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Basic Sciences Study Guide

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Abstract

This thesis is the beginning of a study guide to be completed for Pacific University students that are intending on taking Part I - Basic Sciences for the National Board of Examiners in Optometry. The sections covered in this section include Neuroscience, Biochemistry, Physiology and Psychology. It presents up-to-date, consistently formatted information that was compiled for, and follows directly along with, the required topics for Part X of the board exams and it provides an alternative resource to the Berkeley Guide. The subjects indicated for Part I but not covered within this thesis will be compiled by students in following years.

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STUDY GUIDE

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Advisor:

Dennis Smith, OD, MS

Signatures

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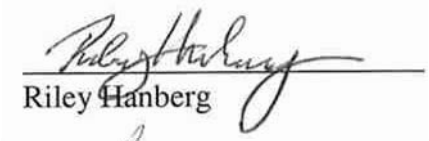
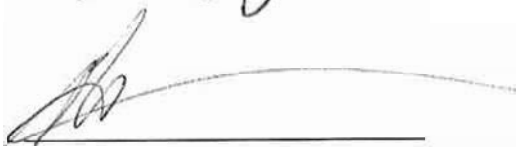
Calvin Alonzo



Riley Hanberg



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Biography of Authors

Calvin Alonzo

Mr. Alonzo was born on Travis Air Force Bases near Fairfield, CA and spent most of his life growing up in Mililani, Hawaii. He attended the University of Puget Sound where he obtained a bachelors of science degree before moving to Forest Grove to study optometry at Pacific University College of Optometry.
His future plans are to return to Hawaii where he can enjoy family, friends and sun while practicing in a private clinical setting.

Riley Hanberg

Mr. Hanberg grew up in Tsawwassen, British Columbia and later attended Queen's University in Kingston, Ontario where he obtained a bachelors degree with honours in Life Sciences.
His future plans are to practice in northwest Washington or southwest British Columbia in a multi-disciplinary setting while dedicating time to his wife and family who have provided great support to him throughout his education at Pacific University College of Optometry.

Matthew Pearce

Mr. Pearce was born in Winnipeg, Manitoba in 1976 and lived in Edmonton, Alberta for most of his life. He later attended the University of Alberta obtaining a B.Sc with a biological science major and a minor in physical science. He was an Academic All Canadian in his fourth year of undergraduate studies, having competed in the CIAU cross-country championships that year while maintaining the required grade point average of at least 3.0.
Mr. Pearce plans to use his optometric education to help better the lives of people around the world by pursuing economic, and social justice while caring for people's eyes. He desires to dedicate his financial resources, his time, and his heart to bring about physical and emotional healing to the people of the world who are often overlooked both in terms of eyecare and economics.

John Riley

Mr. Riley attended both Arizona State University and The University of Arizona, where he attained a B.S. in Veterinary Sciences in 1996 from the latter. While attending the University of Arizona he was awarded the W. Larkin Fitch Scholarship in 1994 and the Charles R. Coughlin Scholarship in 1995. He was later awarded a scholarship from the state of Washington through the WICHE program to attend Pacific University College of Optometry.
Mr. Riley is currently a member of the AOSA, OEP, and the Sports Vision Section of the AOA. His areas of optometric interest include contact lenses, pediatric optometry, vision therapy and sports vision. His future plan is to seek employment in the state of Washington, hopefully in a private practice setting.

Abstract

This thesis is the beginning of a study guide to be completed for Pacific University students that are intending on taking Part I – Basic Sciences for the National Board of Examiners in Optometry. The sections covered in this section include Neuroscience, Biochemistry, Physiology and Psychology. It presents up-to-date, consistently formatted information that was compiled for, and follows directly along with, the required topics for Part I of the board exams and it provides an alternative resource to the Berkeley Guide. The subjects indicated for Part I but not covered within this thesis will be compiled by students in following years.

Introduction

The purpose of this thesis is to fill a need for an alternate source of information pertinent to the National Board of Examiners in Optometry Part I – Basic Sciences. The Berkeley Guide is currently the only comprehensive study guide compiled for the purpose of studying for this test. With time constraints, and a desire to have information easily available for all subject areas within one study guide, most optometry students use the Berkeley Guide as their primary resource while studying for Part I of the exams. However, many have indicated that they find the Berkeley Guide hard to follow with spelling mistakes, misplaced or missing figures, errors in information, and poor continuity.

This guide is intended to provide students with an alternative study guide. Care was made to provide a more consistent format for presenting the information, continuity between and within sections, elimination of grammar and information errors, and inclusion of appropriate figures within the text when indicated.

The subjects covered within this thesis (neuroscience, biochemistry, physiology and psychology) were chosen secondary to the need for a better study guide expressed by students that had used the Berkeley Guide, or tried to compile information on their own, and felt that they would have liked an alternative resource to study from. As well, areas of strength and interest of the authors was considered to best serve the needs of presenting the information in a smooth and coherent manner.

Students in following years who continue to compile this study guide may choose to complete another section or to update an existing section along with changing NBEO requirements.

Table of Contents

NEUROSCIENCE

Pertinent Classes: OPT 535 Functional Neuroanatomy and Neurobiology
Useful Text: **Principles of Neural Scence, 2nd Ed.** Kandel and Schwartz, Elsivier Science Publishing Co., Inc. 1985
Neuroscience in Medicine. P. Michael Conn, J.B. Lippincott Co. 1995
Clinical Neuroanatomy: made ridiculously simple, Goldberg, S. MedMaster, Inc. 2000.

A. Neurohistology

1. Histogenesis in the nervous system

All cells in the nervous system (neurons and glial cells) originate from the ectoderm which forms the outer layer of the emryo. The first process of development is determination in which the precursor ectoderrn cells are transformed into the cells that will form the nervous system (neuroectoderm). This occurs by a process called neural induction and is dependent upon the presence of underlying mesoderm. Collectively the neuroectoderm form the neural plate (125,000 cells). By day 18 the formation of the neural tube, or neurulation, begins. The neural plate thickens, and folds in on itself with the elevated lateral edges forming the neural folds around a central neural groove. The folds meet and fuse at the prospective cervical region and then progress rostrally and caudally. The rostra1 portion will form three swellings or neural vesicles for the forebrain (prosencephalon), midbrain (mesencephalon) and hindbrain (rhombencephalon) which then divide into five vesicles as shown in figure 1.

Figure 1

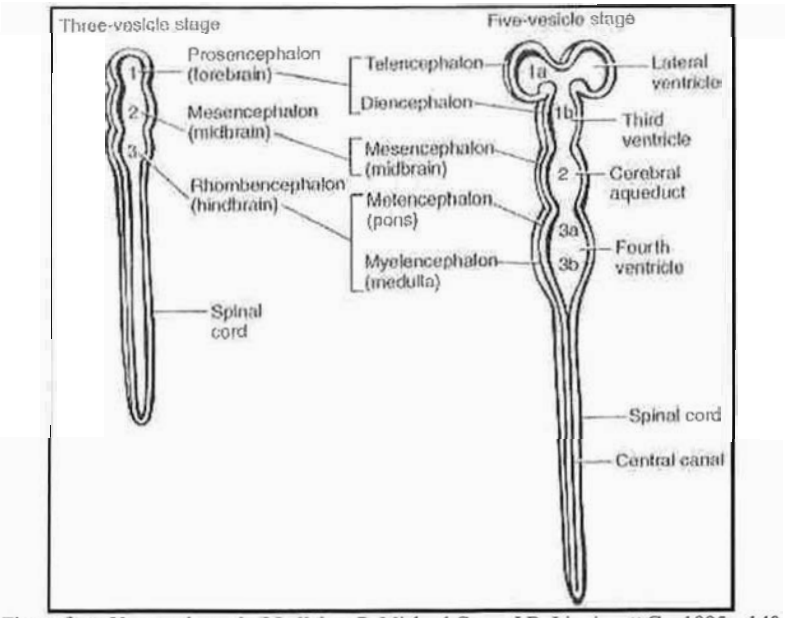


Figure from **Neuroscience in Medicine.** P. Michael Conn. J.B. Lippincott Co. 1995. p140

Meanwhile, the caudal portion gives rise to the spinal cord and grows longitudinally with the vertebral column. Rootlets form from the first sacral column and travel through the lumbar cistern and exit the spine as the cauda equina.

The neural crest cells from the lateral edges of the neural folds become a band of cells extending longitudinally between the neural tube and the overlying ectoderm. The differentiation of the crest cells is dependent on the location as in the following table:

Table 1

Rostra1	Caudal
1, Cranial nerve ganglia 2. Digestive tract parasympathetic autonomic ganglia 3. Ciliary ganglion 4. Schwann cells *5*. Melanocytes *6*. Meninges of pia-arachnoid	1. Dorsal root ganglia 2. Sympathetic autonomic ganglia 3. Adrenal medulla chromaffin cells 4. Postumbilical intestinal tract ganglia

2. Degeneration and regeneration in the nervous system

Upon transection (also called axotomy) of a nerve, degenerative changes occur at the zone of trauma of both the proximal segment and the distal segment.

Zone of trauma: Axoplasm is quickly lost at the time of transection from both sides of the lesion. Fusion of the axon membrane then seals off these leaks and forms *retraction bulbs* that swell with mitochondria, vesicles and membranous material that normally travel by axoplasmic flow (proximal bulb only due to one way flow) and axonal flow (both bulbs due to two direction flow). As this time macrophages and glial cells begin to phagocytose the degenerating axons and myelin sheaths.

Proximal segment: All degeneration proximal to the lesion is called retrograde degeneration (Figure 2). Degeneration happens quickly reaching the cell body in 2-3 days. The cell body then swells and the nucleus moves towards the side of the cell body (often away from the axon hillock). The rough ER of the cell bodies, called *Nissl bodies* (for chromophil/ "stain lover") undergo dissolution, or *chromatolysis* and spread to the periphery of the cell. Chromatolysis lasts 1-3 weeks and is a key histological indicator of neuronal lesions. As well, the increase in free polysomes and protein from chromatolysis indicates the enhanced protein synthesis in the cell body.

Distal segment: All degeneration distal to the lesion is called anterograde degeneration. Degeneration of the distal axon fiber and myelin is called *Wallerian degeneration* and occurs slowly, forming fragments that are phagocytized and removed by macrophages. Meanwhile, degeneration

of the presynaptic terminal occurs rapidly. Accumulation of mitochondria and neurofilaments cause swelling while glial and Schwann cells proliferate and phagocytize any degenerated segments.

In some cases degeneration will pass to adjacent cells that synapse with the compromised cell by a process called transneuronal degeneration (Figure 2).

Figure 2

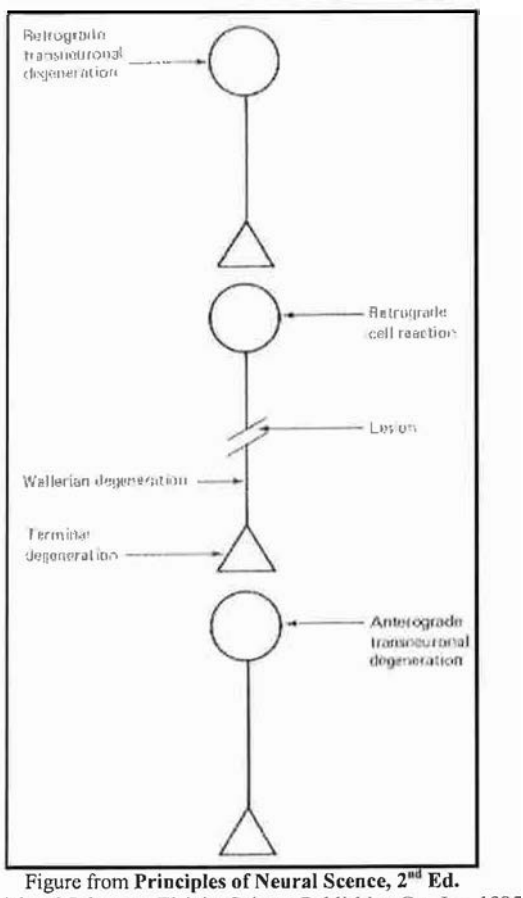


Figure from **Principles of Neural Scence, 2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985

Regeneration occurs by the following steps:

i. The proximal stump gives rise to a growth cone that progresses at an average of 1 mm/day.
ii. Schwann cells proliferate and co-migrate with the growth cone.
iii. Linearly oriented Schwann cells (*neurilemma*) remaining from Wallerian degeneration produce growth factors and form a tube or "cellular highway" along which the axon grows.
iv. Myelin internodes increase (distance between the Nodes of Ranvier) to maturation. Note that the final length is shorter than before the lesion and therefore the conduction velocity is slower.
v. However, the final result is that only fibers that terminate in the proper nerve endings will survive and function.

Collateral nerve regeneration can also occur. The stimulation of an adjacent undamaged nerve, most likely by chemicals released by the denervated nerve, may cause a sprout to branch out and reinnervate the area distal to the lesion. In the CNS this process is called *reactive synaptogenesis.*

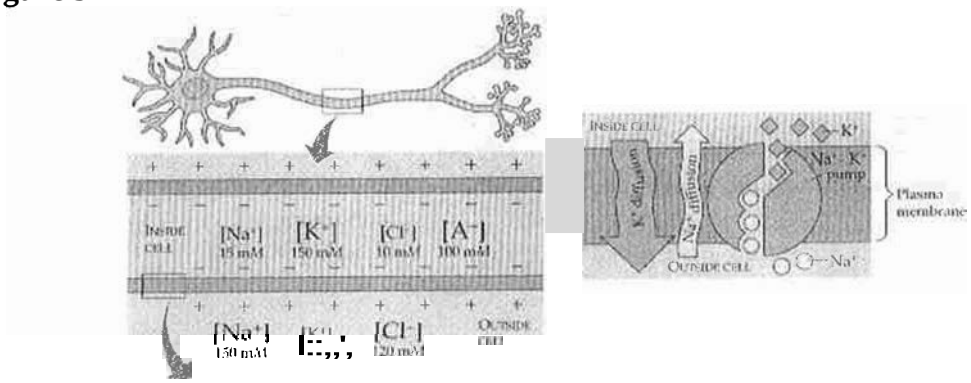
Regeneration in the PNS is robust but success depends on achieving the target. In the CNS (brain, spinal cord and retina) most cells undergo *abortive regeneration* where the axons sprout initially then cease growing and are resorbed.

B. Electrophysiology of the Nerve Cell

1. Basis of Resting Potential

Before we begin discussion look at the following figure (Figure 3). Note the concentration of each of the players and the charge inside and outside of the cell in the first picture. Then note the big arrow for K^+ **,** the little arrow for Na^+ and the 3 Na^+ out - 2 K^+ in pump.

Figure 3



Biology, 3rd Ed. Campbell, N. Benjamin/Cummings Publishing Co., Inc. 1993

The only ion that does not cross the phospholipid bilayer is the anion (actually a collection of proteins, amino acids, sulfates, phosphates etc.) as it is too big. Chlorine crosses passively while Na^+ and K^+ cross passively and actively. Passive transmission is through selective ion channels that only allow one type of ion to pass. The resting potential is a result of the distribution of ions across the membrane and the two forces that move ions from intracellular to extracellular and vice versa. These forces are the concentration gradient, moving ions from higher concentrations to lower concentrations, and the electrical gradient, moving ions from like charged environment to that of the opposite charge. The ease with which the ions can cross the membrane determines their contribution to the resting potential.

Lets start with potassium the biggest player in the resting potential. K^+ has a relatively high permeability. It is drawn out of the cell (efflux) by the concentration gradient. As it leaves the cell it transfers positive charge with it leaving the negative anion to create a negative interior. At some point the electrical gradient begins to attract K^+ back into the

cell (influx). The point at which these two forces balance each other and influx equals efflux is around –85 mV called the *equilibrium potential* of K^+.

What about sodium? Na^+ has a lower permeability (less channels) than K^+ and therefore large changes in extracellular Na^+ will have little effect on the resting potential. As well, Na^+ is attracted to the inside of the cell by both concentration and electrical gradient. This influx of a positive ion elevates the resting potential to about –70mV.

If this were all that happened we would end up with a high concentration of Na^+ inside the cell, K^+ outside of the cell and the resting potential would gradually dissipate. To counterbalance this effect we have the sodium-potassium pump that moves K^+ back into the cell and Na^+ out of the cell.
Our last ion Cl^- has no effect on the resting potential. It reaches a net flux of zero as it is drawn into the cell by concentration and out of the cell by electrical charge. Cl^- is referred to as passively distributed across the membrane while Na^+ and K^+ are actively distributed.

2. Basis of Action Potential

As we have mentioned the unequal concentration of the ions across the neuron membrane gives us an electrochemical gradient that is about –70mV. Excitatory neurotransmitter molecules at synaptic connections can passively depolarize a neuron (increase positive charge inside the neuron). These small depolarizing events will trigger voltage-gated Na^+ and K^+ channels to open for ion passage. The first step in the action potential is the increase in permeability of the Na^+ ion and it increases passage into the cell. The point at which Na^+ influx equals K^+ efflux is the *threshold* of the neuron. This depolarization of the cell gives positive feedback to the membrane and opens more Na^+ channels resulting in the explosive all-or-none response. Just below the Na^+ equilibrium potential (+55mV) around +40-50mV the Na^+ channels close and the K^+ channels open and efflux of this ion repolarizes the membrane. These channels are slower in their response to changes in membrane potential and at the resting level they will continue to be permeable. This continued K^+ efflux will result in a slight undershoot making Na^+ channels inactive for a short period called the *refractory period*. The overall movement of ions in an action potential is relatively small in comparison to overall intracellular concentrations.

