parkinson's disease & Huntington's disease.*

Degenerative Diseases – Spinocerebellar Motor Neuron: *Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease, Werdnig-Hoffman disease, also known as infantile spinal muscular atrophy, Poliomyelitis and Friedreich's ataxia*

Poliomyelitis: is caused by the polio virus which has fecal-oral transmission.

Demyelinating & Dysmyelinating Diseases: *Multiple sclerosis (MS), Progressive multifocal leukoencephalopathy (PML), Metachromatic leukodystrophy, Postinfectious acute disseminated encephalomyelitis & Guillain-Barre syndrome.*

Guillain-Barre Syndrome: is a condition of inflammation and demyelination of peripheral nerves and motor fibers of ventral roots.

Seizures: are categorized as either partial or generalized.

- *Partial seizures: **Simple & Complex partial seizures***
- *Generalized seizures: **Absence/petit mal, Myoclonic and Tonic-clonic/grand mal, Tonic & Atonic/drop seizures***

Intercranial Hemorrhage: *Epidural hematoma, Subdural hematoma, Subarachnoid hemorrhage & Parenchymal hemorrhage*

Berry Aneurysms: occur at bifurcations around the circle of Willis.

Hydrocephalus: is a condition in which there is an abnormal increase in amount of CSF in the ventricles of the brain.

Neurocutaneous Disorders: *Neurofibromatosis, Tuberous sclerosis, Sturge-Weber Syndrome and Von Bippel-Lindau disease*

Primary Brain Tumors-Adult: *Glioblastoma Muliforme, Meningioma-2nd, Schwannoma-3rd, Oligodendroglioma, Pituitary adenoma*

Primary Brain Tumors - Childhood: *Pilocytic astrocytoma, Medulloblastoma-2nd, Ependymoma-3rd, Hemangioblastoma & Craniopharyngioma*

Posterior Fossa Malformations: *Arnold-Chiari malformation & Dandy-Walker Syndrome*

Cranial Nerve & Cerebellar Lesions: *CN V motor lesion, CN X lesion, CN XI lesion and CN XII LMN lesion.*

Facial Lesions: *UMN lesion, LMN lesion & Bell's palsy.*

Herniation Syndromes: *Cingulate gyrus herniation, Downward central transtentorial herniation, Uncal herniation and Cerebellar tonsillar herniation.*

Pharmacological Treatment of Neural Abnormalities

Opioid Analgesics: *morphine, codeine, heroin, methadone, fentanyl, meperidine and dextromethorphan.*

Phenytoin: is an antiseizure medication.

Barbiturates: *phenobarbital, pentobarbital, thiopental & secobarbital.*

Benzodiazepines: *diazepam, lorazepam, alprazolam triazolam, temazepam, oxazepam, midazolam and chlordiazepoxide.*

Anesthetics: Anesthetic drugs that affect the CNS must be lipid soluble to pass the BBB or be actively transported across the BBB.

Inhaled Anesthetics: *Nitrous oxide, halothane, enflurane, isoflurane, sevoflurane and methoxyflurane.*

Intravenous Anesthetics: *Barbiturates, Benzodiazepines, Arylcyclohexamines, Opiates and Propofol*

Local Anesthetics: Esters – procaine, cocaine and tetracaine. **Amides** – lidocaine, mepivacaine and bupivacaine.

Neuromuscular Blocking Drugs: are used to paralyze muscle during surgery or mechanical ventilation. **Depolarizing** – succinylcholine and Nondepolarizing – tubocurarine, atracurium, mivacurium, pancuronium, vecuronium.

Dantrolene: is used to treat malignant hyperthermia and neuroleptic malignant syndrome.

Therapeutics for Parkinson's disease: **Agonize dopamine receptors** – bromocriptine, pramipexole, ropinirole, **Increase dopamine** – amantadine, L-dopa/carbidopa, **Prevent**

dopamine breakdown – selegiline, entacapone, tolcapone and **Curb excess cholinergic activity** – benztropine.

Levodopa & Carbidopa: are used to treat Parkinsonism.

Seligiline: is used as an adjunctive drug to L-dopa in the treatment of Parkinson's disease.

Sumatriptan: is used to treat acute migraine headaches and cluster headache attacks.

20: The Skin and Musculoskeletal Systems

Chapter Summary:

This tutorial reviews two interrelated topics frequently addressed on the USMLE Step 1 Exam: the skin and musculoskeletal system. The skin provides the body's first line of defense against injury and invading pathogens, while the musculoskeletal system supports locomotion. This tutorial reviews anatomy, physiology and pathology of the skin and musculoskeletal systems. This includes skin, bone, connective tissue and major muscle groups. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Anatomy and physiology of skin and musculoskeletal system
- Pathology of skin and musculoskeletal system
- Pharmacology of skin and musculoskeletal system

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Anatomy and physiology of skin and musculoskeletal system
- Pathology of skin and musculoskeletal system
- Pharmacology of skin and musculoskeletal system

Chapter Review:

Anatomy and Physiology

Epidermis Layers: Stratum **C**orneum, Stratum **L**ucidum, Stratum **G**ranulosum, Stratum **S**pinosum & Stratum **B**asalis

Epithelial Cell Junctions

- *Zona occludens* – a tight junction made up of claudins and occludins that prevent diffusion.
- *Zona adherens* – an intermediate junction made up of cadherins connecting to actin just below the zona occludens.
- *Macula adherens* – a desmosome made up of cadherins connecting to intermediate filaments forming small, focal sites of attachment.
- *Gap junction* – allows adjacent cells to communicate for metabolic and electric functions.
- *Hemidesmosome* – connects cells to their underlying extracellular matrix.

Rotator Cuff Muscles: *Supraspinatous* – abduction, *Infraspinatous* – lateral rotation, *teres minor* – adduction and lateral rotation & *Subscapularis* – adduction and medial rotation.

Brachial Plexus: is a complex arrangement of nerves emanating from the cervical spine, to the neck, and into the axilla, all controlling the movements of the upper extremity. **Roots, Trunks, Divisions, Cords and Branches.**

Radial Nerve: aka the "great extensor nerve" innervates the following muscles:

Brachioradialis, Extensors of the wrist and fingers, Supinator & Triceps.