3. Action Potential Conduction

Simple concept. Strong depolarization at one region of the cell causes its neighboring region to depolarize above the threshold resulting in an action potential. This potential passes along the neuron carrying the signal towards the synapse. Retrograde excitation does not occur due to the refractory period after an action potential inhibiting further excitation back along the axon.
The speed of transmission can be affected in 2 ways:

i) Diameter of Axon: Bigger axons are faster due to decreased resistance to flow within the axon. The depolarization can travel further down the interior of the axon before setting up a new action potential.

ii) Myelin: Myelin sheaths also increase the distance within the cell that the excitatory positive current will travel. It limits ion flow across the membrane to the *Nodes of Ranvier* (gaps in the glial cells) which are rich with Na^+ voltage-

gated channels. The jumping of action potentials is called *saltatory conduction.*

4. Synapses, Classification, Transmission

There are two types of synapse:
i) Electronic Synapse (electrical transmission): Low-resistance gap junctions provide for direct current passage between neurons (Figure 4). Depolarization of partnered neurons may be subthreshold, suprathreshold (resulting in an action potential) or *rectifying* in which current flows in one direction more easily thus limiting the direction of information transferred. Interconnected cells tend to fire synchronously. Although a rare type of synapse, they can be found in the inferior olive and the occulomotor nuclei.

Figure 4 – Electronic Synapse

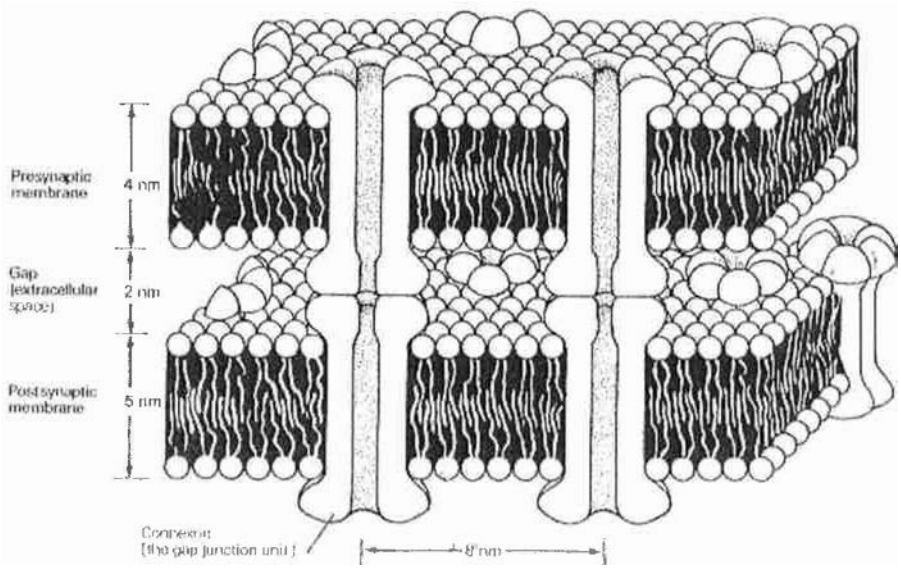


Figure from Principles **of** Neural **Scence, 2**nd Ed.
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p90

Chemical transmission: a five step process

1) The action potential triggers Ca^{++} influx at the presynaptic terminal
2) Increased Ca^{++} causes fusion of the synaptic vesicles to the presynaptic membrane resulting in the release of neurotransmitters.
3) Neurotransmitters diffuse across the synaptic cleft and bind postsynaptic receptors
4) Receptors open ion channels changing the postsynaptic membrane voltage up/down.
5) Neurotransmitter molecules are then enzymatically degraded or taken up by another neuron allowing the ion channels to close.

For a compound to be classified as a neurotransmitter (NT) it must: a) be contained in the presynaptic vesicles that will be released when stimulated and affect the potential of the postsynaptic membrane, b) be able to cause an excitatory postsynaptic potential or an inhibitory postsynaptic potential, and c) be removable from the synaptic cleft. The most common NT is acetylcholine occurring as both an excitatory and inhibitory NT. Other common NTs are the biogenic amines norepinephrine, epinephrine, dopamine and seratonin (the NEDS), the amino acids glycine, glutamate, and gamma aminobutyric acid/GABA (the 3 G's) and some neuropeptides such as the endorphins.

5. Membrane physiology, receptors, membrane channels

Neurotransmitters bind and interact with receptor molecules to open ion channels in order to change the potential across the postsynaptic membrane. There are three types of receptors (Figure 5):

i. Ion channel-gated receptors: The receptor and channel are the same molecule. Duration of the postsynaptic action is tightly controlled with this direct linking during release and removal of neurotransmitters.
ii. Distinct receptor and channel: The two are coupled by a G protein (named for hydrolyzing GDP). This allows an increased number of actions for a neurotransmitter as their receptor can bind numerous types of channels.
iii. Transcellular receptors: The receptor is coupled to a second messenger enzyme system within the neuron which, when activated, opens/closes ion channels. This action is longer lasting.

Figure 5 – Receptor Types

Ion Channel-gated Distinct Receptor Transcellular

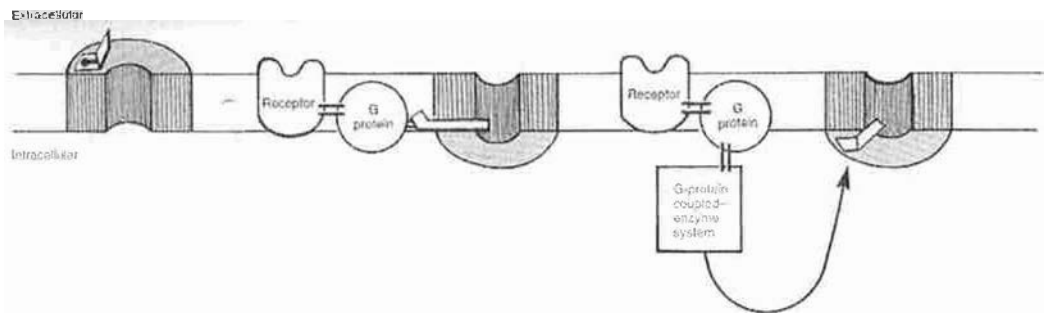


Figure from **Neuroscience in Medicine. P.** Michael Conn. J.B. Lippincott Co. 1995. p91

6. Inhibitory and Excitatory Postsynaptic Potentials (and summation)

Excitatorypostsynapticpotentials (EPSP) and *Inhibitory postsynaptic potentials (IPSP)* are graded potentials that, in order to create an action potential, must summate to depolarize the axon hillock to the threshold potential (around –50mV). The further from the axon hillock the lower the electrical impact on "spike" initiation. To initiate an EPSP the NTs must bind channels that open Na^+ channels. Na^+ influx will depolarize/excite the cell. To initiate an IPSP the NT must bind receptors that open K^+ channels (causing efflux) or Cl^- channels (influx due to concentration gradient) to repolarize and/or

hyperpolarize the cell. However, a single EPSP alone will not stimulate and action potential. Either *temporal summation* (sequential transmission of signals before repolarization occurs) or *spatial summation* (additive stimulation of a cell by different presynaptic terminals) must occur to bring the axon hillock to threshold (Figure 6).

Figure 6 – Spatial vs Temporal Summation

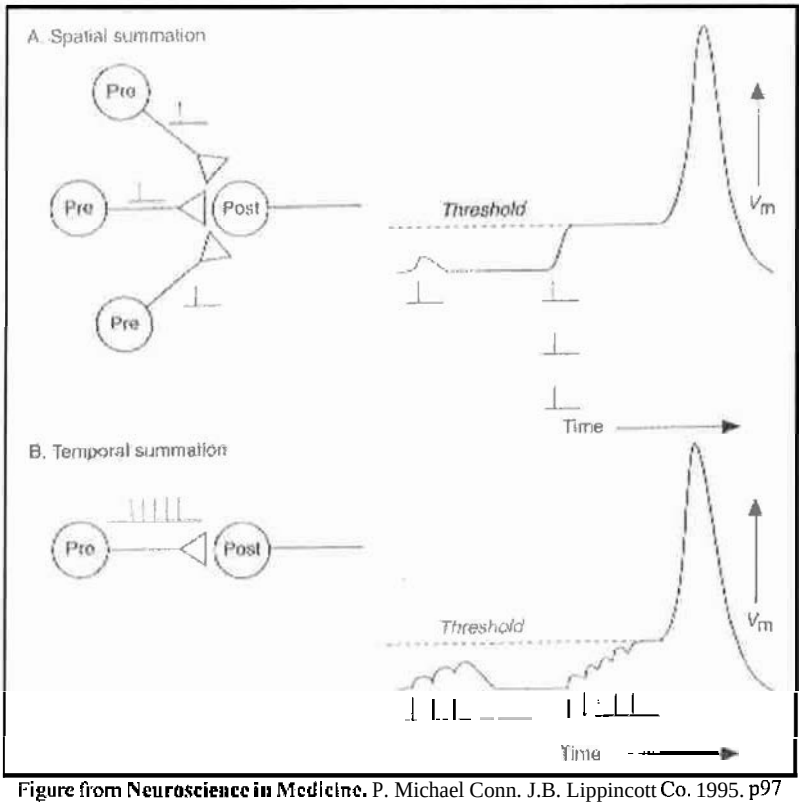


Figure from **Neuroscience in Medicine.** P. Michael Conn. J.B. Lippincott Co. 1995. p97

7. Strength – Duration Curve (Figure 7)

The amplitude of the action potential no matter what strength of stimuli will always be the same due to the all-or-none response of the cell. Therefore, the strength of the stimuli is coded by the repeated firing of neurons (action potential/second) within the limits of the refractory period.

Figure 7 - Duration curve

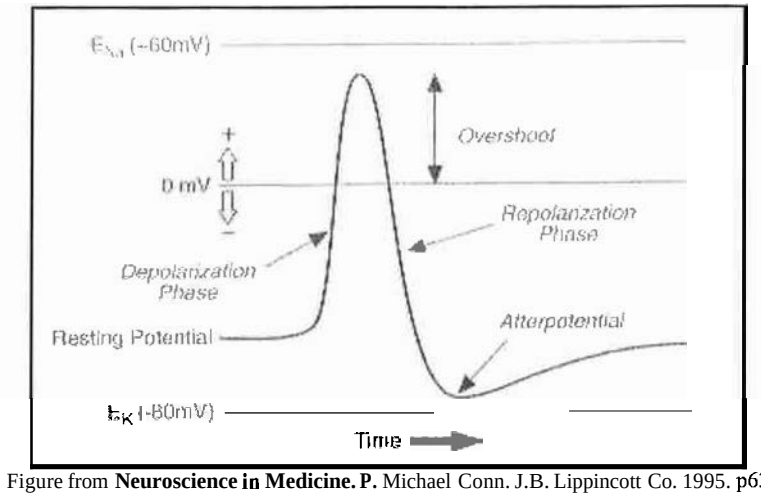


Figure from **Neuroscience in Medicine. P.** Michael Conn. J.B. Lippincott Co. 1995. p63

C. Neuroanatomy (including functions and connections)

1. Spinal Cord

The spinal chord is made up of a central butterfly shaped region of gray matter surrounded by white matter (Figure 8). The gray matter is made up of cell bodies and their processes (ie. dendrites, and unmyelinated axons) giving it a gray appearance while the white matter is made up of mostly myelinated axons giving it a white appearance. As with the rest of the brain it is covered with its PAD (the pia, arachnoid and dura mater).

Figure 8 –Spinal Cord

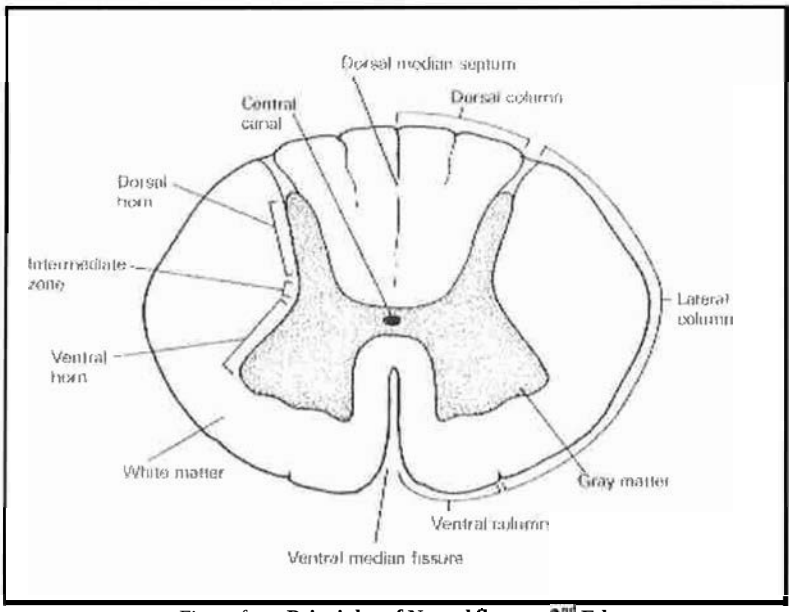


Figure from **Principles of Neural Science, 2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p225

The spinal cord serves three main functions:
i) Relay of sensory information
ii) Carrier for ascending afferent pathways and descending motor tracts of the trunk and limbs
iii) Controls trunk and limb movement through interneuron and motor neuron pathways

a. Gray matter

It can be divided into two main sections (see Figure 7). The *dorsal (posterior) horn*, is the sensory receiver. While the *ventral (anterior) horn*, like the anterior of a car, is the motor system containing the interneurons and motor neurons that innervate skeletal muscles. The *intermediate zone* in between the ventral and dorsal horns contains neurons that are bound for autonomic ganglia (nervous tissue clusters outside of the brain or spinal cord-mostly cell bodies) or the cerebellum as afferent fibers. The central canal of the gray matter is lined with a type of macroglia called *ependymal cells.*

Functionally related clusters of gray matter can be divided into six different nuclei (Figure 9).

Figure 9 – Nuclei of the Spinal Gray Matter

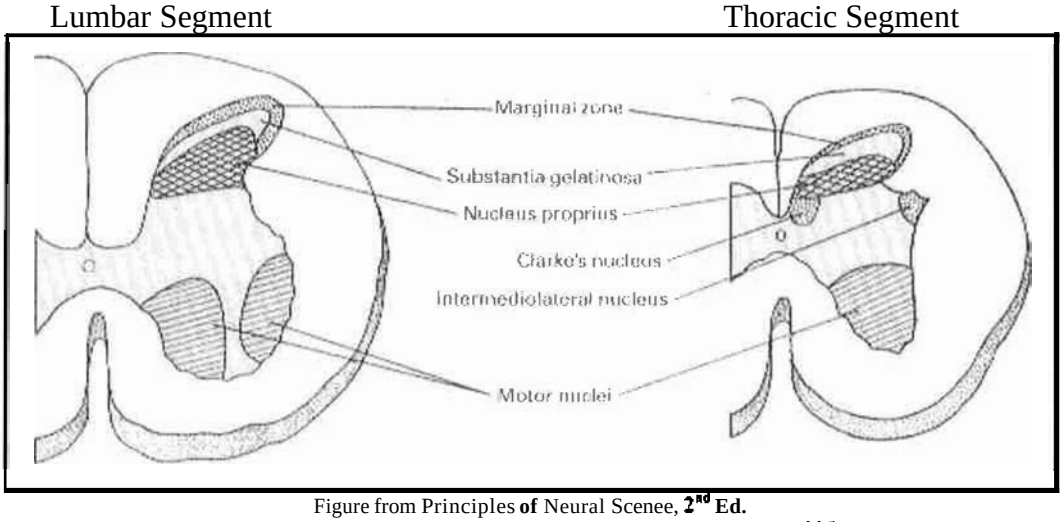


Figure from Principles **of** Neural Scenee, **2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p305

i.	*Marginal zone:*	Outer dorsal horn. Relay for pain and temperature.
ii.	*Substatntia gelatinosa:*	Dorsal horn. Integration of afferent information.
iii.	*Nucleus proprius:*	Dorsal horn. Integrates sensory information from the brain.
iv.	*Clark's nucleus:*	Intermediate zone. Relays limb movement and position to the cerebellum.
v.	*Intermediolateml nucleus:*	Intermediate zone. Autonomic preganglionic neurons.
vi.	*Motor nuclei:*	Ventral horn. Motor neurons of skeletal muscle.

These clusters of related matter can also take on a laminated appearance on cross section leading some to classify sections by histologically different lamina (ten in total).

To understand the spinal reflexes we need to know who the players are. Striated muscles have a large number of extrafusal muscle fibers and fewer intrafusal fibres containing the muscle spindles and Golgi tendon organs which lie close to the tendon-bone junction.

Motor: The extrafusal fibers are innervated by the large alpha motor neurons, the intrafusal by the smaller gamma motor neurons while both can be served by the intermediate sized beta motor neurons.

Sensory: Ia and II fibers innervate intrafusal fibers and Ib innervate Golgi tendons. Ia makes either a direct synapse with an alpha motor neuron of the agonist muscle or with an inhibitory interneuron of the anagonist muscle. Ib afferent fibers synapse on an inhibitory homonymous muscle (muscle of origin) neuron and an excitatory heteronymous muscle (antagonist muscle) motor neuron. Therefore, we can see that the response of the muscle to stimulation of Ia or Ib is the exact opposite to the stimulation of the other.

Types of reflex include:

The stretch reflex – The stretching of a muscle stimulates spindle fiber neurons (Ia and II) which then synapse with homonymous muscle excitatory cells and with inhibitory intemeurons of heteronymous muscles. Results in tension of the stretched muscle.

Tendon organ reflex – The stretching of a muscle stimulates Golgi tendon neurons (Ib) which then synapse with intemeurons inhibiting the homonymous muscle and stimulating the heteronymous muscles. Results in relaxation of the stretched muscle and defends against overexertion.

Flexor and crossed extensor – Noxious or thermal stimulation results in ipsilateral flexor stimulation and extensor inhibition and vice versa on the contralateral side. Both sides use interneurons to transmit information. Results in ipsilateral flexion and contralateral extension.

b. White matter

It can be divided into three main sections (Figure 10) the dorsal, lateral and ventral columns. The following describes the composition and responsiblilities of each column:

Figure 10 – White Matter

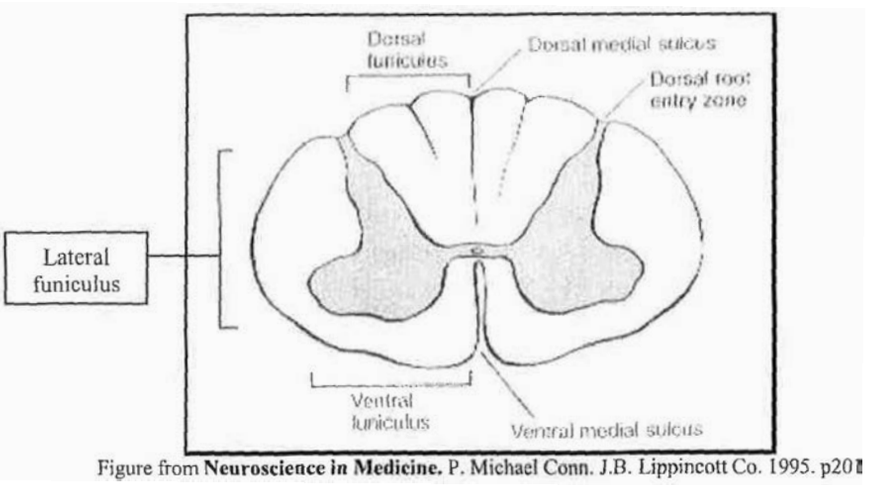


Figure from **Neuroscience in Medicine.** P. Michael Conn. J.B. Lippincott Co. 1995. p201

The dorsal columns/funiculus carry somatic sensory information registering conscious proprioception and stereognosis (to recognize tho form of a solid object) ascending to the medulla. It can be further broken down into two main sections.

- **Fasciculus gracilis (long and graceful)** is the medial section that relays information from the lower part of **the body.**
- Fasciculus cuneatus (cunning of the **mind)** is the lateral section that relays information from the upper parts of the body.

The fibers that leave the dorsal column cross over the midline as the *internal arcuate fibers* and collect into a bundle of fibers referred to as the *medial lemniscus* before continuing to the thalamus.
The lateral columns/funiculus carry sensory, motor and autonomic function axons descending from the brain and somatic sensory axons ascending to the brain. It can be broken down into five main sections.

Ascending:

i. Spinocerebellar (ant. and post.) tract carries information of unconscious proprioception and stereognosis (ie. walking)
ii. Spinotectal tract carries information on reflex activity and motor control.
iii. Lateral spinothalamic carries higher threshold sensations such as pain and temperature.

Descending:

iv. Lateral corticospinal tract is part of the motor tract. It arises from the motor and premotor cortex, most axons cross at the spinomedullary junction (meeting of spinal cord and brain stem) and synapses in the anterior horn of the spinal cord.
v. Rubrospinal tract is part of the motor tract. It arises from the red nucleus (rubro-red), cross over and synapse in the anterior horn of the spinal cord.


neurons controlling distal muscles

The ventral columns/funiculus carry axial muscle motor neurons. It can be broken down into four main sections.

- Anterior corticospinal tract (same as lateral)
- Tectospinal tract
- Vestibulospinal tract
- Reticular tract

→ Neurons controlling axial and proximal limb muscles.

c. Spinal nerves and sensory ganglia

The dorsal root and the ventral root of the spinal chord join together to form a common *spinal **newe*** that leaves the vertebral column (Figure 11). The dorsal root has an enlarged area composed of the cell bodies of somatic and visceral afferent neurons called the *dorsal root ganglion.*
In total there are 31 spinal nerves (8 cervical, 12 thoracic, 5 lumbar, 5 sacral and a lone coccygeal). Two things to note on spinal nerves:

- The cervical nerves 1-7 exit the vertebral column above their corresponding vertebrae (through the intervertebral foramen), cervical 8 is below the 7th vertebrae. Then from thoracic 1 and down they are below their corresponding vertebrae.
- The vertebrae is longer than the spinal cord which ends at about the L2 level. Therefore, the L2 to Coccygeal nerves travel caudally within the vertebrae as the *cauda equina* (horse's tail).

Figure 11 – Spinal Nerve

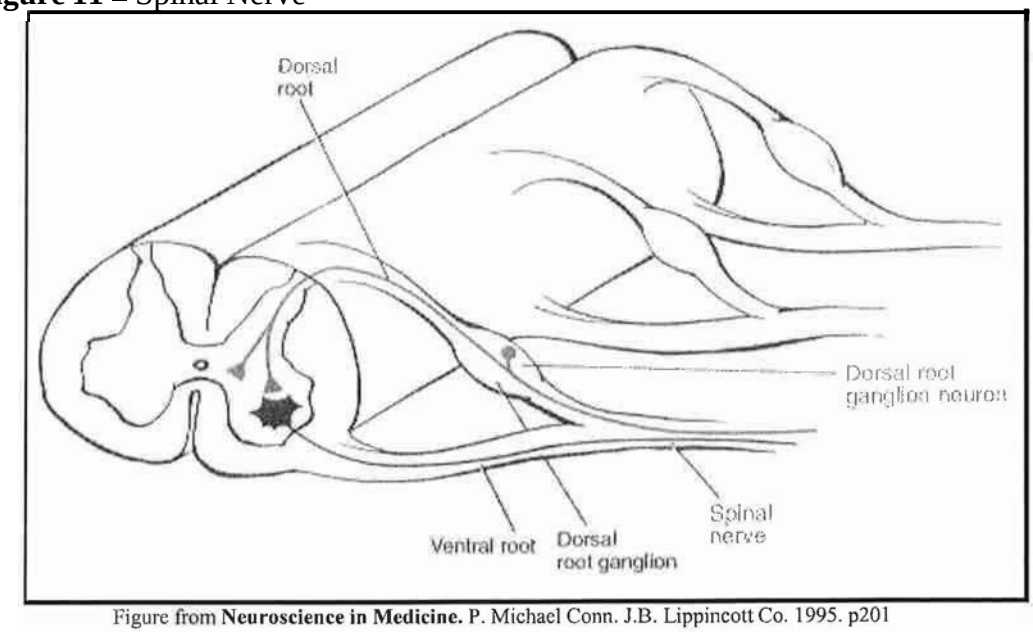


Figure from **Neuroscience in Medicine.** P. Michael Conn. J.B. Lippincott Co. 1995. p201

Once the spinal nerves pass through the intervertebral foramen they generally divide into four branches:

i. Recurrent branch
ii. Dorsal ramus: Innervate muscles of the dorsal trunk

iii. Ventral ramus: Innervate muscles of the extremities and the ventral trunk. Many form plexuses (ie. cervical, lumbar) before innervating their target structure.
iv. 2 rami communicates: Connect the spinal nerve and a ganglion of the sympathetic trunk.

2. Autonomic Nervous System

The ANS controls involuntary bodily functions. It is also called the autonomic motor system due to its primary association with motor activity. The ANS is divided into the parasympathetic and sympathetic that monitor the body's physiological, motivational and emotional states.

a. Parasympathetic		b. Sympathetic
• Also called the craniosacral division due to the origin of its cell bodies in the cranial nerves (CN 3,7,9 and 10) and the sacral spinal nerves (S2-S4)	⟺	• Also called the thoracolumbar division due to the origin of its cell bodies in the T1-L2 spinal cord.
The preganglionic fibers are long (esp. CN 10-Vagus nerve that reaches throughout the body) and synapse with short postsynaptic neurons.	⟺	• The preganglionic fibers are short traveling to the paravertebral or prevertebral ganglion where they synapse or travel up and down these trunks to their synapse. The postganglionic neurons are, therefore, long.
The primary function of the parasympathetic system is to conserve resources during non-stressful situations with actions such as slowing of heart rate, bronchial constriction, peristalsis and GI secretion for digestion, pupillary constriction, thin saliva secretion, and constriction of the urinary bladder.	⟺	• The primary function of the sympathetic system is for fight or flight responses with actions such as skeletal muscle vasodilation, skin and viscera vasoconstriction, increased heart rate, bronchial dilation, decreased peristalsis and GI secretion, pupillary dilation, thick saliva secretion, conversion of glycogen to glucose by the liver and hair standing on end.

c. Neurotransmitters

Both sympathetic and parasympathetic use acetylcholine (cholinergic) at their first synapse. The parasympathetic uses acetylcholine again for its final synapse***(visceral effector)***. Whereas the sympathetic uses norepinephrine (adrenergic) for its visceral effector except in sweat glands where it reverts to cholinergic (most secretions are cholinergic).

The following sections 3-8 discuss in detail the structures seen in diagram (Figure 12). Note the location of each part relative to the others and the three part composition of the brain stem (MPM: pon in the middle). Discussion proceeds from bottom up.

Figure 12 – The Central Nervous **System**

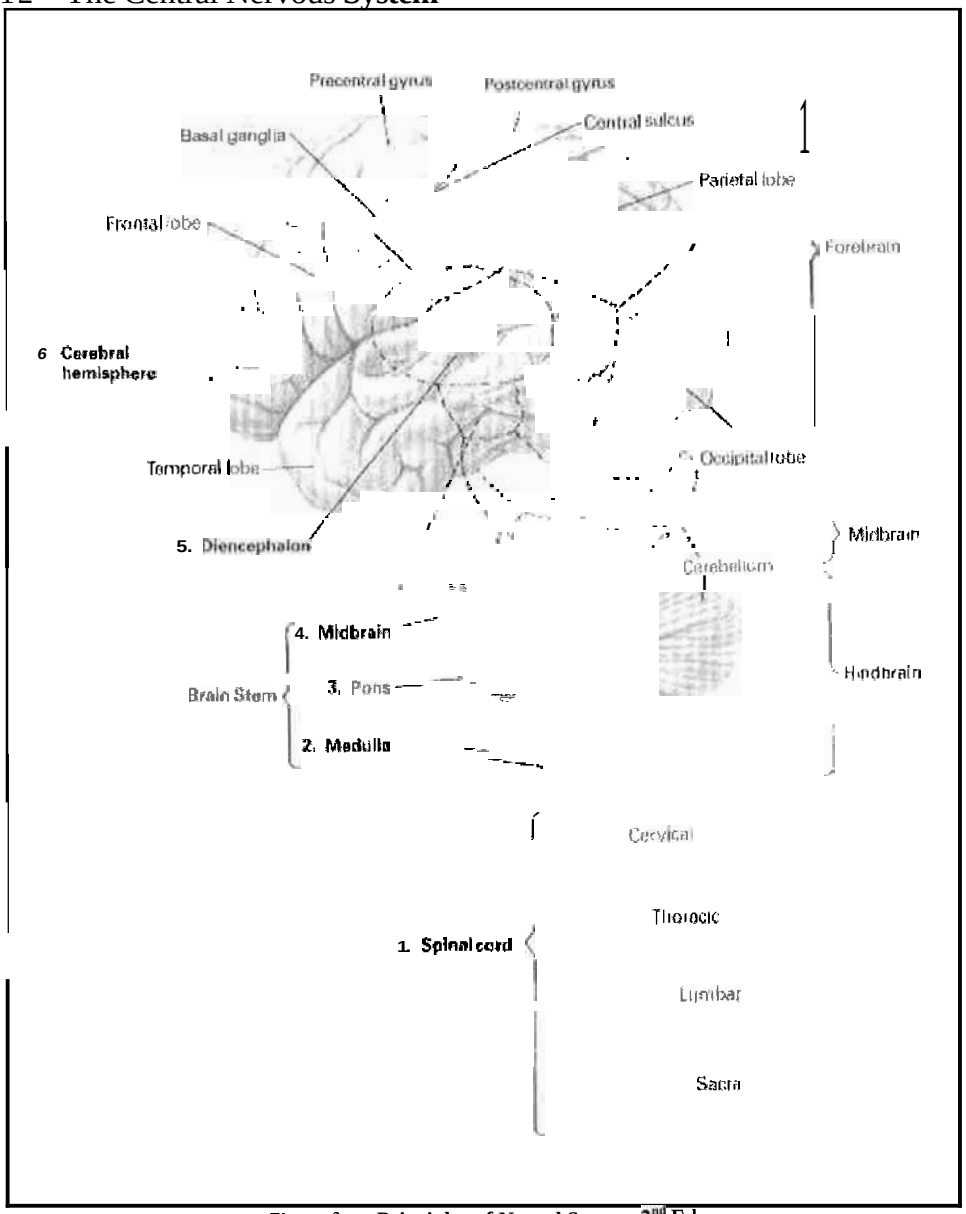


Figure from **Principles of Neural Scence, 2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p5

3. *Medulla*

Contains CN nuclei 9,10,11 and 12.

a. Level of motor decussation (crossing in the shape of an X)

The two bulges of the medulla are referred to as the pyramids (not referring to their shape). The fibers that make up these pyramids are voluntary motor tracts (corticospinal) and are passing from the cerebrum to the spinal cord. Near the lower end of the medulla 80% of these fibers decussate travel posterior and enter the spinal cord on the contralateral side. The other 20% continue on the ipsilateral side. Therefore, injury above this spot affects the contralateral side while injury below affects the ipsilateral side.

b. Level of sensory decussation

Just above the pyramidal decussation described above, the fasciculus gracilis and fasciculus cuneatus (remember these sensitive fasciculi) terminate in their like named nuclei. Myelinated fibers called the internal arcuate fibers decussate and move anterior where they turn upwards and continue on under the alias of the medial lemniscus. Once again this is the origin for the contralateral representation of sensory input from the limbs and trunk to the brain.

c. Level of inferior olives

The olives (oval shaped) live on either side of the medulla just behind the pyramids. They serve primarily as a relay center to the cerebellum gathering information from the motor cortex, spinal cord, a variety of nuclei and the accessory optic tract. The accessory optic nerve transmits information from the optic nerve (movement on the retina) to the cerebellum (coordinates visual tracking reflex) via the inferior olive.

d. Level of open medulla

The open medulla is the upper region of the medulla that opens dorsally to allow room for the fourth ventricle.

e. Dorsal and ventral cochlear nuclei

These nuclei within the posterior lateral medulla receive afferent auditory information from CN VIII (vestibulochoclear). They contain a *tonotopic* map due to the ordering of frequency sensitivity within the nuclei.

f. Vestibular nuclei

The superior, inferior, medial and lateral vestibular nuclei are located in the medulla and the lower pons. Receive information from the hair cells of the semicircular canals, the saccule and the utricle. Superior and inferior divisions (receptor end) join and form the

vestibular ganglion in the acoustic meatus then continue into the brain stem where they ascend or descend to one of the vestibular nuclei.

Other important medullar components:

- Reticular formation-Filters sensory information for the reticular activating system responsible for alerting the brain.
- Cranial nerves: IX-XII. XII exits anterior to the olive while the rest exit posterior to it.
- It forms the floor of the fourth ventrical.

4. Pons

Serves as a passage for tracts from the medulla and the cerebellum (through the midcerebellar peduncles/brachium pontis) to the rest of the brain. Contains CN nuclei 5,6,7 and 8.

a. Low or caudal pons

Along with the medulla, the lower pons are regulatory centers for respiration and cardiovascular functions.

b. Abducens nerve: CN VI

A motor nerve that originates on the anterior side of the fourth ventricle and exits from the pons on it's anterior side. It does not cross before it travels a long course from the brain stem to innervate the lateral rectus

c. Mid pons

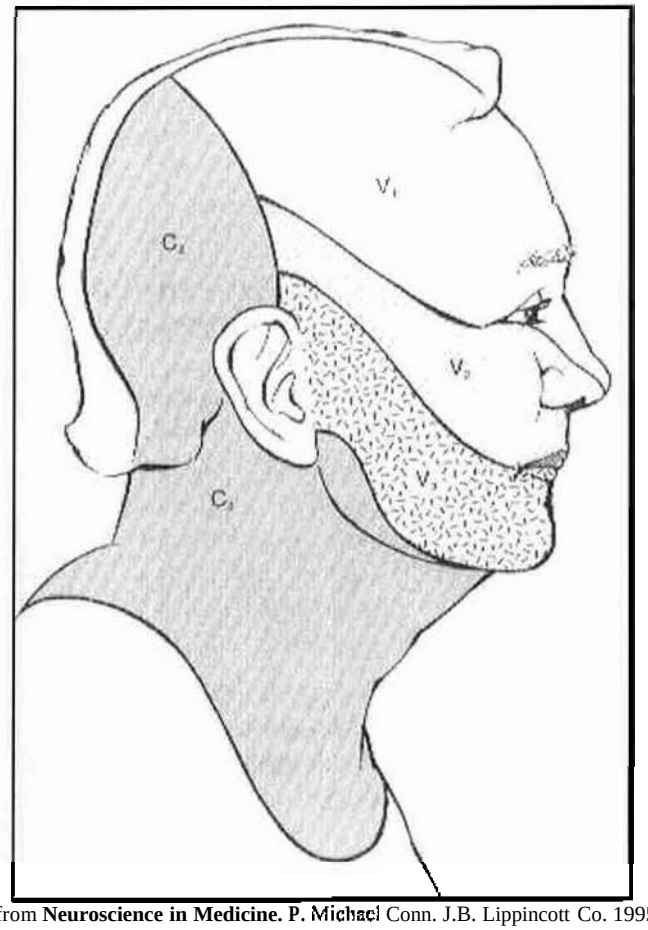
Small diameter neurons carrying pain and temperature sensation enter at mid pons. As well, the Trigeminal motor and chief sensory nucleus lie in this region.

d. Trigeminal nerve: CN V

As a mixed nerve it has both motor and sensory nuclei. Its motor nuclei are small and located solely in the pons while its sensory nucleui are very long and extend down through the medulla into the posterior horns of the spinal cord. The motor component exits the side of the pons travels anterior and innervates the muscles of mastication. The sensory component can be divided into the three branches of ophthalmic, maxillary and mandibular which innervate the areas shown in Figure 13. These branches join and form an enlargement called the trigeminal (gasserian/semilunar) ganglion which contains the majority of the primary sensory cell bodies. The remaining neurons are in the trigeminal mesencephalic nucleus. Ultimately, these sensory neurons synapse on the ipsilateral side of the trigeminal nucleus but are contralateraly represented by the crossing over of the axons to form the trigeminal lemniscus (part of the medial lemniscus). These axons travel

to the contralateral thalamus which is the relay station for information traveling to the cerebral cortex.

Figure 13 - Sensory innervation of CN V



Note: C2 and C3

cervical spinal nerves

Figure from **Neuroscience in Medicine. P. Michael** Conn. J.B. Lippincott Co. 1995. p247

e. Facial nerve: CN VII

As well a mixed nerve with a motor nucleus that travels an unusual path. Its nucleus is located anterior and lateral to the sixth nerve nucleus within the pons. However, it starts its path in the medial and posterior direction taking it back in a loop around CN 6 before it heads back and out of the pons anterolaterally. The motor aspect innervates the lacrimal and salivary glands. Sensory aspects from the anterior 2/3 of the tongue enter alongside of the motor component as the *nervus intermedius* and terminate on the ***solitary tract nucleus*** (a shared nucleus with CN 7,9 and 10).