Hand Muscles: *Thenar muscles, Hypothenar muscles, Dorsal interosseous muscle, Palmar interosseous muscle & Lumbrical muscle.*

Skeletal and Cardiac Muscle Contraction: *Cocked state, Cross-bridged state, Power-stroke state & Released state*

Formation of Bone

- *Endochondral ossification* – chondrocytes form cartilage, which is replaced with osteoclasts and osteoblasts to form woven bone, which is later remodeled into lamellar bone.
- *Membranous ossification* – osteoclasts and osteoblasts form woven bone in the absence of cartilage, which is later remodeled into lamellar bone.

Pathology

- **Achondroplasia:** is an autosomal dominant disorder that result in dwarfism due to a failure of longitudinal bone growth resulting in short limbs.
- **Osteoporosis:** refers to a reduction in bone mass despite normal bone mineralization. There are 2 types.
- **Osteopetrosis:** aka marble bone disease is a rare inherited disorder in which bones become very dense and thickened due to osteoclast malfunction.
- **Osteitis Fibrosa Cystica:** refers to an abnormal bone condition that results from hyperparathyroidism in which osteoclastic activity is increased causing cystic spaces in bone lined with osteoclasts and filled with fibrous stroma and possible heme products.
- **Paget's Disease:** is a disorder of bone which may be viral in origin and is the result of an increase in both osteoblastic and osteoclastic activity causing a very rapid turnover of bone with resulting enlarged and deformed bones which are soft and subject to fracture.
- **Polyostotic Fibrosa Dysplasia:** aka *Albright's disease* refers to fibrous dysplasia involving more than one bone where bone is replaced with fibroblasts and collagen, resulting in irregular bony trabeculae and thinning of bone making the bone subject to fractures.
- **McCune-Albright Syndrome:** refers to a condition in which there is polyostotic fibrous dysplasia associated with premature puberty and unilateral pigmented spots of the skin – café au lait spots.
- **Benign Primary Bone Tumors:** *Osteoma, Osteoid osteoma, Osteoblastoma, Osteoclastoma, aka giant cell tumor, Osteochondroma & Enchondroma*
- **Malignant Primary Bone Tumors:** *Osteosarcoma, aka osteogenic sarcoma, Ewing's sarcoma & Chondrosarcoma*

Primary Bone Tumor Locations

- *Epiphysis:* benign – giant cell tumor, aka osteoclastoma.
- *Metaphysis:* benign – osteochondroma; malignant – osteosarcoma.
- *Diaphysis:* benign – osteoid osteoma; malignant – Ewing's sarcoma.
- *Intramedullary:* benign – enchondroma; malignant – chondrosarcoma.

Osteoarthritis: aka degenerative arthritis is a mechanical disorder involving the degradation of joints with destruction of articular cartilage, the formation of subchondral cysts, osteophytes, sclerosis, and Bouchard's nodes at the PIP joints and Heberden's nodes at the DIP joints.

Rheumatoid Arthritis: is an autoimmune inflammatory disorder that affects synovial joints and causes pannus formation in the MCP and PIP joints.

Sjogren's Syndrome: is an autoimmune disorder in which the exocrine glands that produce saliva and tears are attacked; there is a high association with rheumatoid arthritis. Its classic triad is: **Xerophthalmia – dry eyes, Xerostomia – dry mouth & Arthritis**

Gout: is an inflammatory arthritis more common in men that is caused by elevated blood levels of uric acid which crystallizes and deposits in joints and their surrounding tissues.

Pseudogout: is a disorder caused by the deposition of calcium pyrophosphate crystals in joints, most commonly the knee.

Seronegative Spondyloarthropathies: occur more often in males and have a strong association with the HLA-B27 gene; there is no associated rheumatoid factor. (*Ankylosing spondylitis, Psoriatic arthritis and Reiter's syndrome*)

Systemic Lupus Erythematosus: (SLE) is an autoimmune disorder that affects females 90% of the time, usually from 14 – 45 years old.

Sarcoidosis: is an autoimmune disorder most commonly seen in black females and is associated with arthritis, restrictive lung disease, bilateral hilar lymphadenopathy, erythema nodosum, epithelial granulomas, uveoparotitis and hypercalcemia.

Polymyalgia Rheumatica: is an inflammatory condition that may occur in patients > 50 years old causing muscle aches and stiffness primarily of the neck, shoulders and hips.

Polymyositis/Dermatomyositis

- *Polymyositis* is caused by CD8+ T-cell-induced injury to muscle fibers resulting in progressive, symmetric, proximal muscle weakness.
- *Dermatomyositis* is similar to polymyositis, but has associated heliotrope rash, "shawl and face rash" and has an increased incidence of malignancies.

Myasthenia Gravis & Lambert-Eaton Syndrome Connective Tissue Disease: (MCTD) is an autoimmune disorder with overlapping features of SLE, scleroderma and polymyositis, usually affecting females from 20 -40 years old.

Scleroderma: is an autoimmune disorder characterized by diffuse fibrosis and collagen deposition throughout the body, usually involving skin and the pulmonary, cardiovascular, GI and renal systems.

Soft Tissue Tumors: *Lipoma, Liposarcoma & Rhabdomyosarcoma*

Common Skin Disorders: *Atopic dermatitis (eczema), Allergic contact dermatitis, Urticaria, Psoriasis, Seborrheic dermatitis & Verrucae*

Pigmentation Disorders: *Vitiligo, Albinism & Melasma*

Infectious Skin Disorders: *Impetigo, Cellulitis, Necrotizing fasciitis, Staphylococcal scalded skin syndrome (SSSS) & Hairy leukoplakia*

Blistering Disorders: *Bullous pemphigoid, Pemphigus vulgaris, Dermatitis herpetiformis, Erythema multiforme, Stevens-Johnson syndrome & Toxic epidermal necrolysis*

Other Skin Disorders: *Lichen Planus, Actinis keratosis & Acanthosis nigricans.*

Skin Cancer: *Squamous cell carcinoma, Basal cell carcinoma & Melanoma*

Knee Injury: Knee anatomy is clinically significant, particularly for injury with regard to the multiple ligaments and the menisci

Injuries of the Upper Extremity Nerves

Injuries of the Lower Extremity Nerves: *Obturator nerve, Femoral nerve, Common perineal nerve, Tibial nerve, Superior gluteal nerve and Inferior gluteal nerve.*

Erb-Duchenne Palsy: may result in newborns due to a traumatic delivery or in general from a blow to the shoulder causing traction or tear of the upper trunk (C5 and C6 nerve roots) of the brachial plexus.