5. Midbrain

The midbrain can be divided into three main sections. The most dorsal section behind the cerebral aqueduct is the ***tectum*** (superior and inferior colliculi-2x each). Anterior to the aqueduct are the two cerebral peduncles (one on either side) which are divided into a

posterior section called the *tegmentum* which contains mostly nuclei and an anterior section called the crus cerebri which contains mostly descending fibers. The dividing line is a group of pigmented gray matter called the *substantia nigra*. The midbrain contains CN nuclei 1,2,3 and 4.

a. Level of inferior colliculus

- Crus Cerebri: From medial to lateral there are the frontopontine fibers, corticospinal and
  corticonuclear fibers and the temporopontine fibers.
- Tegmentum: Decussation of superior cerebellar peduncles anterior to the 4th CN nuclei.
- Tectum: The inferior colliculli act as reflex centers. They receive primarily auditory and some visual input and send signals to influence head and neck movement.

b. Trochlear nerve (CN 4)

Nuclei are ventral to the cerebral aqueduct. Note that it is the only cranial nerve that exits the brain stem dorsally and that it crosses over as it wraps around the back side before making its way to the superior oblique EOM.

c. Level of superior colliculus

- Crus Cerebri: Same tracts as the inferior level (frontopontine, corticospinal, corticonuclear and temporopontine fibers). Oculomotor nerve travels anterior and exits between the two cerebral peduncles in the interpeduncular fossa.
- Tegmentum: Important nuclei are the oculomotor, Edinger-Westphal, and red nuclei (start of the rubrospinal tract). As well, it houses the Medial and lateral lemniscus and the medial longitudinal fasciculus.
- Tectum: The superior colliculli act as reflex centers. They receive primarily visual and some auditory and tactile input and send signals to influence head and neck movement.

d. Oculomotor nerve (CN 3)

Divided into subnuclei for each of the muscles controlled (IR, SR, MR, IO and levator). Note that each of the muscle nuclei are present on both left and right sides of the occulomotor nucleus except the levator which is a single nuclei. As well, as the SR fibers decussate they pass through the other side of the SR nuclei and therefore both sides are partially represented in both nuclei. The EW nucleus sits on top of the 3rd nucleus as a parasympathetic center for the ciliary and iris sphincter muscles (↑ accommodation, ↓ pupil size).

e. Level of pretectum (eg. Light reflex)

Reflex center for all those pupil tests you've been doing. The pathway is as follows:

Retina → Optic Nerve → Optic tract (w/ nasal decussation) → superior brachium → pretectal nucleus → tectotegrnental tract (fibers are equally split with crossing fibers forming the posterior commissure) → EW nucleus → iris sphincter

6. Diencephalon

Diencephalon (syn. Thalamencephalon) is just the collective name for all the thalamus sounding structures (hypothalamus, epithalamus, subthalamus, thalamus)

a. Dorsal thalamus

The thalamus (meaning "chamber") is the most rostral part of the brain stem forming the lateral walls of the third ventricle. Originally it was thought that all of the optic fibers could be traced to an oval mass in the ventricles so it was called the optic thalamus. The actual fact is that all of the sensory modalities, except for olfaction, are processed here so the "optic" was dropped but thalamus remained. Included in the dorsal thalamus are the lateral and medial geniculate bodies responsible for visual and auditory information respectively. Sensory information synapses in the thalamus then passes on to the cortex via the internal capsule.

b. Hypothalamus

Lies below the thalamus and medial to the subthalamic region. It acts as the "homeostasis manager" by integrating the bodies sympathetic and parasympathetic activity through both the nervous and endocrine systems. Areas of nervous system control include cardiovascular, thermoregulatory and visceral regulation as well as behavioral modification of sexual, maternal, emotional and ingestive drives. Areas of endocrine control include anterior pituitary hormone release via hypothalamic neurosecretions and adenohypophysis hormone release via a microscopic vascular portal system.

c. Epithalamus

Uppermost portion of the diencephalon composed of the pineal gland, that makes melatonin for sleep-wake cycles (melatonin production is inhibited by light on the retina), and the habenular trigone containing nuclei that communicate via the habenular comrnissure and are connected to the pineal gland by the habenula/stalk.

d. Subthalamus

Lies ventral to the thalamus and lateral to the hypothalamus. It is a motor control region of the diencephalon.

7. *Cerebrum*

Cerebrum refers to the cerebral cortex and basal ganglia and is the largest portion of the brain. It is derived from the telencephalon and in its developed state forms two hemispheres with multiple folds (peaks are gyri, valleys are sulci or furrows). There are four major lobes of the cerebrum (frontal, temporal, parietal and occipital) and an oft forgotten central lobe (insula or island of Reil).

a. Gray matter (cytoarchitecture (layers), Brodmann's cortical areas)

The gray matter (neocortex) of the cerebrum is composed of the basal ganglia and the cell bodies of the neurons within the cerebral cortex. There are two main neurons of note within the cortex:

i. The pyramidal cells (Figure 14) are conical cell bodies with their apex towards the brains pia matter. Dendrites extend from either the apex of the cell projecting towards the pial surface or from the base projecting laterally within the same layer as the cell body. The axon of a pyramidal cell will extend inwards forming collaterals that branch out to adjacent areas from a central myelinated portion that enters the cerebral white matter and travels distally to another cortical region. Information to the pyramidal cells comes primarily from the climbing fibers.
ii. The stellate (star shaped) cells are smaller and rounder cell bodies with dendritic branches projecting from all aspects of the cell. Axons from the stellate cells form many branches but generally stay within the same cortical region. Information to the stellate cells comes primarily from the mossy fibers.

There are six layers to the neocortex:

i. Layer I – Primarily glial cells and axons traveling between adjacent cortical regions.
ii. Layer 11 – Primarily pyramidal cells. Short range output to other cortical regions.
iii. Layer III – Even bigger pyramidal cells. Short to medium range output.
iv. Layer IV – Primarily stellate cells. Receives afferent input (from thalamus).
v. Layer V – The biggest pyramidal cells! Long range output. These cells axons form descending pathways to the brain stem and spinal cord.
vi. Layer VI – Primarily neurons that communicate with the thalamus.

Figure 14 - Neocortex

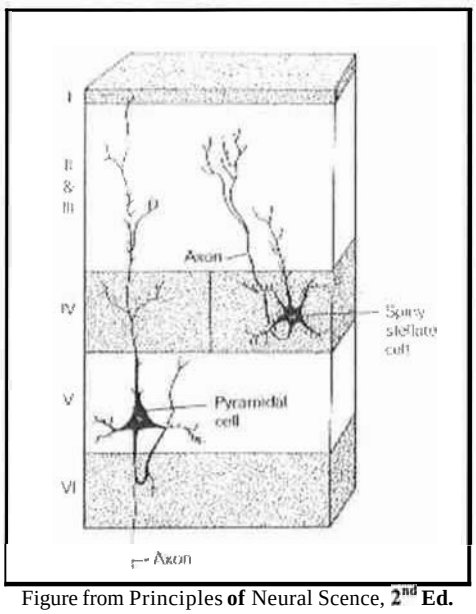


Figure from Principles **of** Neural Scence, **2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p236

Brodmann mapped out 52 regions within the cerebral cortex that distinct functions based on the distribution of the layers and cell types described above. Some areas of note are:

i. Area 1,2 & 3: Primary somatic sensory cortex
ii. Area 4: Motor cortex
iii. Area 6: Premotor cortex.
iv. Area 17: Primary visual cortex.
v. Area 41& 42: Auditory cortex

Deep within the cortex are masses of gray matter that make up the basal ganglia. These masses are called the caudate, lentiform and amygdaloid nuclei and the claustrum. The basal ganglia is thought to be involved in the initiation of movement and the ongoing control of complex motor activity.

b. White matter (projections, internal capsule, optic radiations, commissural and associational fibers)

The white matter is composed of collections of myelinated axons forming one of three types of pathways:

i. Projections: Carry information to and from the cerebral cortex. The internal capsule is one of the largest of these tracts connecting the thalamus with the cortical layers. The optic radiations are also projection fibers traveling from the lateral geniculate nucleus to the primary visual cortex.
ii. Commissural fibers: Connect cerebral hemispheres. The three main bundles are the anterior cerebral, the posterior cerebral and the corpus collosum (which is the largest of the three).
iii. Associational fibers: Connections between cortical regions within the same hemisphere.

c. Functions

The cerebrum is responsible for motor functions, cognition and perception with each lobe having its own specialties. Our voluntary motor activity is primarily provided by the frontal lobes while our sensory components can be found in the occipital lobe(vision), parietal lobes(touch and taste) and the temporal lobes(hearing and smelling).

8. Cerebellum

The cerebellum lies in the posterior cranial fossa and forms its connections with the brain stem through the inferior, middle and superior peduncles. It is the second largest portion of the brain and, like the cerebrum, has two hemispheres. These hemispheres are connected medially by the vermis. As well, the cerebellum can be divided into lobes by the dividing landmarks of the primary fissure (dividing the anterior lobe from the posterior lobe) and the posterolateral fissure (dividing the posterior lobe from the smaller flocculonodular lobe). Again like the cerebrum, the cerebellum has an outer gray matter that surrounds an inner white matter. . The folding of the gray matter of the cerebellum forms a tree-like appearance on cross section that is referred to as the arbor vitae. There are three paired nuclei within the cerebellum called the fastigial, the interposed (composed of globose and emboliform) and the dentate nuclei

The cortex of the cerebellum can be divided into three layers (Figure 15):

i. Molecular: Primarily granule cell axons (called parallel fibers). Also contains interneurons, stellate and basket cells and dendrites from the Pwkinje layer.
ii. Purkinje: Only output of the cerebellum. Dendrites in the molecular layer. Axons pass through the granular layer to the brain stem.
iii. Granular: Dense region of small neurons

Figure 15 – Cerebellar Gray Matter

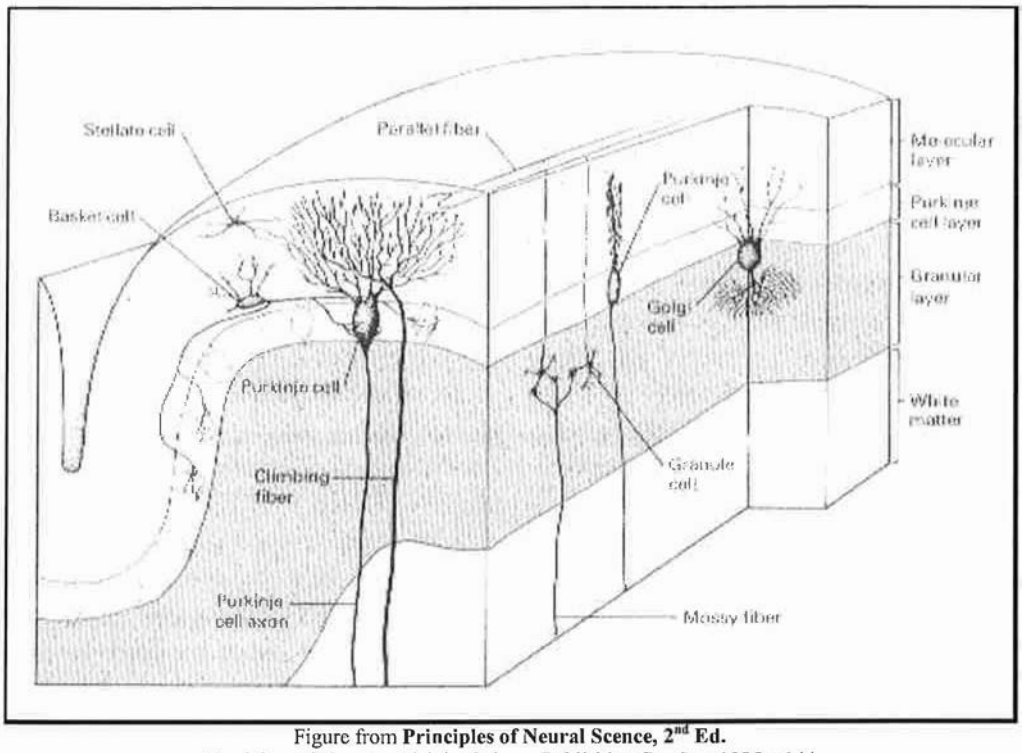


Figure from **Principles of Neural Scence, 2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p144

The cerebellum plays a major role in the regulation of motor activity. It cannot initiate movement but acts by regulating the planning of movement (corollary discharge) and the progression of motor activity (external feedback).

9. Blood supply

The blood supply to the brain is designed not to fail. In total there are four different pathways that blood can take to get to the central vascular connection of the Circle of Willis. These are the paired common carotid arteries and the paired vertebral arteries. This topic is covered extremely well in the **Neuroscience: made ridiculously simple** book and it has an excellent visual aid of the "Spider" of Willis that takes away a good deal of memorization work. It is worth a look. However, here is a quick synopsis of how we feed our brain.

a. Surface arteries

Carotids: The common carotids first divide to become the internal (ICA) and external (ECA) carotid arteries at the upper border of the thyroid cartilage. The external carotids proceed to supply blood to regions of the head other than the brain. However, the internal carotids travel up through the carotid canals of the petrous temporal bones and, after passing through the canal, they give off the ophthalmic and posterior communicating arteries before terminating as the anterior and middle cerebral arteries.

Vertebrals: The vertebral arteries are the first and largest bifurcations from the subclavian arteries. From there they travel up through the cervical transverse foramen into the cranium and join to form the basilar artery at the level of the pons. They then bifurcate again to terminate as the posterior cerebral arteries.

b. Circle of Willis and its branches

The Circle of Willis is comprised of the anterior communicating artery connecting the two anterior cerebral arteries, which are in turn connected to the internal carotids. The ICAs are then connected by the posterior communicating arteries to the posterior cerebral arteries which in turn originated at the bifurcation of the basilar artery. And there you have your circle.

Other branches of the circle include from anterior to posterior:

i.	Recurrent artery.	Origin: Anterior cerebral.
ii.	Anterior choroidal artery.	ICA
iii.	Chiasmatic (optic chiasm) artery	Posterior communicating
iv.	Thalamic and hypothalamic arteries.	Posterior communicating
v.	Oculomotor nerve branch.	Posterior communicating
vi.	Superior cerebellar arteries.	Basilar

D. Neurophysiology

1. ***Integration of nerve signals*** (e.g. synaptic processes, reflexes, feedback, adaptation and habituation)

There are two types of neural transmission:
1) Electrical transmission/bridged – metabolic and/or electrical communication passes through gap junctions formed by connexons (hexagonal channels formed by 6 units of connexin). This system allows for rapid communication and two-way flow of information but it is limited in function.
2) Chemical transmission – pre- and post- synaptic neurons are separated by a cleft. Information is transmitted via chemical mediators (neurotransmitter) released from vescicles in the pre-synaptic neuron. The transmitters travel across the cleft and interact with the post-synaptic neuron causing excitation or inhibition. The transmitter undergoes reuptake into the pre-synaptic neuron or is degraded by enzymes and then taken up by the pre-synaptic neuron.

Types of synapses:

1) Axodendritic:	most common
2) Axosomatic:	either efferent axons to muscles (motor end plates) or autonomic axons to secretory cells
3) Axoaxonic:	presynaptic inhibition
4) Dendodendritic:	in the olfactory bulb
5) Synaptic triad:	in the IPL (bipolar, amacrine and ganglion)

Reflexes: An automatic response of a muscle or gland brought on by stimulation of a sensory receptor. The neural pathway is called the reflex arc.

Simple Reflex – Sensory receptor → afferent neuron → Reflex center (C/PNS)
efferent neuron effector organ

Feedback: The system output becomes the input for self regulation of that system. There are two types of feedback:

i. Positive feedback reinforces the system activity and increases its response.
ii. Negative feedback reverses the systems activity and decreases its response.

Habituation: Habituation should follow adaptation because it is a higher level of adaptation that occurs to reduce brain activity secondary to an irrelevant stimuli. Information traveling to the brain is filtered out before it can be processed. Habituation is a learned process.

Adaptation: The process of becoming accustomed to frequent exposure of a novel stimulus. On a neural level short-term adaptation happens at the point of transmission. Continued stimuli results in the same action potential at the sensory neuron, however, it will inactivate the Ca^{++} channels in the presynaptic terminal. This reduces the transmitter release and resultant post-synaptic potential change. Long-term adaptation occurs with a decrease of active zone size and number (active zone=presynaptic sites of transmitter release)

2. Sensory Coding

This is simply the process by which a stimulus is converted to a nerve impulse by a specialized receptor. This allows each sensory system to receive, process (encode) and then transmit the sensory information of a specific type to a higher neural level. Most systems will have neurons that will both encode and then transmit the information as action potentials along their axons to second order neurons. However, of special note, the visual and auditory systems encode and transmit by separate neurons. The region from which the receptor will encode stimuli is called the receptive field. Higher order neurons will also have receptive fields made up of all the excitatory neurons, inhibitory neurons and/or interneurons that can influence their level of activity. Each sensory system is organized in a serial (or hierarchical) manner with information passing directly through from lower to higher neural levels. However, many sensory modalities will have parallel pathways serving similar functions that allow for continued perception even if one serial pathway is damaged.

3. Somatosensory system

There are four modalities:

1. Tactile (size, shape, texture and movement across the skin) – there are four types of touch receptors:
   a) Meissner corpuscle (flutter, motion)
   b) Ruffini corpuscle (possibly skin stretch)
   c) Merkel cell (pressure, form and texture)
   d) Pacinian corpuscle (vibration)

   Each specified by their location and the morphology (shape and makeup) of their terminals. However, the response of each receptor is generally the same: a physical change or compression of the nerve ending will cause the Na^+ channels to open and depolarize the membrane which, if a sufficient amount, will generate an action potential.

2. Proprioception (static and dynamic position of limbs and body) – Three main types of receptors:
   a) Joint afferents - Ruffini-like, Paciniform-like and bare nerve endings (Protective against hyperextension and hyperflexion)
   b) Golgi tendon (muscle tension)
   c) Muscle spindles (muscle length and velocity)

   Overall, proprioception occurs by two phases:
   i. A tonic response to static positions of our muscles produce action potentials that indicate position by varying in frequency.
   ii. A phasic response to muscle movement that produces a rapid burst of action potentials with any change of muscle position.

3. Pain / Nociception (slow and fast) – Nociceptors are bare nerve endings (without connective tissue sheaths) and as such can respond to chemical agents released at the site of injury. There are two types of nociceptors: i) mechanical and ii) Thermal (activated around 40-60^o C)

Pain is transmitted from the site of injury by the A6 (rapid) and C (slow) fibers. The A6 fibers are responsible for the initial pricking pain and has high spatial resolution. The second burning pain is from the C fibers and has poor spatial resolution and is poorly tolerated.

1. Thermoreceptors (temperature) – These receptors are like the nociceptors in that they are bare nerve endings and, as well, they are made up of A6 and C fibers. The A6 fibers are lightly myelinated, faster and more numerous than the C fibers and are called the cold receptors. The C fibers are referred to as the warm receptors and have slower unmyelinated fibers. The perception of warm and cold is caused by the relative level of firing of the two fibers. Both types of fibers will be active in the area of 30-35 ^{o}C. At temperatures above 35 ^{o}C the warm receptors become more active with and at temperatures below 30 ^{o}C the cold receptors become more active. The

receptive fields for these receptors are very small and can be easily localized. As well, they are very sensitive to changes in temperature. However, they are not sensitive to absolute temperature.

4. Auditory System

The auditory system takes the physical property of sound and through a series of events turns it into an electrical signal to be transmitted to the brain. The ear is sensitive to frequencies of 20 to 15,000 Hz and an amplitude up to 120 dB. As sound reaches the ear it is funneled by the external auditory meatus towards the tympanic membrane (Figure 16). As the tympanic membrane vibrates it transfers its energy to the malleus, incus and stapes (hammer, anvil, and stirrup) which collectively are called the ossicles of the middle ear. The stapes attach to the oval window at the start of the inner ear and again transfer the sound energy through to the fluid filled cochlea.
The cochlea is made up of three compartments: the (i) scala vestibula which is continuous with the (ii) scala tympani at the helicotrema (distal end) of the cochlea and the middle compartment called the (iii) scala media. At the terminus of the scala tympani lies the round window between the cochlea and the middle ear which allows for changes in fluid pressure to occur in the inner ear.
Within the scala media is the basilar membrane and the organ of Corti which contain the sensory hair cells. Each hair cell has multiple stereocilia and a single kinocilium. As the hairs bend towards the kinocilium with the movement of cochlear fluid the hair cell will depolarize. As the hairs bend away the cell will repolarize. These changes in polarization will cause the oscillation of chemical transmitter release and a resultant action potential within the auditory nerve.

Figure 16 - Cochlea

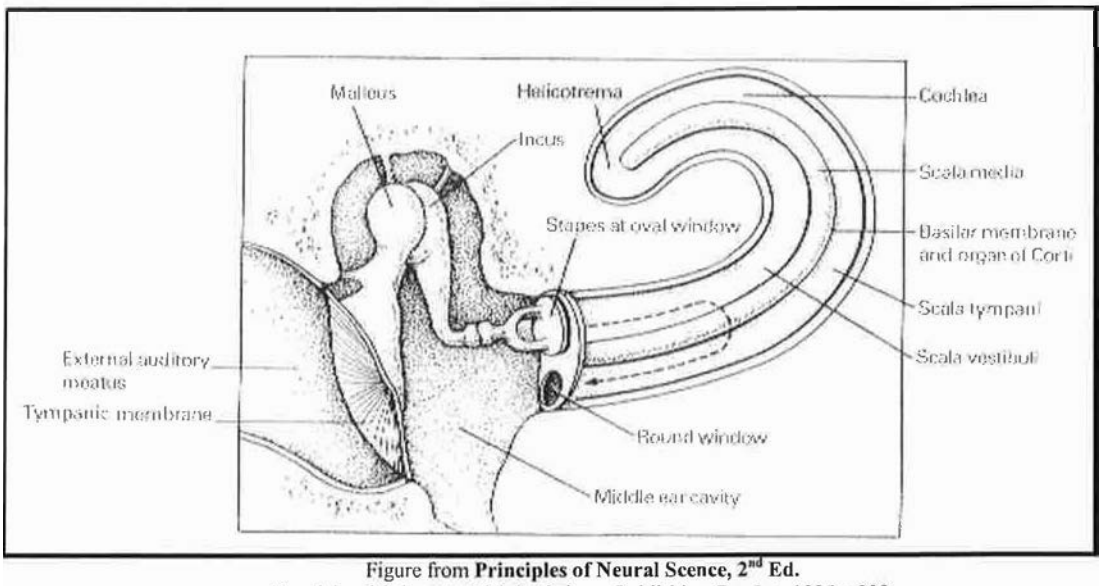


Figure from **Principles of Neural Scence, 2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p398

Our perception of sound depends on the frequency of the sound wave and its corresponding relative peak of amplitude as the wave travels along the cochlea. High frequency sounds will register near the base of the cochlea while low frequency sounds have their peak amplitude closer to the apex. This differentiation in sound is maintained within the 8^{th} nerve with each individual fiber having a characteristic frequency. Although they will respond to a range of frequencies they are most sensitive to their characteristic frequency. As a result we find fibers with high character frequencies closer to the base of the cochlea and those with low character frequencies closer to the apex. As the signal reaches the cochlear nucleus in the lateral walls of the medulla the high frequency fibers travel deep into the nucleus before terminating (Figure 17) while the low frequency fibers terminate superficially. This distribution provides the tonotopic (organized frequencies) map of the nucleus. As well, within the nucleus there are different cells that have varying responses to each stimulus received. They may only respond to the initial signal, they may build up over the course of the signal or wait until after the onset to respond to the signal.

Figure 17 – Cochlear Nucleus

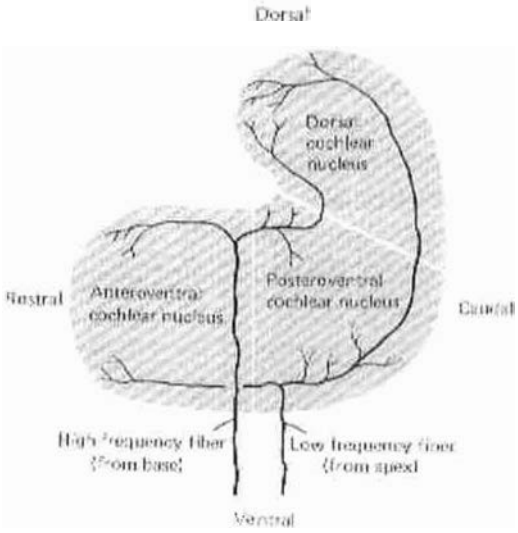


Figure from Principles **of Neural** Scence, **2nd Ed.**
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p405

5. Vestibular System

The vestibular system is involved in the coordination of balance, eye movements and posture and works closely with the visual and proprioceptive systems. As well, it structurally shares the inner ear with the auditory system and works much in the same way when it produces an electrical transmission. The inner ear is made up of the bony labyrinth (containing the vestibular and auditory systems), the membranous labyrinth and the perilyrnph (fluid portion). The vestibular portion contains two types of structure: the otoliths (utricle and saccule) and the semicircular canals. Each responds to varying changes in acceleration of the head with the otoliths primarily responding to linear acceleration and the semicircular canals primarily responding to angular acceleration.

The semicircular canals each have a region of enlargement called the ampulla (Figure 18) that monitor motion with specialized hair cells within a gelatinous mass called the cupula that extend from the ampullary crest to roof. Movement of the endolymph (fluid within the canals) against the cupula cause a receptor potential and transmit that information along to the 8th nerve.

Figure 18 – Ampulla

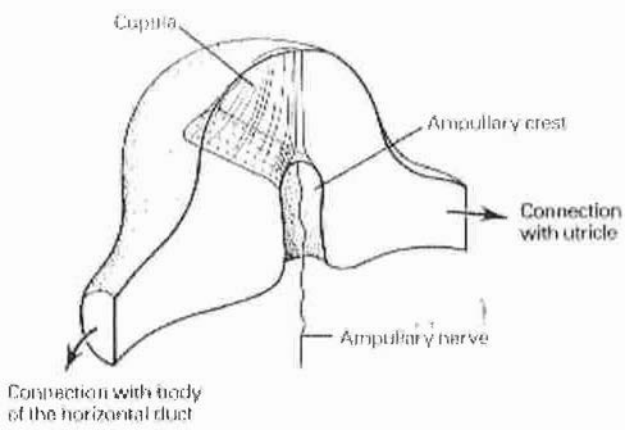


Figure from Principles of Neural Scence, 2nd Ed.
Kandel and Schwartz. Elsivier Science Publishing Co., Inc. 1985. p586

Within the otoliths the receptor region is called the macula. This region is covered by a gelatinous mass with calcium carbonate crystals, called otoliths, that lie directly above the receptor hair cells. As with the auditory hair cells these collections of 40-70 stereocilia are associated with a single kinocilium. These cells emit a constant discharge that with any movement is increased if the cells bend towards the kinocilium and decreased if they bend away from the kinocilium.
Overall, there are two main control functions provided by the vestibular system: the dynamic and static functions.

i. Static function is primarily the responsibility of the otoliths and acts as a monitor of body posture.
ii. Dynamic function is primarily the responsibility of the semicircular canals and monitors movement and rotation of the head. It is responsible for reflexes such as the vestibulo-oculomotor reflex.

6. Motor Pathways

Neuronal control of our body movements can be divided into four subunits: (i) the spinal cord; (ii) the brain stem; (iii) the motor cortex; and (iv) the premotor cortex.

i). Spinal Cord. The most basic motor system is responsible primarily for the automatic/reflex actions of our muscles. The most basic of these is the stretch/myotatic reflex. As a muscle stretches the muscle spindle afferents (Ia fibers) will produce an action potential that travels to the spinal cord and synapses with an alpha motor neuron in the ventral horn. The afferents produce an excitatory

response in motor neurons of the same muscle (homonymous) and lesser so in the synergist muscles (heteronymous). At the same time the afferents initiate reciprocal inhibition mediated by an interneuron that when excited by the afferent will cause inhibition of the antagonist muscle.

With excessive force applied to a muscle we see an inverse reaction to the stretch reflex. In the inverse Myotatic reflex the homonymous and synergist muscles will relax and the antagonist muscle will excite. This reflex is mediated by the golgi tendon organ which detect the level of force applied by the muscle and are stimulated by excessive force. Again, the signal is transmitted to the spinal cord (Ib fibers) where they synapse with interneurons that inhibit agonist muscle fibers and stimulate antagonist muscle fibers.

As well, we have flexor reflexes. These reflexes occur with the stimulation of group II muscle fibers. It results in a response of flexor stimulation and extensor inhibition causing withdrawal of the stimulated region. This reflex is often the result of pain reception and can have a long latency secondary to the level of interneuron activity.

ii). The brain stem serves an important role in motor control both as a relay center and processing center. With the exception of the corticospinal tract all descending motor tracts originate in the brain stem. As well, the processing center for afferent information arriving from the vestibular system lies within the brainstem and regulates the postural changes that must be made to stabilize.

iii). The motor is the center for the corticospinal system which sends cortical commands to the spinal cord and the corticobulbar system which sends commands to the brain stem motor nuclei. The distribution of cells in the motor cortex are directly proportional to the degree of motor control necessary for that region of the body (fingers vs arms). The distribution of regions within the motor cortex start medially with lower motor control (feet and legs) and move laterally into upper motor control (face and arms).

iv). The premotor cortex is the primary control region for organized movement. It is here that information from the prefrontal cortex and posterior parietal cortex come together and allow for a target to be identified, a course of action to be decided, organized movement to be planned and finally sent to the motor cortex for initiation.

These four subunits are under constant monitoring and control by the cerebellum and basal ganglia. The cerebellum receives information from descending tracts about intended motor response and from sensory tracts relaying results of the motor actions so far. It is here that movement can be refined or redirected and balance restored. Along with these responsibilities the cerebellum will intake information from the parietal and motor cortices and participate in the planning and initiation of movement. Output from the cerebellum is to the brain stem and motor cortex. The basal ganglia (caudate, putamen and globus pallidus) is less understood but it receives information from the cortex, thalamus and substantia nigra and provides output to the premotor cortex (via the thalamus). The basal ganglia is involved in control of both unconscious motor activities (walking) and some voluntary activities.

7. Autonomic Nervous System

The autonomic nervous system (ANS), along with the endocrine system, regulate respiration, circulation and blood chemistry, digestion and immune system responses in order to maintain homeostasis within the body. The ANS is responsible for the phasic responses of the body while the endocrine system responds with greater latency. The ANS works to innervate the bodies smooth muscle organs and tissues known as the viscera, or hollow organs (heart, lungs, genital, urinary and GI tracts). It is the autonomous nature of the ANS that allow us to focus on other cognitive activities without worrying about our next breath.

The outflow of the ANS (visceral motor outflow) is broken into two well known and distinct systems: (i) the sympathetic nervous system and the (ii) the parasympathetic nervous system. Both of these systems have their origin and preganglionic neurons within the CNS. However, these neurons project outside of the CNS to postganglionic neurons originating between the CNS and their target tissue.

i. The sympathetic nervous system (SNS) the fight or flight regulator of the body that prepares for action when hormonal response is too slow. However, the SNS is not only active in emergency situations. It maintains an operating tone at all times that allow for ongoing control of certain systems (such as heart rate and REM sleep). The SNS preganglionic neurons lie in the region of T1 (thoracic) to L3 (lumbar) resulting in the alternate name for the SNS of thoracolumbar division.

   The preganglionic axons are myelinated as they leave the ventral root of the spinal cord and form the white ramus. On either side of the backbone some of these fibers will form the sympathetic (also called paravertebral) chain with preganglionic axons running rostrally/caudally to adjacent ganglia.

   The postganglionic neurons that travel from the sympathetic ganglia to the visceral effectors with unrnyelinated axons form the gray ramus. Other preganglionic fibers will travel to distal ganglia referred to as prevertebral ganglia. These ganglia, from rostra1 to caudal, are: celiac (responsible for stomach, foregut, liver and pancreas); superior mesenteric (midgut) and inferior mesenteric (hindgut and pelvic) ganglia.

   The primary neurotransmitter at the visceral effector is norepinephrine (adrenergic) which acts on the alpha and beta receptors.

   A special feature of the SNS is the adrenal medulla which can be thought of as another prevertebral ganglia but instead of postganglionic fibers it releases the catecholamines epinephrine and, lesser so, norepinephrine into the blood stream. This results in a slower and longer acting reinforcement of SNS activity.

ii. The parasympathetic nervous system (PNS) in contrast to the SNS is dominant in nonstressful situations. Its preganglionic neurons originate in the brain stem and sacral region of the spinal cord which give rise to its alternate name of the

craniosacral division. Within the brain stem it contains fibers from cranial nerves 3, 7, 9 and 10. In contrast to the SNS, these preganglionic fibers send their axons to ganglia located near to the target organs. The primary neurotransmitter at the visceral effector is acetylcholine (cholinergic) which acts on the muscarinic receptors.

The neurotransmitter from all preganglionic neurons of the SNS and PNS is acytylcholine which acts on the nicotinic receptors of the postganglionic neurons.

8. Significance of Evoked Potentials, CT and PET scanning, and MRI

Evoked potentials: By using electroencephalography we are able to detect cortical activity as a result of peripheral stimulation of any sensory system, This allows for assessment of peripheral and central nervous system function.

CT: Computerized Tomography. Provides a "slice" image of bone and calcified tissue, gray and white matter, blood and cerebrospinal fluid. The technique involves an X-ray tube with highly collimated beams of radiation that pass through the area of interest and onto a film of scintillating crystals. The separation of tissue is accheived by analysis of the radiodensity of each structure. Injected radiopaque contrast material can be used to enhance structures involving blood flow.

PET: Positron Emission Tomography. Allows for a functional assessment of the metabolic activity of the brain. It combines the image capturing principles of CT with the use of inhaled or injected isotopes that emit radiation. Positron-emitting isotopes are bound to compounds such as water, glucose or transmitter molecules to observe their activity within the brain.

MRI: Also involved in function but it has higher resolution. It is based on the concept that when atomic nuclei are placed within a magnetic field they will emit a radiofrequency by resonating. Hydrogen, being a large component of our bodies, is also a strong resonator. Each tissue (even gray vs white matter) contains differing amounts of water and can therefore be resolved with an MRI. Bone on the other hand has little water content and does not produce an image on an MRI.

General Biochemistry

Pertinent Classes: **Opt 531, Ocular Anatomy, Physiology and Biochemistry**
Useful Text: **Principles of Biochemistry, 2nd edition.** Lehninger, Nelson, and Cox. 1993. Worth Publishers. New York, NY.

A. Cellular Biochemistry

1. Compartmentalization

The body keeps opposing metabolic reactions/pathways physically separate (i.e., fatty acid synthesis occurs in the cytosol of the cell, while fatty acid oxidation occurs in the mitochondria) to enhance metabolic regulation.

2. Cell Organelles

Nucleus – contains DNA, site of DNA replication and packaging, RNA synthesis and processing.
Mitochondria – enzymes of citric acid cycle and fatty acid oxidation.
Ribosomes – site of protein synthesis.
Endoplasmic reticulum – transport of newly made proteins to golgi apparatus.
Golgi Apparatus – sorts and modifies proteins for transport within cells and to export out of cell.
Lysosomes – contain enzymes, and processes macromolecules.
Cytosol – site of glycolysis, fatty acid synthesis, and the pentose phosphate pathway.