Thoracic Outlet Syndrome: aka Klumpke's palsy may also result in newborns due to a traumatic delivery or by trauma to or mass effect on the subclavian artery and inferior trunk of the brachial plexus (C8 & T1).

Pharmacology

Arachidonic Acid Products: Lipoxygenase pathway generates Leukotrienes. LTB₄, LTC₄, D₄ and E₄ and PGI₂ (Platelet Gathering Inhibitor) inhibits platelet aggregation and encourages vasodilation.

NSAIDs: nonsteroidal anti-inflammatory drugs: *ibuprofen, naproxen, indomethacin, & ketorolac.* Their mechanism of action is to reversibly inhibit cyclooxygenase (COX-1 & COX-2) & block prostaglandin synthesis.

COX-2 Inhibitors: An example of a COX-2 inhibitor is celecoxib. Its mechanism of action is to reversibly inhibit COX-2 which mediates pain and inflammation, but spares COX-1 which helps preserve GI mucosa and alleviate the risk of GI ulcers.

Acetaminophen: trade name Tylenol. Its mechanism of action is to reversibly inhibit cyclooxygenase, primarily in the CNS.

Drugs to Treat Gout: 3 main drugs to treat gout: **Colchicine, Probenecid & Allopurinol.**

Etanercept: is a recombinant form of human TNF receptor which binds TNF.

Infliximab: is an anti- TNF antibody.

21: The Renal System

Chapter Summary:

The kidneys are the primary site of excretion from the body. In this tutorial, we review normal and abnormal processes of the kidney, focusing on core concepts likely to be addressed during the USMLE Step 1 Exam. The tutorial includes a review of kidney structure and function, with an emphasis on the nephron and methodologies for assessing kidney function. Also reviewed are kidney diseases and therapeutics.

Tutorial Features:

Specific Tutorial Features:

- Normal renal processes
- Abnormal renal processes
- Renal system therapeutics

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Normal renal processes
- Abnormal renal processes
- Renal system therapeutics

Chapter Review:

Normal Renal Processes

Kidney Structure

- There are two kidneys, one on each side of the abdomen.
- The internal structure of the kidney can be divided into the 3 regions, the innermost being the pelvis, then the medullary pyramids and the outermost being the cortex.

Nephron Structure:

- Nephrons are the processes in the kidney through which the exchange of substances takes place to form urine. They are found in the medulla & cortex of the kidneys & it consists of the glomerulus where filtration takes place.

Glomerular Structure

- The glomerulus consists of a tuft of capillaries that flow through the Bowman's capsule. The afferent arteriole brings blood to the glomerulus.

Ureters: pass under the uterine artery and under the ductus deferens.

Fluid Compartments

- Total body weight is made up of 40% of nonwater mass & 60% of total body water.
- Extracellular fluid consists of $\frac{1}{4}$ plasma volume & $\frac{3}{4}$ interstitial volumes.

Renal Clearance: The creatinine clearance is the volume of plasma from which the substance is completely cleared per unit time. It can be calculated using the equation: $C_x = \frac{U \times V}{P_x}$

- **P_x = plasma concentration of X. U_x = urine concentration of X.**
- **C_x = clearance of X. V = urine flow rate.**

Glomerular Filtration Rate: can be calculated using the creatinine clearance of insulin since this compound is freely filtered but not reabsorbed or secreted.

- $GFR = U_{\text{inulin}} \times V / P_{\text{inulin}} = C_{\text{inulin}}$;
- $= K_f [(P_{GC} - P_{BS}) - (\pi_{GC} - \pi_{BS})]$.
- (GC = glomerular capillary; BS = Bowman's space.)
- π_{BS} normally equals zero.

Effective Renal Plasma Flow: (ERPF) can be estimated using PAH, since this compound is both filtered and actively secreted in the proximal tubule.

- $ERPF = U_{PAH} \times V / P_{PAH} = C_{PAH} \cdot RBF = RPF / (1 - Hct)$.
- It is estimated that the ERPF underestimates true RPF by ~10%.

Filtration: can be calculated using the equation: **Filtration fraction = GFR/RPF**

- **Filtered load = GFR × plasma concentration** whereby the GFR can be estimated with creatinine.

Effects of Changes in Renal Function: Different types of changes in renal function are indicative of different conditions.

Free Water Clearance: is the ability of the kidney to dilute water. It can be calculated using the urine flow rate and the the osmolarity of urine and plasma.

- $C_{H_2O} = V - C_{osm}$; $V = \text{urine flow rate}$; $C_{osm} = U_{osm} V / P_{osm}$.
- With ADH: $C_{H_2O} < 0$; W/out ADH: $C_{H_2O} > 0$. Isotonic urine: $C_{H_2O} = 0$.

Glucose Clearance

- The normally functioning kidney has the ability to completely reabsorb glucose in the proximal tubule.
- If there is too much glucose in the blood, it spills over and is classified as glucosuria at plasma glucose levels of 200mg/dL or above.

Amino Acid Clearance: At least 3 distinct carrier systems have been identified in the reabsorption of amino acids. Each of these have been shown to demonstrate competitive inhibition process.

The Nephron – Early Proximal Convulated Tubule: The Early Proximal Convulated Tubule, also known as the "workhorse of the nephron" contains a brush border that allows for reabsorption of all the glucose and amino acids and most of the bicarbonate, sodium and water via isotonicity.

The Nephron – Thin Descending Loop of Henle: Passive reabsorption of water via intermedullary hypertonicity occurs in the thin descending loop of Henle, making the urine hypertonic.

The Nephron – Thick Ascending Loop of Henle: The thick ascending loop of Henle is the primary site for active reabsorption of Na, K and Cl ions. This in turn induces the reabsorption of Mg and Ca.

The Nephron – Early Distal Convulated Tubule: As urine passes into the early distal convulated tubule, Na and Cl continue to be actively reabsorbed. Reabsorption of Ca ions also takes place in this part, but this is under the control of the parathyroid hormone.

The Nephron – Collecting Tubules: The collecting tubules reabsorb Na in exchange for secreting K or H ions, an action that is regulated by aldosterone.

Renin-Angiotensin System: is a series of actions that release angiotensin II.

Juxtaglomerular Apparatus (JGA): consists of juxtaglomerular cells (JG) and the macula densa.

Endocrine Functions of the Kidney: The kidney is specialized to carry out various endocrine functions.

Hormones that act on the Kidney: Aldosterone, Atrial Natriuretic, Renin, Parathyroid Hormone & Vasopressin (ADH)

Acid-Base Physiology

- **Acidosis:** Occurs when the pH is less than 7.4.
- **Alkalosis:** Occurs when the pH is greater than 7.4.

Types of Renal Tubular Acidosis

- Renal tubular acidosis can be defined as type 1, 2 or 4.

Abnormal Renal Processes

Potter's Syndrome: Causes a typical physical appearance, is the result of oligohydramnios secondary to renal diseases such as bilateral renal agenesis.

Horseshoe Kidney: Occur when the inferior poles of both kidneys fuse.

Casts: Different types of casts can be found in the urine and may indicate different problems.

RBC casts, WBC casts, Granular casts, Waxy casts & Hyaline casts

- **Nephritic Syndrome:** is characterized by hematuria, hypertension, oliguria and azotemia. The different **types of nephritic syndrome** are: Acute poststreptococcal glomerulonephritis, Membranoproliferative glomerulonephritis, Rapidly progressive (crescentic) glomerulonephritis, Goodpasture's syndrome (type II hypersensitivity), IgA nephropathy (Berger's disease) & Alports Syndrome

Nephrotic Syndrome: is characterized by massive proteinuria, hypoalbuminemia, peripheral and periorbital edema, hyperlipidemia.

Kidney Stones: can lead to severe complications such as hydronephrosis & pyelonephritis.

Renal Cell Carcinoma: is associated with von Hippel Lindau and gene deletion in chromosome 3 and originates in the renal tubule cells.

Wilms' Tumor: can be caused by the deletion of the tumor suppression gene WTI on chromosome 11.

Transitional Cell Carcinoma: is the most common tumor of urinary tract system and may be found in the renal calyces, renal pelvis, ureters and bladder.

Pyelonephritis: Acute pyelonephritis affects the cortex with relative sparing of glomeruli.

Diffuse Cortical Necrosis: is an acute generalized infarction of the cortices of both kidneys.

Drug-Induced Interstitial Nephritis: is an acute interstitial renal inflammation.

Acute Tubular Necrosis & Renal Papillary Necrosis

Acute Renal Failure: is associated with an abrupt decline in renal function & an increase in creatine and BUN over a period of several days.

Consequences of Renal Failure: Patients with renal failure lack the ability to make urine & excrete nitrogenous wastes. (Acute & Chronic) **Fanconi's Syndrome:** is due to a defect in proximal tubule transport of amino acids, glucose, phosphate, uric acid, protein, and electrolytes.

Cysts: Adult polycystic kidney disease: multiple large bilateral cysts that ultimately destroy the parenchyma.

Electrolyte Disturbances: Low or high serum concentrations of electrolytes can greatly affect the functioning of the renal system.

Therapeutics

Diuretics: Site of Action

- **Acetazolamide:** PCT, **Osmotic agents such as mannitol, Loop diuretics such as furosemide, Thiazides such as hydrochlorothiazide:** DCT, **Potassium sparing diuretics such as spironolactone:** DCT

Mannitol: is an osmotic diuretic that increases the osmolarity of the tubular fluid and increases urine flow.

Acetazolamide: is a carbonic anhydrase inhibitor that causes self limited sodium bicarbonate diuresis and reduction in total body bicarbonate stores.

Furosemide & Ethacrynic Acid:

- **Furosemide** is a sulphonamide loop diuretic that inhibits the cotransport system of the thick ascending loop of Henle.
- **Ethacrynic acid** is a phenoxyacetic acid derivate that has essentially the same action as furosemide but can be used in patients with a sulfa allergy.

Hydrochlorothiazide: is a thiazide diuretic that inhibits the reabsorption of NaCl in the early distal tubule reducing the diluting capacity of the nephron.

ACE Inhibitors: are a relatively new group of drugs and include captopril, enalapril and lisinopril.

22: The Reproductive System

Chapter Summary:

This tutorial reviews the reproductive system in both male and female humans. The tutorial provides an overview of normal functioning of the reproductive system as a foundation for learning about abnormal function and diseases of the reproductive system. The tutorial includes an overview of the development of gender-specific structures, and concludes with a review of common reproductive therapeutics.

Tutorial Features:

Specific Tutorial Features:

- Reproductive system structure
- Normal reproductive function
- Abnormal reproductive function
- Therapeutics of the reproductive system

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Reproductive system structure
- Normal reproductive function
- Abnormal reproductive function
- Therapeutics of the reproductive system

Chapter Review:

Genital Embryology

Female development is the default development with disappearance of the mesonephric duct or Wolffian duct and development of the *paramesenteric or Mullerian duct*, which progresses to form the fallopian tubes, uterus and a portion of the vagina.

Male development is dependent on the *SRY* gene of the Y chromosome which is responsible for testis-determining factor. The developing testes secrete a paramesenteric or Mullerian duct inhibiting factor & androgens which promote development of the **Mesonephric or Wolffian duct**.

Male/Female Genital Homologues:

- **Genital tubercle** develops into the glans penis in the male, and the glans clitoris in the female.
- **Urogenital sinus** develops into the corpus spongiosum, bulbourethral glands of Cowper, prostate gland in males, and the vestibular bulbs, greater vestibular glands of Bartholin, urethral and paraurethral glands of Skene in females.
- **Urogenital folds** develop into the ventral shaft of the penis and penile urethra in males, and the labia minora in females.
- **Labioscrotal swelling** develops into the scrotal sac in males, and the labia majora in females.

Gonadal Drainage: The body accomplishes gonadal drainage in two ways, by the venous system and by the lymphatic system.

Ligaments of the Uterus: *Suspensory ligament of ovary, Broad ligament, Cardinal ligament & Round ligament of uterus*

Autonomic Innervation of the Male Sexual Response: The male sexual response consists of erection and ejaculation.

Sperm: A spermatozoon consists of 3 main parts. **Head, Midpiece & Tail**

Sperm Development: begins with spermatogonia (type A+B) at puberty and continues throughout a man's life.