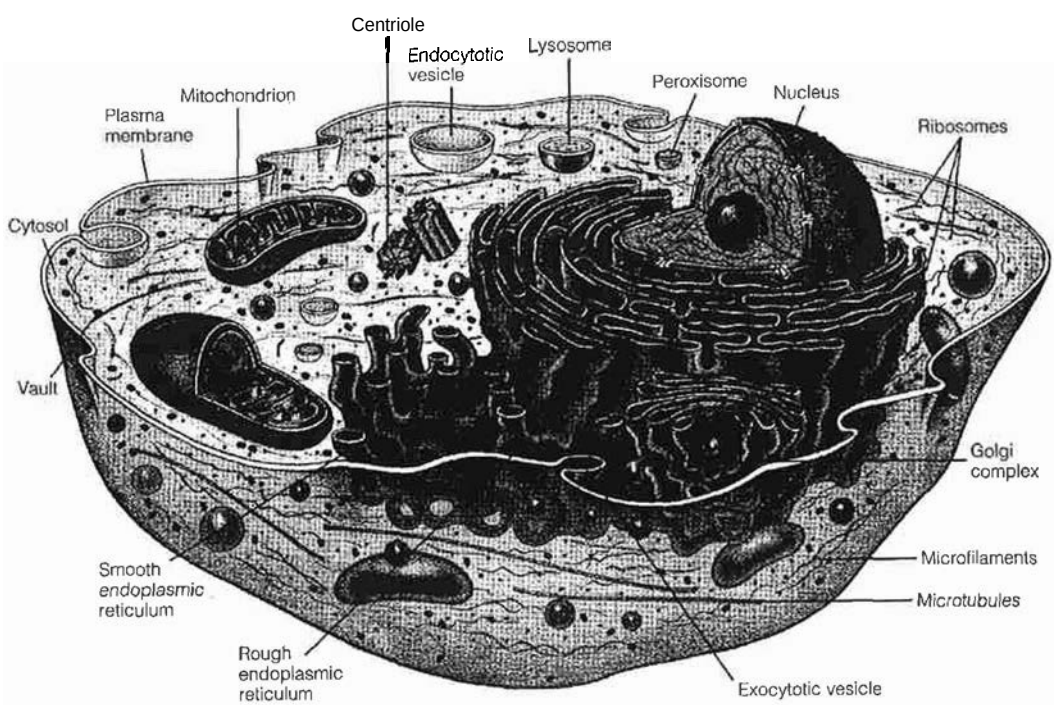


Figure **from Human Physiology: From Cells to Systems, 3rd Ed.** Lauralee Sherwood. Wadsworth Publishing Co. 1997. p21.

3. Intracellular/Extracellular

Intracellular refers to things within cells. Extracellular refers to things outside cells.

4. Cell Communication

Endocrine cells secreting hormones accomplish *hormonal* cell communication. Neurons secrete neurotransmitters to accomplish *neuronal* cell communication.

5. Bonds and Molecular Interactions

Carbon is the main element upon which living organisms are built. Shown on the next page are examples of functional groups found in biological systems.

Functional Groups Commonly found in Biological Systems

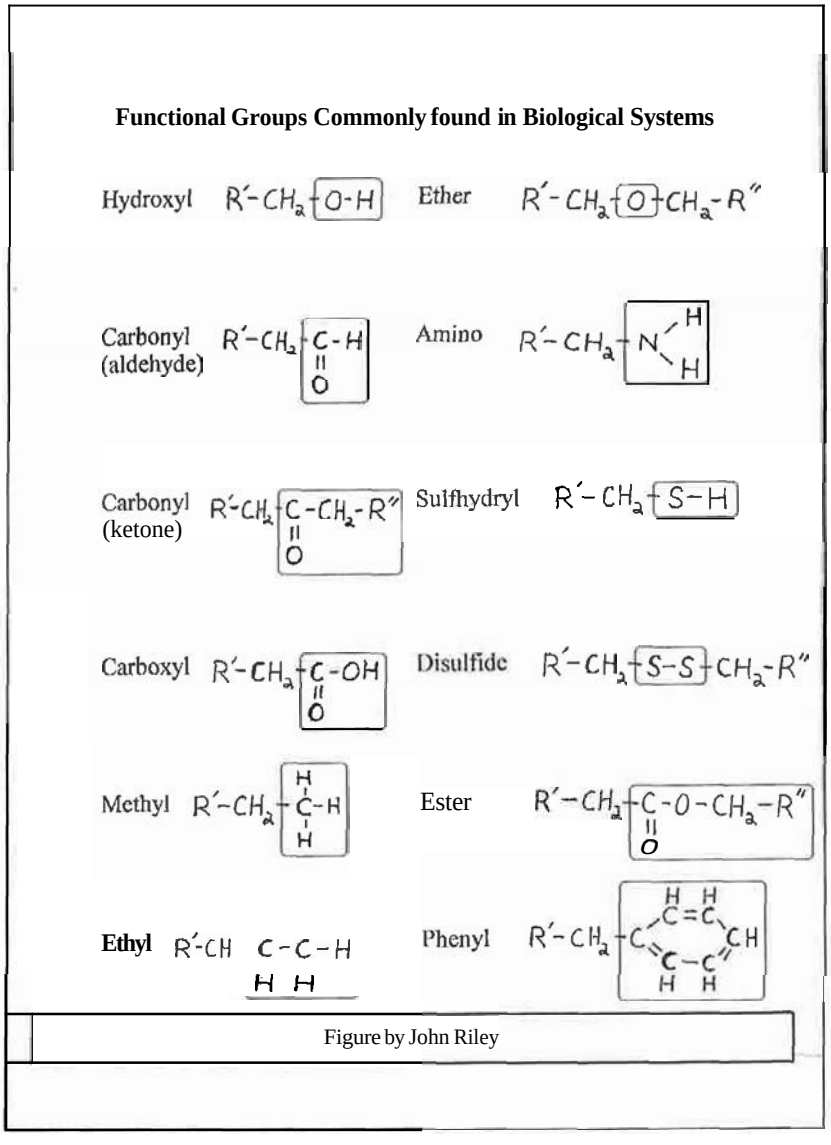


Figure by John Riley

There *are* **5** types **of** general reactions that occur within **cells:**

1. Functional group transfers
2. Redox reactions (reduction and oxidation]
3. Reactions that rearrange the chemical structure around 1 or more of the carbon atoms
4. Carbon **to** carbon bond cleavage.
5. Condensation reactions, where *2* molecules condense with **the** elimination of water

B. Proteins

1. Structure and types

a) Alpha amino acids, peptide bond

Called "alpha" due to the alpha carbon where the carboxyl group is attached. These 20 amino acids are the building blocks that make up all proteins in living organisms. They differ only by their side chains. The general structure of all amino acids is shown below:

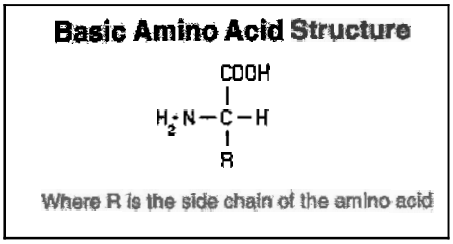
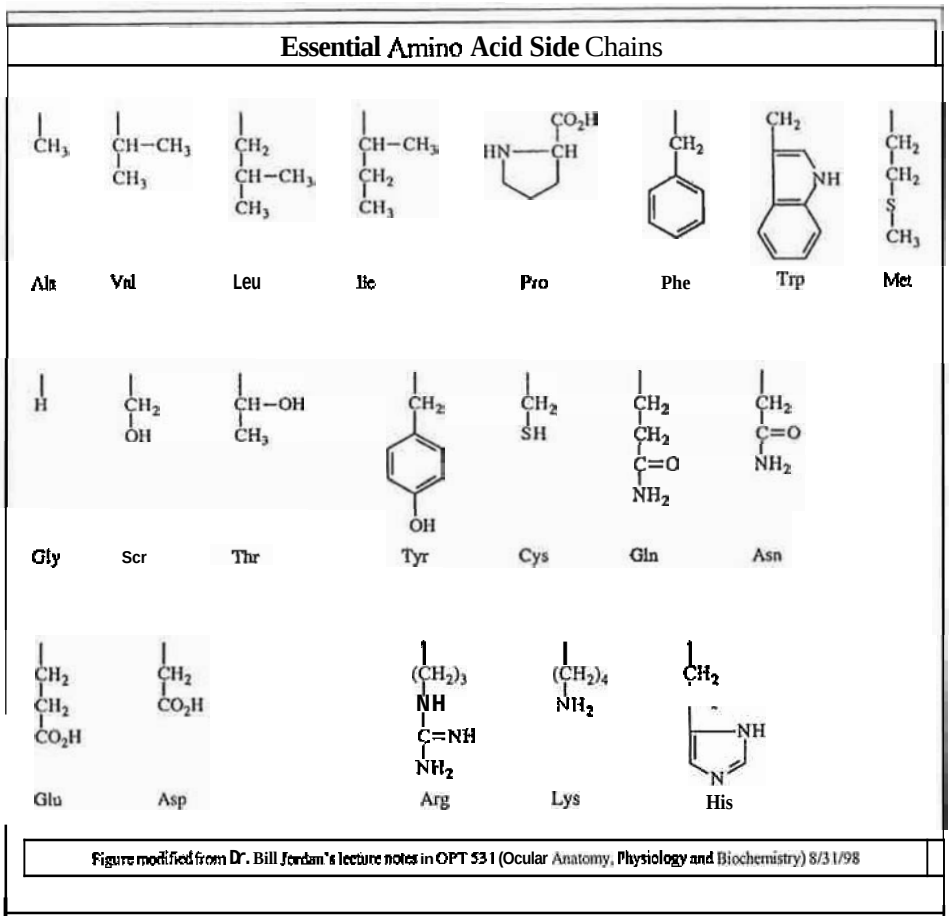


Figure above by John Riley

Below are the side chains that make **up** the 20 **essential** amino **acids:**



Peptide bonds are covalent bonds that link 2 amino acids. It is a substituted amide linkage, formed by the removal of the **elements** of water. **See the example** below:

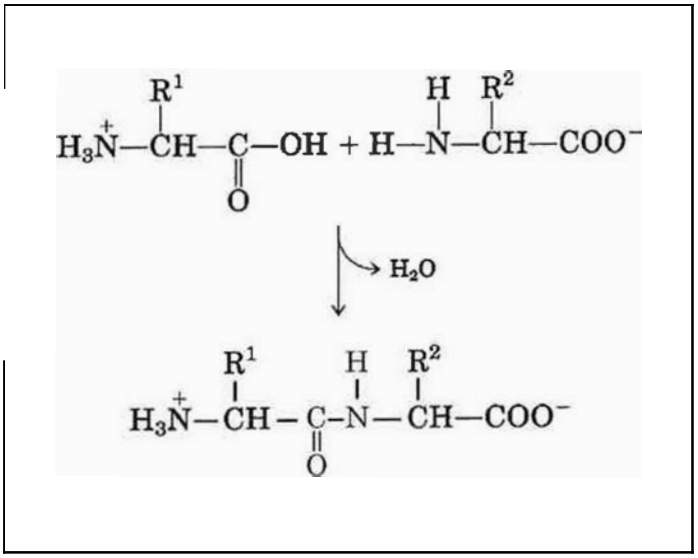


Figure above by John Riley

b. Primary, secondary, **tertiary** and quaternary structure

The primary structure is the *sequence* of amino acids in the protein:

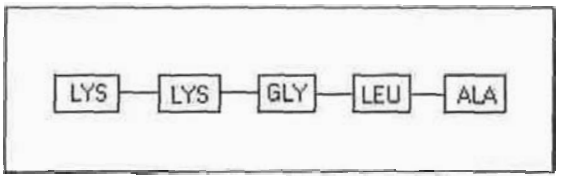


Figure above by John Riley

Secondary structure *is the regular spacing of adjacent amino acid residues in apolypeptide chain (i.e., alpha helix or beta-conformation).* See figure on next page.

Tertiary structure is *the spatial organization among all amino acids in a polypeptide, usually involving multiple secondary structures.* See figure on next page.

Quaternary structure relates to the *spatial arrangement of subunits (made up of polypeptides) within the protein.* See figure on next page.

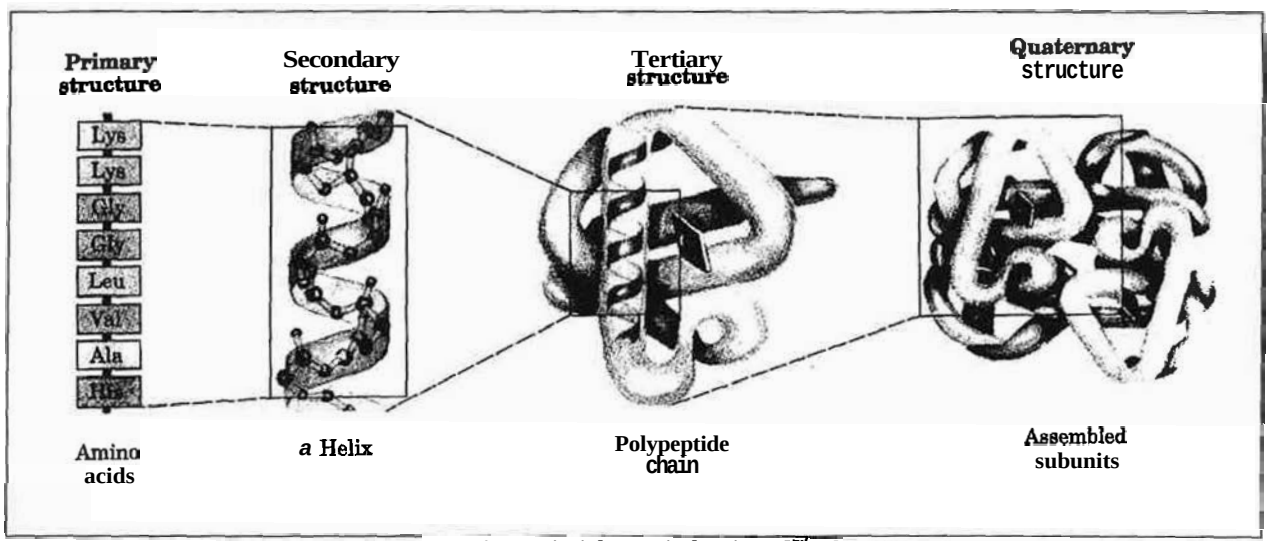


Figure from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p161.

c) Multimers - Sorry, we couldn't find a reference for this term in 4 different biochemistry texts!

d) Globular/Fibrous

These are the two major groups when considering secondary structure of proteins. Fibrous proteins have polypeptide chains in long strands or sheets. Whereas, the polypeptides of globular proteins **are folded** into spherical or globular shapes.

e) Enzymes

These are specialized proteins that catalyze reactions within biological systems.

f) Antibodies

These are proteins produced by the immune system. (AKA: Immunoglobulins).

g) Connective-tissue/collagen

These proteins give physical support to living structures, and provide strength and/or protection. Collagen has very high tensile strength and is the major component of tendons and cartilage.

h) Hemoglobins

Are oxygen transport proteins in the blood, consisting of nearly 600 amino acids, covalently linked into 4 long chains, bound up into globular shapes and configured in a tetrameric structure with a diameter of 5.5nm.

2. Mechanism of Enzyme Action

a) Biocatalysis

Enzymes catalyze nearly all biochemical reactions. They do so by lowering the activation energy between reactants and products. See figure on following page.

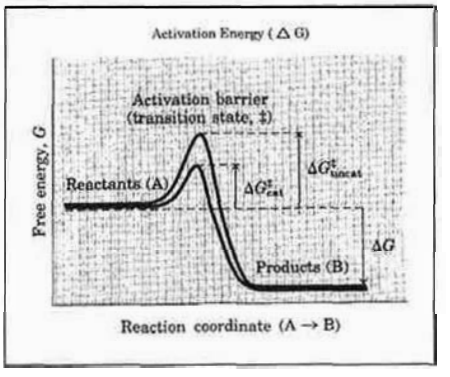


Figure adapted from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p11.

Below is an example of how reaction rates can be affected by enzymatic interactions:

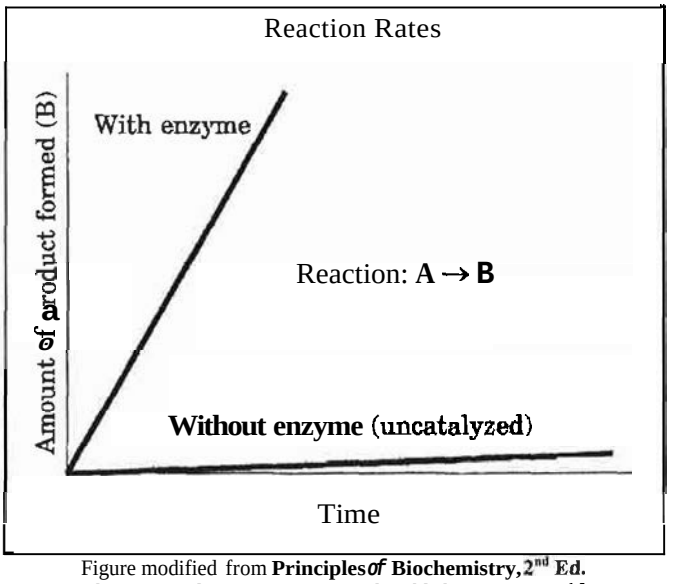


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p10.

b) Activation Energy
This is the amount of energy required to force the reaction to form products.

c) Michaelis-Menten model, equations
This is the model of enzyme action. The basic model shows enzyme (E) plus substrate (S) reacting to form product (P) and free enzyme. This reaction however, occurs in two steps as seen on the following page.