Spermatogenesis: the hypothalamus which stimulates the anterior pituitary to release LH (luteinizing hormone) and FSH (follicle-stimulating hormone). FSH is needed for sperm remodeling and FSH stimulates the Sertoli cells to produce ABP and Inhibin (which inhibits FSH) which are necessary for sperm production. LH leads to the Leydig cells releasing testosterone (which is essential for germ cell mitosis and meiosis).

Normal Reproductive Function

Androgens: are masculinizing hormones. They are listed as follows in order of potency from strongest to weakest:

- **Dihydrotestosterone (DHT) (secreted from the testis)**
- **Testosterone (secreted from the testis)**
- **Androstenedione (secreted from the adrenal cortex)**

Estrogens: is a feminizing hormone found in the ovaries (in the form of estradiol), placenta (in the form of estriol), and blood. The forms of estrogen listed from strongest to weakest in potency are: **Estradiol** → **Estrone** → **Estriol**

Progesterone: is a hormone that elevates during ovulation and acts to prepare the body for pregnancy. It is produced in several places in the body including the: **Corpus luteum, Placenta, Adrenal cortex & Testes**

Menstrual Cycle: is a typically takes 28 days and consists of 3 phases: *Menstrual phase, Proliferative phase & Secretory (or progestational phase)*

Ovulation: usually occurs on the 14th day after the first day of the last menstrual period.

Meiosis & Ovulation: The development of an ovum is a lengthy process.

Intercourse & Orgasm: **Intercourse** is often more than a reproductive activity, but is also an activity sought for pleasure. **Orgasm** is the peak of the sexual response cycle, characterized by intense pleasure.

hCG: Human Chorionic Gonadotrophin (hCG) is secreted by the syncytiotrophoblast of the placenta.

Puberty & Menopause: puberty marks the beginning of a woman's childbearing years, menopause marks its end.

Abnormal Reproductive Function

Sex Chromosome Disorders: *Klinefelter's, Turner's, Double-Y Males, Pseudo-Hermaphroditism & True Hermaphroditism*

Hormone-Related Disorders: *Androgen-Insensitivity Syndrome & 5 α -Reductase Deficiency*

Developmental Disorders: *Pathologic ovum & Hydatidiform moles*

Pregnancy Complications 1: Several complications of pregnancy involve the placenta.

Abruptio placentae, Placenta accrete, Placenta previa & Ectopic pregnancy

Pregnancy Complications 2: Two complications of pregnancy involve amniotic fluid volumes. **Polyhydramnios & Oligohydramnios**

Polycystic Ovarian Syndrome and Ovarian Cysts

- *Polycystic Ovarian Syndrome* is an endocrine imbalance with \uparrow LH, \downarrow FSH, and \uparrow testosterone.
- *Ovarian Cysts* are fluid or semisolid sacs that develop in or on the ovary.

Neoplastic Disorders – Gynecological Tumor Epidemiology: Gynecological tumors may occur in the endometrium, uterus, and/or cervix.

Neoplastic Disorders – Cervical Pathology: Cervical dysplasia can begin at the basal layer of the squamo-columnar junction and extend outwards. They are classified as CIN1, CIN 2, or CIN 3.

Neoplastic Disorders – Uterine Pathology: Several neoplastic disorders can occur that involve the uterus. Such as *Endometriosis, Adenomyosis, Endometrial hyperplasia, Endometrial carcinoma, Leiomyoma (fibroid) & Leiomyosarcomas.*

Neoplastic Disorders – Ovarian Germ Cell Tumors: There are multiple types of germ cell tumors: *Dysgerminoma, Choriocarcinoma, Yolk sac or endodermal sinus tumor & Teratomas.*

Neoplastic Disorders – Ovarian Non-Germ Cell Tumors: There are many ovarian non-germ cell tumors. Some benign types include: *Serous & Mucinous cystadenoma, Brenner tumor & Fibromas.* Some malignant types include: *Serous & Mucinous cystadenocarcinoma, Granulosa cell tumor & Krukenberg tumor.*

Neoplastic Disorders – Vaginal Carcinoma: Three types are: *Squamous cell carcinoma, Clear cell adenocarcinoma & Sarcoma botryoides (rhabdomyosarcoma variant)*

Neoplastic Disorders – Breast Tumors: *Benign & Malignant tumors*

Common Breast Conditions and Prostate Pathology: *Acute mastitis, fat necrosis, Gynecomastia & Fibrocystic disease*

Neoplastic Disorders – Benign Prostatic Hyperplasia: is when the urethra is compressed by an enlarged prostate gland.

Neoplastic Disorders – Prostatic Adenocarcinoma: is characterized by a slowly progressing prostate tumor.

Neoplastic Disorders – Cryptorchidism, Testicular Germ Cell Tumors

Neoplastic Disorders – Testicular Non-Germ Cell Tumors: are an often benign group that can cause approximately 5% of testicular tumors.

Tunica Vaginalis Lesions: occur in the serous covering of the testis and present as a testicular mass that can be evaluated via transillumination: *Varicocele, Hydrocele & Spermatocele.*

Penile Pathology: include: *Carcinoma in situ, Squamous cell carcinoma (SCG), & Peyronies disease.*

Therapeutics of the Reproductive System

Antiandrogens: *Finasteride (Propecia), Flutamide, Ketoconazole & Spironolactone*

Leuprolide: which is a GnRH analog is used to treat several reproductive system problems: Infertility, Prostate & Uterine cancer.

Sildenafil & Vardenafil: are both used to treat erectile dysfunction.

Mifepristone, Dinoprostone and Ritodrine

- Mifepristone (RU 486) is a competitive inhibitor of prostins at progesterone receptors that is often administered with Minsoprostol (PGE1) to terminate a pregnancy.
- Dinoprostone is a PGE2 analog that induces labor by dilating the cervix and contracting the uterus.
- Ritodrine/Terbutaline is used to relax the uterus.

Oral Contraception: Synthetic progestin & estrogen are therapeutics commonly used by women to prevent pregnancy, and to regulate menstrual flow.

Hormone Replacement Therapy: (HRT) utilizes therapeutics to prevent osteoporosis and to diminish menopausal symptoms such as: hot flashes and vaginal atrophy.

Anastrozole: is an Aromatase inhibitor.

Testosterone (Methyltestosterone): is a therapeutic that works as an androgen receptor agonist.

Estrogens: are a group of therapeutics that includes Ethinyl Estradiol, DES, and Mestranol. These bind receptors are used for: *Hypogonadism, Ovarian failure, Menstrual abnormalities, HRT in postmenopausal women & Androgen-dependent prostate cancer.*

Progestins: are bind progesterone receptors that are used for: *Oral contraceptives, Endometrial cancer & Abnormal uterine bleeding.*

Estrogen Partial Agonists: (selective estrogen receptor modulators – SERMs) include: **Clomiphen**- which is used to treat infertility and PCOS, **Tamoxifen**- which is used to treat ER positive breast cancer & **Raloxifen**- which is used to treat osteoporosis.

23: The Respiratory System

Chapter Summary:

The tutorial begins with an overview of normal respiratory system structure and function, which lays the foundation for understanding the general principles of lung damage and disease. The tutorial reviews key respiratory diseases, and reviews important therapeutics.

Tutorial Features:

Specific Tutorial Features:

- Normal respiratory processes
- Abnormal respiratory processes
- Respiratory therapeutics

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Normal respiratory processes
- Abnormal respiratory processes
- Respiratory therapeutics

Chapter Review:

Respiratory System Function

Respiratory System

- Conducting zone – consists of the nose, pharynx, trachea, bronchi, bronchioles and terminal bronchioles.
- Respiratory zone - is where gaseous exchange takes place and consists of the bronchioles, alveolar ducts and alveoli.

Pneumocytes

- pseudocolumnar ciliated cells that extend to the respiratory bronchioles
- goblet cells that extend only into the terminal bronchioles

Gas Exchange Barrier: Comprises of alveolar cells in close contact with the network of capillaries.

Bronchopulmonary Segments: Each segment has a tertiary bronchus & 2 arteries in the center, veins & lymphatics drain along the borders.

Lung Relations

- The right lung has 3 lobes and the left has 2 lobes. Instead of a middle lobe, the left lung has a space occupied by the heart.
- The right lung is the more common site for an inhaled foreign body because the right main stem bronchus is more vertical than the rest.

Structures of the Diaphragm

- **Perforations:** T8: Inferior Vena Cava, T10: Esophagus, T12: Aorta, thoracic duct and azygous vein.
- **Nerves:** C3, 4 & 5 phrenic nerves

Muscles of Respiration

- During quiet breathing, the diaphragm is utilized during an inspiration and expiration is a passive process.

- In the course of exercise, the external intercostals, scalene muscles & sternomastoids are utilized in inspiration & rectus abdominus, internal and external obliques, transverses abdominals & internal intercostals assist with expiration.

Products of the Lungs

- 1) Surfactant 2) Prostaglandins, 3) Histamine that increases bronchoconstriction, 4) Angiotensin converting enzyme (ACE), & 5) Kallikrein that activates bradykinin.

Ways to Calculate Lung Volumes

- 1) Residual Volume (RV), 2) Expiratory reserve volume (ERV), 3) Tidal Volume (TV), 4) Inspiratory Reserve Volume (IRV), 5) Vital Capacity is the sum of the TV+ IRV+ ERV, 6) Functional residual capacity (FRC)-RV+ ERV, 7) Inspiratory capacity (IC) = IRV + TV & 8) Total Lung Capacity (TLC) = IRV + TV + ERV + RV

Determining Physiologic Dead Space: The physiological dead space (VD) is the anatomical dead space of the conducting airways plus the functional dead space in alveoli.

- $V_d = V_t \times (P_{aCO_2} - P_{eCO_2}) / P_{aCO_2}$; Where V_t is the tidal volume, P_{aCO_2} is the arterial PCO_2 , P_{eCO_2} is the expired air PCO_2

Oxygen-Hemoglobin Dissociation Curve

- A plot of the haemoglobin (Hb) saturation against the partial pressure of oxygen gives a sigmoidal curve.
- The curve shifts to the left in increase in oxygen affinity, decrease in P_{50} , decrease metabolic needs, decrease PCO_2 , decrease temperature, decrease H^+ , increase pH, decrease 2,3-DPG and fetal Hb.

Pulmonary Circulation: is a relatively low resistance and highly compliant system.

- Perfusion can be limited by oxygen, CO_2 and N_2O . Gas equilibrates early along the length of the capillary.
- Diffusion can be limited by oxygen in emphysema and fibrosis or carbon monoxide.

Pulmonary Vascular Resistance

- $PVR = P_{pulm\ artery} - PL_{atrium} / Cardiac\ Output$
- Remember: $\Delta P = Q \times R$, so $R = \Delta P / Q$. $R = 8\eta l / \pi r^4$
- $P_{pulm\ artery}$ = pressure in pulmonary artery.
- PL_{atrium} = pulmonary wedge pressure.
- η = the viscosity of inspired air; l = airway length;
- r = airway radius.

Oxygen Content of the Blood: is calculated as follows. $O_2\ content = (O_2\ binding\ capacity \times \% \text{ saturation}) + dissolved\ O_2$.

Alveolar Gas Equation

- $PAO_2 = PIO_2 - (PACO_2/R)$; this can normally be approximated at: $PAO_2 = 150 - PaCO_2 / 0.8$
- Whereby: PAO_2 = alveolar PO_2 (mmHg). $R\ PIO_2$ = PO_2 in inspired air (mmHg). $PACO_2$ = alveolar PCO_2 (mmHg). R = respiratory quotient. A-a gradient = $PAO_2 - PaO_2 = 10-15$ mmHg.

V/Q Mismatch: In order for adequate gaseous exchange to occur, ventilation is matched to perfusion.

CO_2 Transport: Carbon dioxide is transported from the tissues to the lungs 3 ways.

- **Bicarbonate** - 90% of the carbon dioxide is transported in this way. **Bound to Hb** - 5% of the carbon dioxide binds to Hb to form carbaminohemoglobin. **Dissolved** - 5% of the carbon monoxide is transported dissolved in body fluids.

Response to High Altitude: 1) Acute increase in ventilation, 2) Chronic increase in ventilation, 3) Increased erythropoietin and increase in the hematocrit & the amount of hemoglobin, 4) Increase in 2,3-DPG that binds to Hb so that the Hb releases more O_2 , 5) Cellular changes such as an increase in the number of mitochondria, 6) Increased renal excretion of bicarbonate & 7) Chronic hypoxic pulmonary vasoconstriction resulting in RVH.