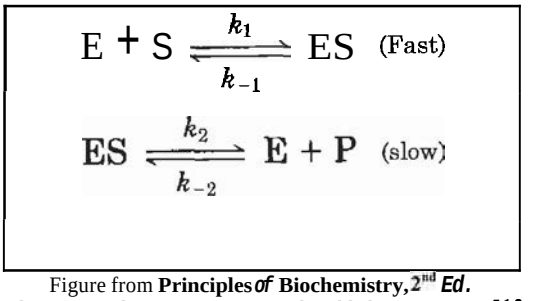


Figure from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p212

k_1 = formation rate of 1st reaction
k_{-1} = breakdown rate for 1st reaction
k_2 = formation rate of 2nd reaction
k_{-2} = breakdown rate for 2nd reaction

The rate-limiting step is the breakdown of ES (enzyme-substrate complex) in the second reaction. Therefore, the enzyme-catalyzed reaction is proportional to the concentration of ES. The Michaelis-Menten equation is shown below:

$$V_0 = \frac{V_{max}[S]}{K_m + [S]}$$

V_o = the initial reaction rate (AKA: initial velocity)
V_{max} = maximum reaction velocity
K_m = Michaelis-Menten constant = $\frac{K_2 + (K\text{-}1)}{K_1}$

This equation is for one substrate, one enzyme-catalyzed chemical reactions. Its purpose is to show the quantitative relationship between the initial velocity (V,), the maximum velocity (V_{max}), and the initial concentration of substrate ([S]), which are all related through the Michaelis-Menten constant (K_m).

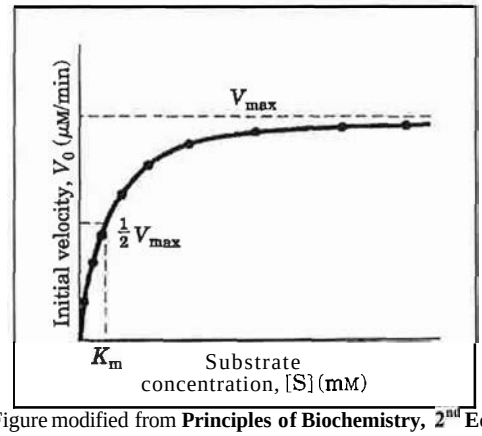


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p212.

K_m is equal to the substrate concentration at which V_o is one-half of V_{max}. The Michaelis-Menten equation can be used to determine K_m, V_{max} and also in the analysis of inhibitor action.

d) Allosteric interaction/positive and negative feedback modulation

Allosteric enzymes are regulatory in nature. Their catalytic activity is modulated by non-covalent binding from a specific metabolite, the modulator, at a site other than the "active" site. The modulators can act either to inhibit or stimulate the allosteric enzyme. Allosteric enzymes show a different relationship between V_o and [S] than the normal enzyme. A sigmoid curve results rather than the hyperbolic curve when V_o is plotted against [S].

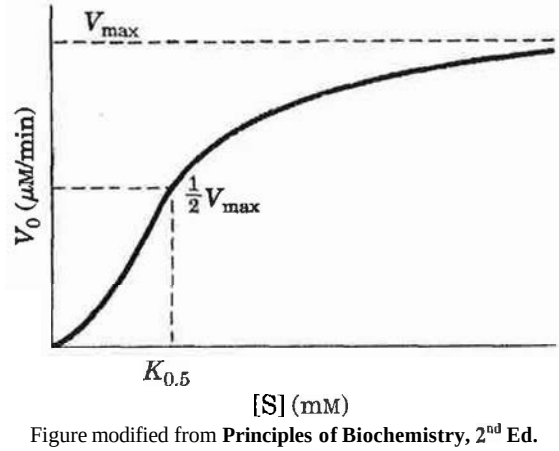


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p231

This sigmoid kinetic behavior is indicative of cooperative interactions between subunits within the allosteric enzyme itself. As one part of the enzyme binds to its modulator, a physical change in the structure of the entire enzyme changes, and this causes subsequence bindings of substrates to be enhanced. Positive feedback modulation results in faster initial velocities (V_o) and a lowered $K_{0.5}$ ($1/2\ V_{max}$), yet without an increase in V_{max}. On the other hand, with negative feedback modulation, as [S] goes up, initial velocity (V,) is slower compared to the un-modulated reaction. Also, $K_{0.5}$ ($1/2\ V_{max}$) is higher in negative feedback modulated reactions. Is this stuff exciting or what?

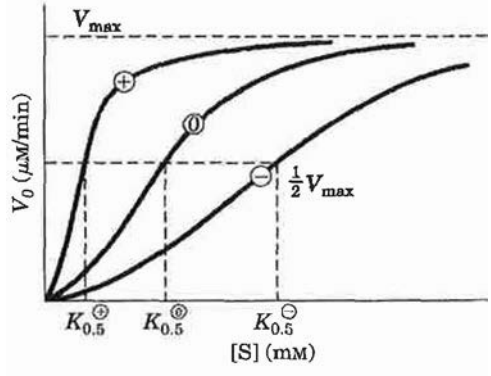


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p231

e) Reversible covalent modification/enzyme cascades

This is another form of regulatory enzyme. The difference is that instead of merely binding to a modulator or substrate and changing the rate of reaction, these regulatory enzymes are covalently modified by other enzymes, creating a temporary new molecule, which is now an active form of the enzyme. Below are some examples of covalent modification.

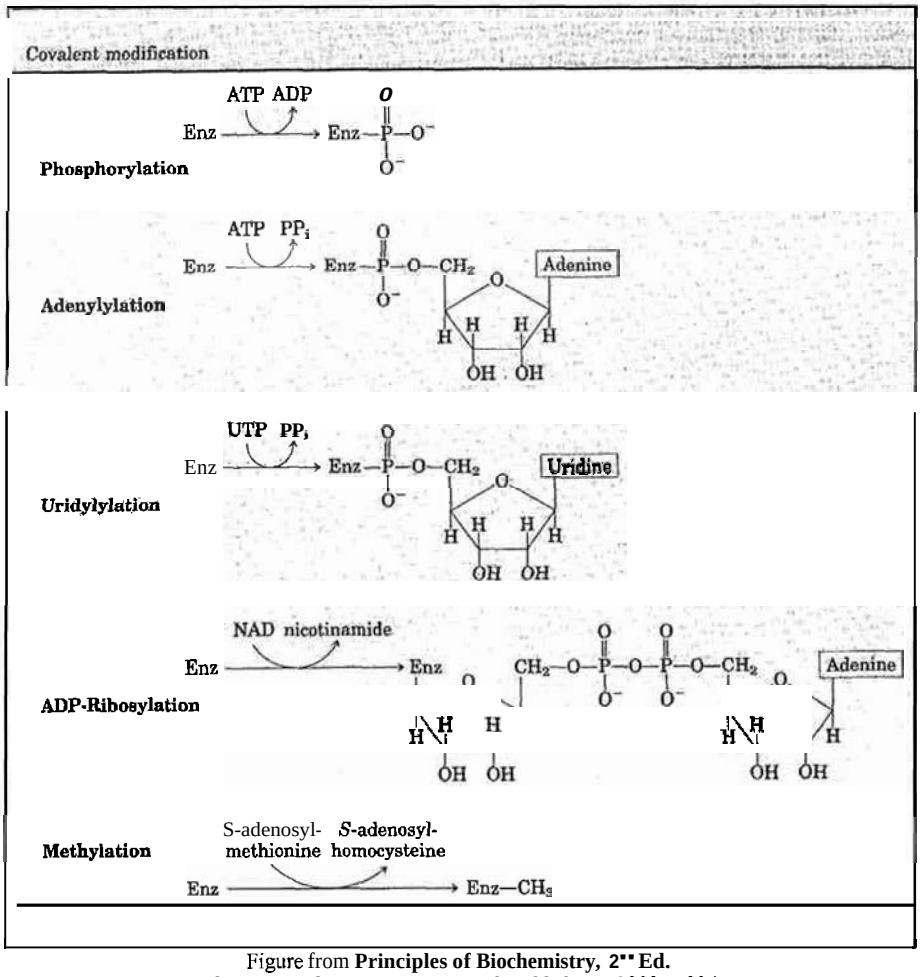


Figure from **Principles of Biochemistry, 2"' Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p234.

These types of reactions can be linked together where one step leads to another, and the product of that reaction may lead to another, etc… This is referred to as a "cascade". The individual steps may or may not be reversible.

a) Proteolytic activation

This is yet another type of regulatory mechanism. This is where an *inactive* form of the enzyme (called a zymogen) is cleaved and the *active* form results. The end product is irreversible, so other mechanisms are required in order to inactivate these enzymes. Usually a binding protein will attach to the active form and it binds to the "active site" which renders the enzyme inactive. An example of the activation of one of these enzymes is trypsinogen to trypsin, which occurs when the enzyme enteropeptidase cleaves trypsinogen to form its active form trypsin.

b) Stimulation and inhibition by control/regulatory proteins

Regulatory enzymes are the ones that catalyze the rate-limiting step in a multi-enzyme system. It is usually the first step in the system. These regulatory enzymes can be either inhibited (usually by a product or byproduct of the reaction itself) or stimulated (by signal molecules – either small metabolites or cofactors). See the example below:

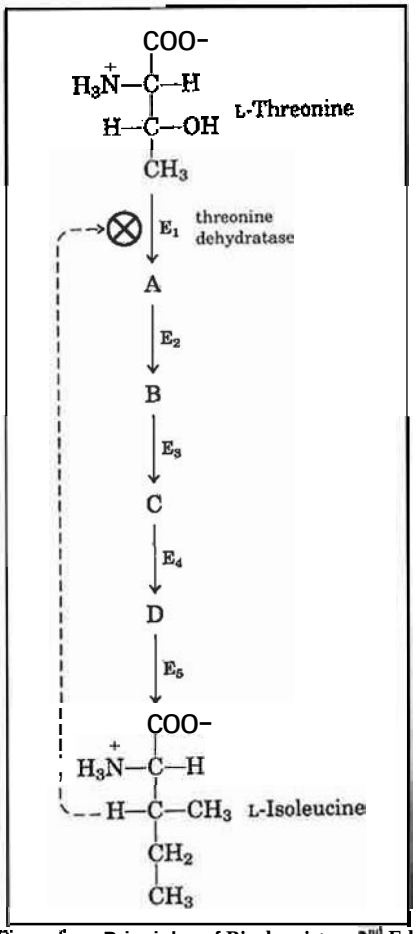


Figure from Principles of Biochemistry, 2nd Ed.
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p229.

C. Bioenergetics and Energy Storage

1. Free energy/entropy/enthalpy/equilibrium

Free energy is the amount of energy that is "freely" available to do work. It is always somewhat less than the total amount of change in energy in the system itself. It can be positive or negative. If it is negative, the reaction proceeds from reactants to products with the release of free energy and can be used to drive or pull an endergonic reaction when the two reactions are linked by a common intermediate. See the example below:

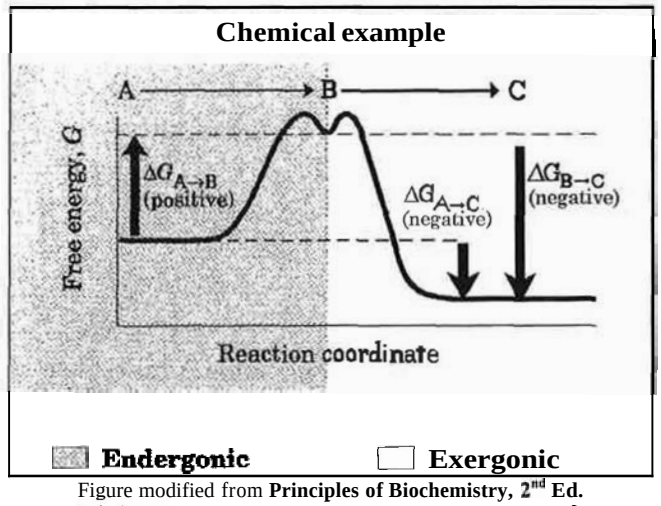


Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p8.

Entropy (S) is known as the amount of randomness in a system. Enthalpy (H) is the heat content of a system. Remember, there is an "H" in enthalpy, for "heat". Equilibrium is where the free energy is at its lowest, and is the point at which no further net change is occurring, unless energy or other input comes from outside the system.

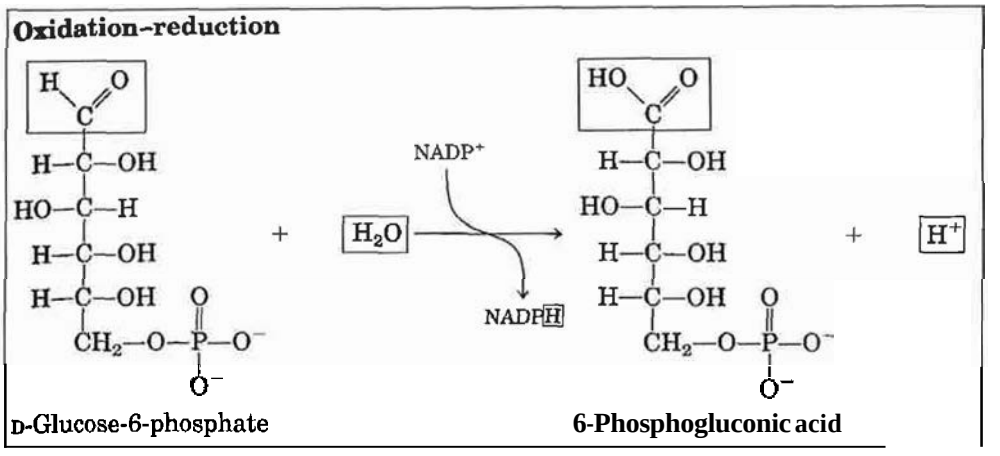
2. Endergonic, exergonic and coupled reactions

Endergonic reactions are those where the *products* have more free energy than the *reactants*. In other words, it's like trying to push a cart up hill. $\triangle G$ is positive for endergonic reactions. Exergonic reactions are the opposite; reactants now have more free energy than the products and $\triangle G$ is negative (this is like trying to push a cart down hill). Coupling of an exergonic reaction with an endergonic reaction is key to the free energy exchanges found in all living systems. The energy produced in one reaction drives the other. The two reactions must share an intermediate (shown as B in the figure above).

3. Oxidation-reduction (Redox Reactions)

These are reactions that involve the transfer of electrons from a donor molecule to an acceptor molecule. The donor molecule is said to be "oxidized," and the acceptor is therefore, "reduced". Redox reactions are the driving force of energy (directly or indirectly) for all the work done by

living systems. In photosynthetic organisms, a molecule in the system is excited by a photon and is the initial electron donor in the photosynthetic pathway. In non-photosynthetic organisms, food is the initial source of electrons. Metabolism has a very complex flow of electrons, which involves many redox reactions. An example of a redox reaction is shown on the next page.



Lehninger, Nelson, and Cox. Worth Publishers. 1993. p67.

4. pH and Henderson-Hasselbalch equation, biological buffers

pH is the negative logarithm of the hydrogen ion concentration.

$$pH = \log \frac{1}{[H^+]} = -\log [H^+]$$

In order to understand the Henderson-Hasselbalch equation, we need to review some acid-base characteristics. Just what you were hoping I'd say! An acid is a proton donor. Strong acids are things like HCl (hydrochloric acid) and H_2SO_4 (sulfuric acid). These acids are so strong that they tend to remain completely dissociated (ionized) in dilute aqueous solutions. Examples of strong bases are NaOH and KOH (sodium and potassium hydroxide). These too like to be ionized completely. Bases are proton acceptors.

In biochemistry, we're not so concerned with strong acids or strong bases. What we're interested in (well, sort of) is weak acids and bases. These are compounds that are *not* completely ionized when dissolved in water. A proton donor (an acid) and its corresponding proton acceptor (a base) are known as a conjugate acid-base pair. For example:

$$\underset{\text{(acid)}}{CH_3COOH} \leftrightarrows H^+ + \underset{\text{(base)}}{CH_3COO^-}$$

Every acid has a specific "desire" to lose its proton in solution. The stronger the "desire," the stronger the acid. The "desire" for any acid (HA) to give up its proton (H^+) and form its conjugate base (A-) is given by its equilibrium constant (K) for the reaction.

$$HA \rightleftharpoons H^+ + A^-$$

$$K = \frac{[H^+][A^-]}{[HA]}$$

Equilibrium constants for ionization reactions are usually referred to as dissociation constants, and abbreviated as K_a. The pK_a is therefore the inverse logarithm of the K_a (dissociation constant). Note, the stronger the acid, the higher the K_a, but the lower the pK_a.

The Henderson-Hasselbalch equation is the quantitative relationship between the pH, the buffering interaction of weak acid and its conjugate base, and the pK_a of the weak acid. Below is the actual equation:

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Can also be written as:

$$pH = pK_a + \log \frac{[\text{proton acceptor1}]}{[\text{proton donor}]}$$

Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p98.

A biologically buffered system consists of a weak acid and its conjugate base. The system is "buffered" when the addition of small amounts of either acid (H^+) or base (OH-) results in very little pH change to the system. To find the "buffer" zone of a system, a titration curve is made (Oh joy, remember that lab from General Chemistry?). Below is an example of the titration curve for acetic acid:

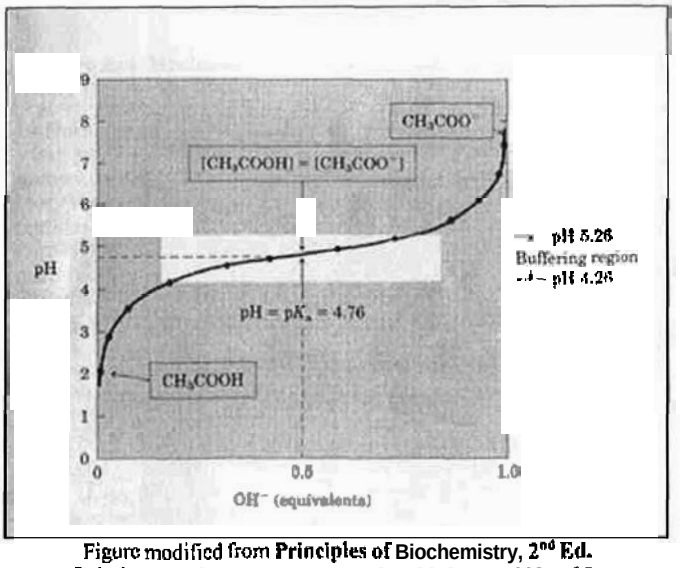


Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p95.