Abnormal Respiratory Processes

CO Poisoning: Carbon monoxide has 50 times greater affinity for Hemoglobin than oxygen. As a result any carbon monoxide present causes a reduction in the oxygen binding capacity with a left shift in the oxygen-hemoglobin dissociation curve.

Pulmonary Hypertensions: This condition is a result if the pressure rises above 25mmHg under normal conditions or over 35mmHg during exercise. Since normal pulmonary artery pressure is 10-14mmHg.

Obstructive Lung Disease (COPD): It's an obstruction of air flow resulting in trapping in the lungs. The airways close prematurely at high lung volumes resulting in an increased RV and decreased FVC.

Restrictive Lung Disease: causes a decrease in lung volumes particularly FVC and TLC. Pulmonary function tests reveal the FEV1/FVC ratio to be > 80%.

Neonatal Respiratory Distress Syndrome: is due to a surfactant deficiency leading to an increase in surface tension resulting in alveolar collapse.

Adult Respiratory Distress Syndrome: may be caused by trauma, sepsis, shock, gastric aspiration, uremia, acute pancreatitis or amniotic fluid embolism.

Obstructive vs. Restrictive Lung Disease: Lung disease can be described as obstructive or restrictive based upon the FEV1/FVC ratio: **Normal: 80%, Obstructive: <80%, Restrictive >80%**

Sleep Apnea: In sleep apnea, the patient stops breathing for at least 10 seconds repeatedly during sleep. Two types: **Central & Obstructive**

Asbestosis: is a diffuse pulmonary interstitial fibrosis caused by inhaled asbestos fibers.

Lung Cancer: is the leading cause of cancer death.

Pancoast's Tumor: is a carcinoma that occurs in the apex of the lung and may affect cervical sympathetic plexus, causing Horner's syndrome.

Pneumonia: is an infection of the lungs.

Lung Abscess: is a localized collection of pus within the parenchyma usually resulting from bronchial obstruction.

Pleural Effusions: 3 types (**Transsudate, Exudate & Lymphatic**)

Respiratory Therapeutics

H1 Blockers: are reversible inhibitors of H1 histamine receptors.

Asthma Drugs - β Agonists (non-specific and β agonists)

- **Non specific β -agonists:** include isoproterenol. This chemical relaxes that bronchial smooth muscle but also causes tachycardia since it is not cardiospecific.
- **Specific β -agonists:** such as albuterol relax the bronchial smooth muscle only & are used clinically during an acute exacerbation.

Methylxanthine: The most commonly used methylxanthine is theophylline that causes bronchodilation by inhibiting phosphodiesterase and thereby decreasing the hydrolysis of cAMP.

Muscarinic antagonists: Ipratropium is a competitive blocker of muscarinic receptors, preventing bronchoconstriction.

Cromolyn & Corticosteroids

- **Cromolyn** prevents the release of mediators from mast cells and is only effective against the prophylaxis of asthma.
- **Corticosteroids** including beclomethasone and prednisone inhibit the synthesis of virtually all cytokine.

Antileukotrienes: Zileuton, a 5-lipoxygenase pathway inhibitor blocks the conversion of arachidonic acid to leukotrienes.

Expectorants: Guaifenesin removes excess sputum but needs to be taken in large doses and it does not suppress the cough reflex.

24: Multisystem Processes

Chapter Summary:

A number of important processes impact multiple body systems. In this tutorial, we review important concepts in nutrients and nutrition; adaptation to changing environments; and discuss the impact of heavy metals that affect multiple body organs simultaneously. The tutorial includes a review of commonly prescribed therapeutics for the treatment of related disorders. Helpful mnemonics are provided throughout the tutorial to aid memorization of the material.

Tutorial Features:

Specific Tutorial Features:

- Nutrients and nutrition
- Adaptation to changing environments
- Heavy metals

Series Features:

- Concept map showing inter-connections of concepts.
- Sample USMLE Step 1 exam questions with full answers.
- Examples given throughout to illustrate how the concepts apply.
- A concise summary is given at the conclusion of the tutorial.

Key Concepts:

- Nutrients and nutrition
- Adaptation to changing environments
- Heavy metals

Chapter Review:

Nutrients and Nutrition

Vitamins: Fall into 2 categories: Fat soluble & Water Soluble.

Fat-Soluble Vitamins

- Include vitamins A, D, E and K, which absorb in the ileum of the GI tract and in the pancreas.
- They tend to accumulate in fat, thus they are more commonly toxic than the water soluble vitamins.

Water-Soluble Vitamins: Include all B vitamins (including B1, B2, B3, B5, B6 and B12), as well as vitamin C, biotin and foliate. All exit the body quite easily, except foliate & B12, which are stored in the liver.

Vitamin A (Retinol): is important for retinal function, as it makes up the visual pigments of the retina. The lack of retinol results in night blindness and dry skin, while excess retinol causes arthralgias & fatigue.

Vitamin B1 (Thiamine): is a co-factor in the HMP shunt pathway & in the oxidative decarboxylation of α -ketoacids.

Vitamin B2 (Riboflavin): is a cofactor in both oxidation & reduction reactions. 1 way to remember this is, "FAD & FMN are derived from riboflavin".

Vitamin B3 (Niacin): is a derivative of tryptophan using vitamin B6, and is used as a constituent of NAD and NADP.

Vitamin B5 (Pantothenate): is a component of the cofactor CoA, which can be remembered using "Pantothen-A is in CoA".

Vitamin B6 (Pyridoxine): is converted to pyridoxal phosphate, a cofactor used for transamination, decarboxylation, glycogen phosphorylase and heme synthesis, and is required for niacin synthesis from tryptophan.

Vitamin B12 (Cobalamin): is a vitamin found only in animal products. B12 is stored primarily in the liver, and B12 deficiency is characterized by neurological symptoms that include abnormal myelination, optic neuropathy and paresthesia, as well as macrocytic, megaloblastic anemia.

Folic Acid: is important for synthesis of the nitrogen bases in DNA and RNA, and is known to play a role in neural tube formation.

Biotin: is commonly used as a cofactor for carboxylation reactions.

Vitamin C (Ascorbic Acid): When present, vitamin C is utilized for collagen synthesis (important for wound healing), iron absorption (hence the link to anemia), and as a cofactor for dopamine β -hydroxylase, which converts dopamine to norepinephrine.

Vitamin D: works by increasing intestinal absorption of calcium and phosphate. There are actually two forms of vitamin D: D2, which is consumed in milk and D3, which is formed in sun-exposed skin.

Vitamin E: is commonly known for its antioxidant properties, which protects erythrocytes from hemolysis (can be remembered using "E is for Erythrocytes").

Vitamin K: is a critical component for blood coagulation (which can be remembered using "K is for Koagulation"). Warfarin is an anticoagulant that acts by antagonizing vitamin K.

Zinc: is an essential component of many enzymes in the body, and zinc deficiency is associated with delayed wound healing, hypogonadism, and decreased hair in adults.

Assessing Nutritional Status

ATP: is the body's energy source. Production of ATP occurs via one of 2 routes:

- Aerobic metabolism of glucose, which in the heart and liver produces 32 ATP via the malate-aspartate shuttle and in the muscle produces 30 ATP via the glycerol-3-phosphate shuttle.
- Anaerobic glycolysis, which produces only 2 ATP for every glucose molecule.

Metabolic Fuel Use: Exercise & Fasting and Starvation

Eating Disorders: Anorexia nervosa & Bulimia Nervosa

Fluid, Electrolyte and Acid-Base Balance

Fluid Compartments

- The total body weight is made up of 40% of nonwater mass and 60% of total body water.
- The total body water comprises 1/3 extracellular fluid that is high in sodium chloride and low in potassium and 2/3 intracellular fluid that is high in potassium and low in sodium chloride.
- Extracellular fluid consists of 1/4 plasma volume & 3/4 interstitial volumes.

Dehydration: is an excessive loss of body fluid, which may be in one of three forms:

- Hypotonic – loss of electrolytes
- Hypertonic – loss of water
- Isotonic – loss of both electrolytes and water

Electrolyte Disturbances: Low or high serum concentrations of electrolytes can greatly affect the functioning of the renal system, since the renal system works on the delicate balance of these electrolytes. Common electrolytes are: Sodium Ions, Chloride Ions, Potassium Ions, Calcium Ions, Magnesium Ions and Phosphate Ions.

Acid-Base Physiology: Through the carefully regulated mechanism of filtration, secretion & reabsorption, the kidneys maintain the acid-base balance in the body. The Henderson Hasselbach equation can be used

Acidosis: occurs when the pH is less than 7.4. If the pCO₂ is greater than 40mmHg, the acidosis is respiratory.

- Respiratory acidosis can be caused by hypoventilation due to airway obstruction, acute and chronic lung disease, medications such as opioids, sedatives & narcotics, weakening of the respiratory muscles.
- Metabolic acidosis with compensation occurs if the PCO₂ is less than 40mmHg. In cases of this, the cause can be narrowed down by checking the anion gap.

Alkylosis: Alkalemia is said to occur when the pH is greater than 7.4.

Types of Renal Tubular Acidosis: can be defined as type 1, 2 or 4.

Acid-Base Compensations: The body tries to compensate acid base disorders in different ways.

- Metabolic acidosis: Winter's formula: $PCO_2 = 1.5 (HCO_3^-) + 8 \pm 2$.
- Metabolic alkalosis
- Respiratory acidosis: Acute & Chronic
- Respiratory alkalosis: Acute & Chronic

Adaption to Changing Environments

Temperature Regulation: is the body's ability to maintain its temperature within a certain range. In humans, most body heat is generated within the deep organs, such as the liver, brain & skeletal muscle.

High-Altitude Sickness: commonly occurs at altitudes above 8,000 feet, due to exposure to low partial pressure of oxygen at these altitudes.

Decompression Sickness: more commonly known as "the bends", is due to the precipitation of dissolved gas bubbles in the body when the body undergoes depressurization, such as when a scuba diver ascends from a depth to the water surface, when a person leaves a high pressure environment, or when a person ascends to an elevated altitude.

Decreased Atmosphere Pressure: At high altitudes there is lower atmospheric pressure than at sea level. During extended periods of time, the human body may adapt to high altitude by breathing faster, increased heart rate, and increased number of red blood cells.

Radiation Burns: is tissue damage due to exposure to ionizing radiation, most commonly sunburn caused by exposure to UV radiation.

Heavy Metals

Arsenic: occurs in multiple inorganic & organic forms, with the trivalent inorganic arsenic compounds being the primary toxic form of arsenic.

Arsenic Poisoning and Treatment: On a molecular level, arsenic inhibits mitochondrial production of ATP through two mechanisms: 1st, it competes with phosphate during oxidative phosphorylation. & 2nd, inhibition of NAD reduction linked to production of ATP.

- Treatment of arsenic poisoning utilizes chelators, such as dimercaprol (BAL) and succimer.

Lead: is found throughout the environment and in all biological systems.

Neurotoxicity of Lead: In the peripheral nervous system, peripheral neuropathy resulting from axonal degeneration is a classic sign of lead neurotoxicity, as resulting from lead-induced Schwann cell degeneration.

Symptoms of Lead Poisoning 1:

- Acute, high levels of exposure in children causes encephalopathy, which includes ataxia, reduced level of consciousness, and eventual coma and death.
- Long-term, low-level exposure has been linked to neuropsychological deficits, such as lower IQ, language deficits and reduced attention span.

Symptoms of Lead Poisoning 2:

- Outside the nervous system, lead causes anemia by impairing heme synthesis and by shortening the lifespan of red blood cells.
- Lead is also linked to renal toxicity resulting from damage to proximal tubular cells, as well as increased blood pressure.

Treatment of Lead Poisoning: utilizes chelators such as CaEDTA, dimercaprol, succimer and penicillamine.

Mercury: is another metal found everywhere in the environment and it is unique in that it is the only metal that is in the liquid form at room temperature in its inorganic state. Mercury is most hazardous in two forms: the 1st is as a mercury vapor & the 2nd is as organic mercury.

Mercury Vapor: is naturally present in the environment through the natural degassing of the earth's crust. It is also created through human industrial activities.

Organic Mercury: is formed through methylation of inorganic mercury by microorganisms, or as a by-product of human industrial activities.

Methyl Mercury: is a highly lipophilic molecule, which means it can easily cross both the placental barrier and the blood-brain barrier.

Treatment of Mercury Poisoning: utilizes chelators such as dimercaprol (BAL) and succimer.