5. *ATP* and other nucleotidephosphates

Nucleotides are molecules that drive many metabolic reactions in all cells (mostly biosyntheses). They are energy-rich compounds made up of three components: 1) A nitrogenous base; 2) A pentose sugar; and 3) A phosphate group. The nitrogenous bases are always derivatives of Pyrimidine or Purine. Note the basic structure of a nucleotide phosphate and that of Purine and Pyrimidine as shown below:

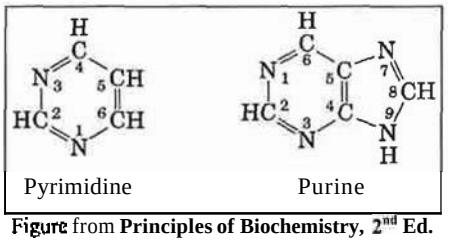


Figure from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p325.

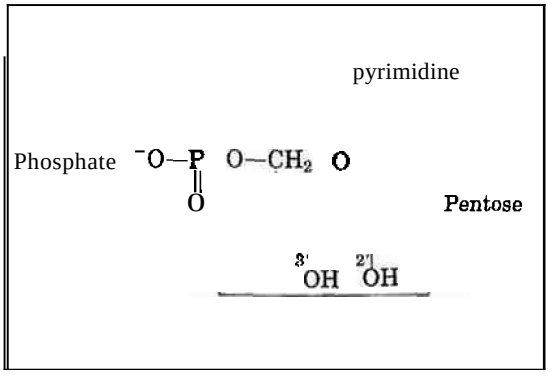


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p325.

Nucleotides are important in the structure of both DNA and RNA. See sections on DNA/RNA structure and function.

Nucleotides may be linked to 1, 2, or 3 phosphate groups at the 5' hydroxyl of the pentose sugar. This makes the compound now a mono-, di-, or tri-phosphate nucleotide. Remember, a nucleoside is a pentose sugar with a nitrogenous base, but without a phosphate group attached. The main energy force behind most biochemical reactions is a nucleotide tri-phosphate called ATP (adenosine tri-phosphate). It is named this for its nitrogenous base (Adenosine). Below is a figure of ATP, showing how the phosphates are esterified to the pentose sugar at the 5' Carbon.

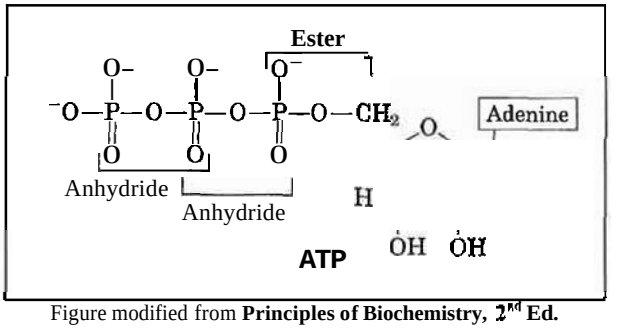


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p352.

Other nucleotides are also used for driving biochemical reactions (i.e., UTP, GTP, and CTP), but ATP is by far the most commonly utilized.

Nucleotides are also the backbone of many enzyme cofactors, such as Coenzyme-A (Co-A), NAD^+ (Nicotinamide adenosine dinucleotide), and FAD (Flavin adenine dinucleotide). The interesting thing to note here is that adenosine is the nucleotide of choice for biological systems to create most enzyme cofactors, just as ATP is the tri-phosphate of choice for these systems for their energy molecule.

A final use for nucleotides is in the structure of "second messengers" inside cells. Cells respond to chemical messages (hormones or other chemicals known as "first messengers") in their surrounding environment. The receptors on the surface of the cell respond to the "first messenger" by producing a "second messenger" inside the cell that will lead to a change within the cell. One of the most common nucleotides that is used as a "second messenger" is cyclic AMP (Adenosine 3',5'-cyclic Mono-Phosphate).

6. NADH and FADH

Metabolism consists of catabolism and anabolism. Catabolism is the process by which cells convert larger, nutrient-rich molecules (like carbohydrates, fats and proteins) into smaller, simpler ones (such as CO_2, H_2O, and NH_3) and release free energy in the form of ATP, NADH, and NADPH. Anabolism is the other half of metabolism, where reactions now require energy and get it from the hydrolysis of ATP and through the reducing power of NADH and NADPH.

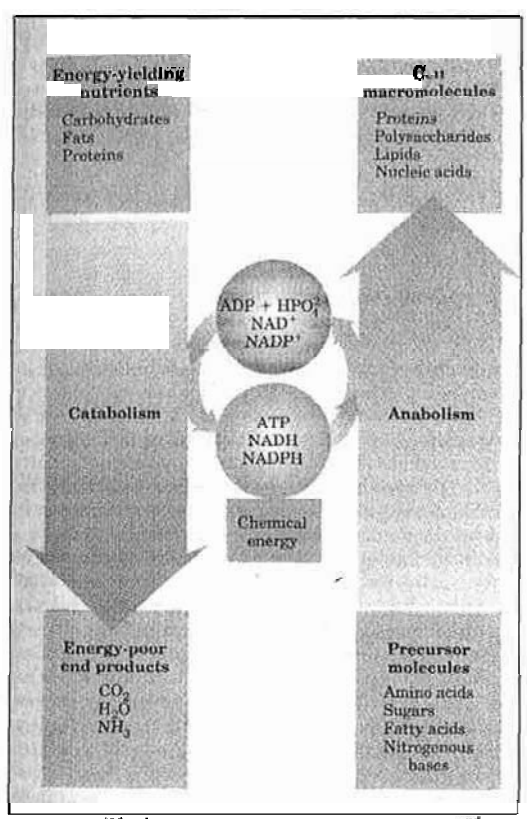
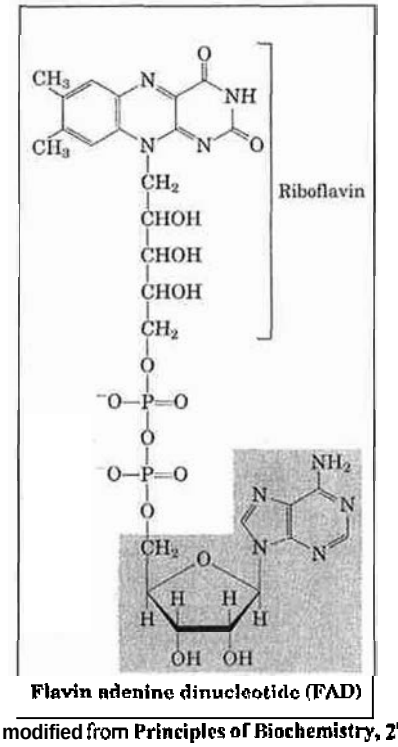


Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p361.

NADH is Nicotinamide adenosine dinucleotide, and is the reduced form of NAD^+. NAD^+ usually act in catabolic oxidations.

FADH is Flavin adenine dinucleotide, in its semiquinolone form. Flavin refers to the riboflavin group that is esterified to the end of the phosphate group. See figure below. FADH is reduced by one hydrogen from FAD and can be further reduced to $FADH_2$. Since it can undergo two reductions, FAD is involved in a greater diversity of reactions than NAD-linked dehydrogenases.



Flavin adenine dinucleotide (FAD)

Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Wonh Publishers. 1993. p353.

7. NADPH

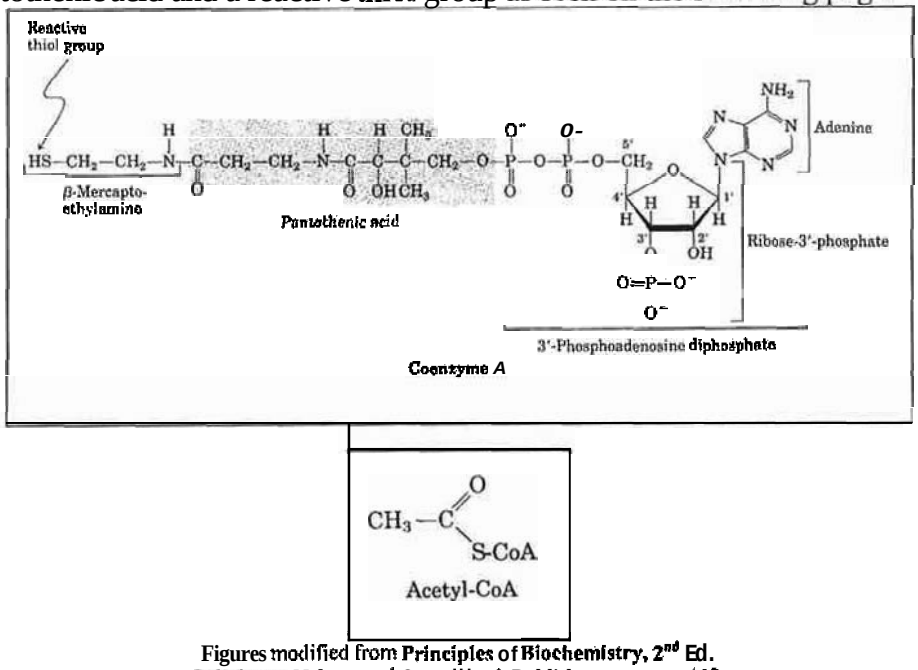
Nicotinamide adenine dinucleotide phosphate, is the reduced form of $NADP^+$. NADPH usually acts as a cofactor in anabolic reactions.

Both NADH and NADPH act with dehydrogenase enzymes to work as electron carriers. There are over 200 different known dehydrogenases. These enzymes catalyze the reactions with NAD^+ and $NADP^+$ so that they accept a hydride ion from a reduced substrate (AH_2) to form an oxidized substrate (A). Another way that NADH or NADPH can work to carry electrons is to have them donate a proton to an oxidized substrate. An example of NAD^+ accepting a proton from an oxidized substrate is the catabolism of ethanol seen below:

$$CH_3CH_2OH + NAD^+ \leftrightarrows CH_3CHO + NADH + H^+$$

8. *Acetyl CoA*

Just know that Coenzyme-A (the CoA part of Acetyl CoA) is a rather large molecule, which contains Pantothenic acid and a reactive thiol group as seen on the following page:



Figures modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p448.

Acetyl-CoA is produced from Pyruvate through oxidative decarboxylation. Acetyl-CoA then can go on to donate its acetyl group to the compound oxaloacetate, in order to start the Citric Acid Cycle. The Citric Acid Cycle occurs in the mitochondria of eukaryotes and in the cytosol of prokaryotes. Cellular respiration tends to occur in three major steps. See figure on the following page.

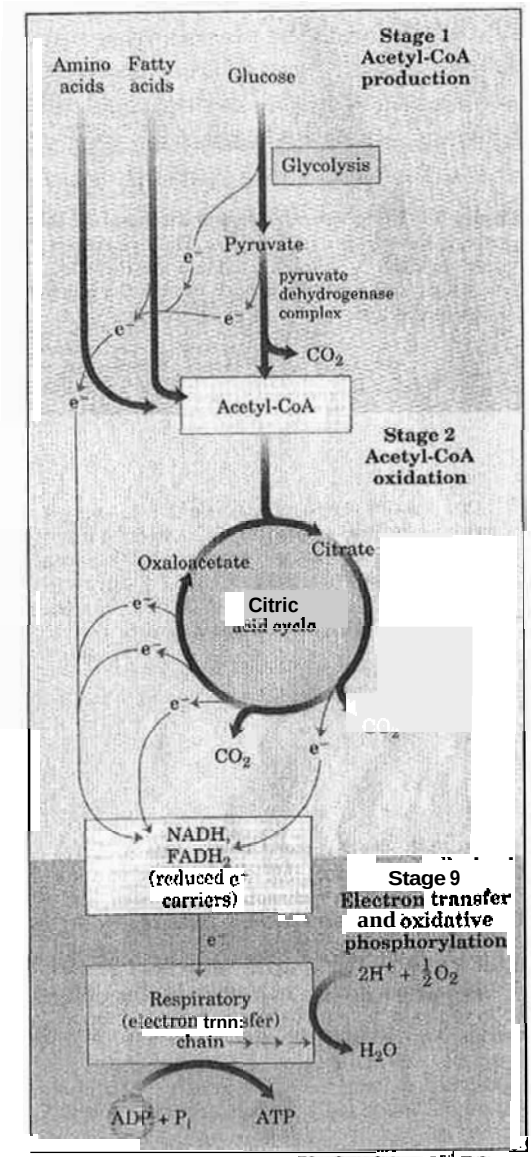


Figure from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p447.

The Citric Acid Cycle will be discussed in the next section.

D. Carbohydrate Biochemistry

1. Structure and Function

a. Monosaccharides, oligosaccharides, polysaccharides

Monosaccharides are simple sugars, made up of a single polyhydroxy aldehyde or ketone. They are colorless, crystalline solids, freely water soluble, but insoluble in nonpolar solvents. Monosaccharides are built with a backbone of an unbranched carbon chain, all with single bonds linking them. One of the carbons is double bonded to an oxygen. If this carbon is on the end of the backbone chain, then the monosaccharide is called an aldose. If, however, the carbonyl group (C=O) is on the chain at any other point, it is referred to as a ketose. The simplest monosaccharides are 3 carbon chains. These are either glyceraldehydes or dihydroxyacetone:

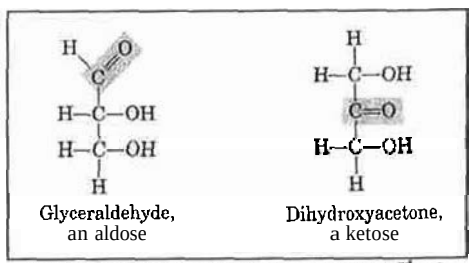


Figure from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p299.

If the monosaccharide has 4 carbons in its chain, it is a tetrose, 5 carbons makes a pentose, 6 makes a hexose, and 7 makes a heptose, etc. Hexoses are the most common monosaccharides in nature (i.e., glucose, and fructose). All monosaccharides, except dihydroxyacetone, have one or more asymmetric (chiral) carbons in their chain. This means that glyceraldehydes can look like either of these two conformations:

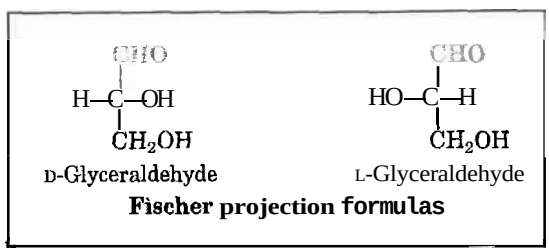


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehnginger, Nelson, and Cox. Worth Publishers. 1993. p300.

These two forms (seen above) of glyceraldehydes are referred to as optical isomers, or enantiomers. Perspective formulas show the 3-dimesional aspects of the compounds. An example of this is shown on the next page.

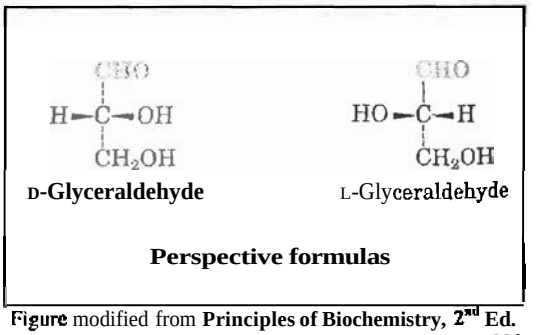


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p300.

In general, molecules with n (numbers of chiral centers) can have 2^n stereo isomers. For example, Glyceraldehyde has n = 1 (one chiral carbon), and therefore has $2^1 = 2$ stereo isomers. Many monosaccharides, especially pentoses and hexoses will exist in cyclic form. For example:

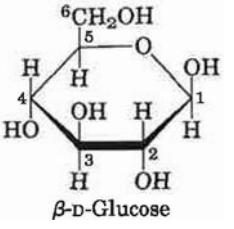


Figure from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p306.

Also, pentoses (D-Ribose and 2-deoxy-D-Ribose) are major components of nucleotides and nucleic acids.

Oligosaccharides are made up of short monosaccharide chains bound together by characteristic glycosidic linkages. The most common are disaccharides, having 2 monosaccharide units. An example is sucrose:

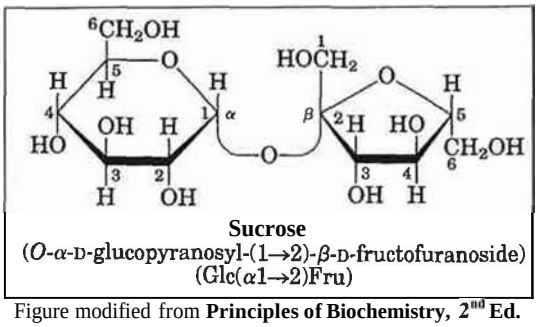


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p307.

All common mono- and disaccharides have names ending in "-ose." Polysaccharides are made up of hundreds or thousands of monosaccharide units. Two common examples are starch (which is made in plant systems) and glycogen (which is made in animal systems). Starch and glycogen are the storage forms of cellular fuel.

b, Glycosaminoglycans
The space between cells in animal tissue (extracellular space) is filled with a gel-like material called extracellular matrix or ground substance. It is composed of an interlocking meshwork of heteropolysaccharides called glycosaminoglycans and fibrous proteins. A common example of glycosaminoglycans is hyaluronic acid. It is found in the eye of vertebrates.

c. Proteoglycans
Proteoglycans are formed when glycosaminoglycans are attached to extracellular proteins. They are composed of a very long strand of hyaluronate, which binds, non-covalently, to numerous molecules of core protein. Each one of the core proteins is covalently bound to many smaller glycosaminoglycan molecules, such as keratan sulfate, or chondroitin sulfate. Interwoven between the giant proteoglycans are fibrous proteins such as collagen and elastin. These proteins form a cross-linked meshwork that provides strength and resiliency to the extracellular matrix.

d. Glycoproteins
Proteins that contain a carbohydrate group (-CHO) are referred to as glycoproteins. Membrane proteins and most proteins secreted by eukaryotic cells are glycoproteins. The biological advantage to adding the disaccharide to proteins is not fully understood. Yet, the -CHO groups are typically located on the external side of plasma membranes and act as messengers that determine whether a given protein will be removed by the liver, or continue to circulate in the blood. Also, carbohydrate groups attached to a newly synthesized protein may target that protein for a specific organelle, or for export, or for placement on the cell's outer surface.

2. Glycolysis/glucose metabolism

Glycolysis is a ten-step process to break down one glucose molecule into 2 pyruvate molecules. See diagram on next page for details of products formed, energy input/output, and catalysts.

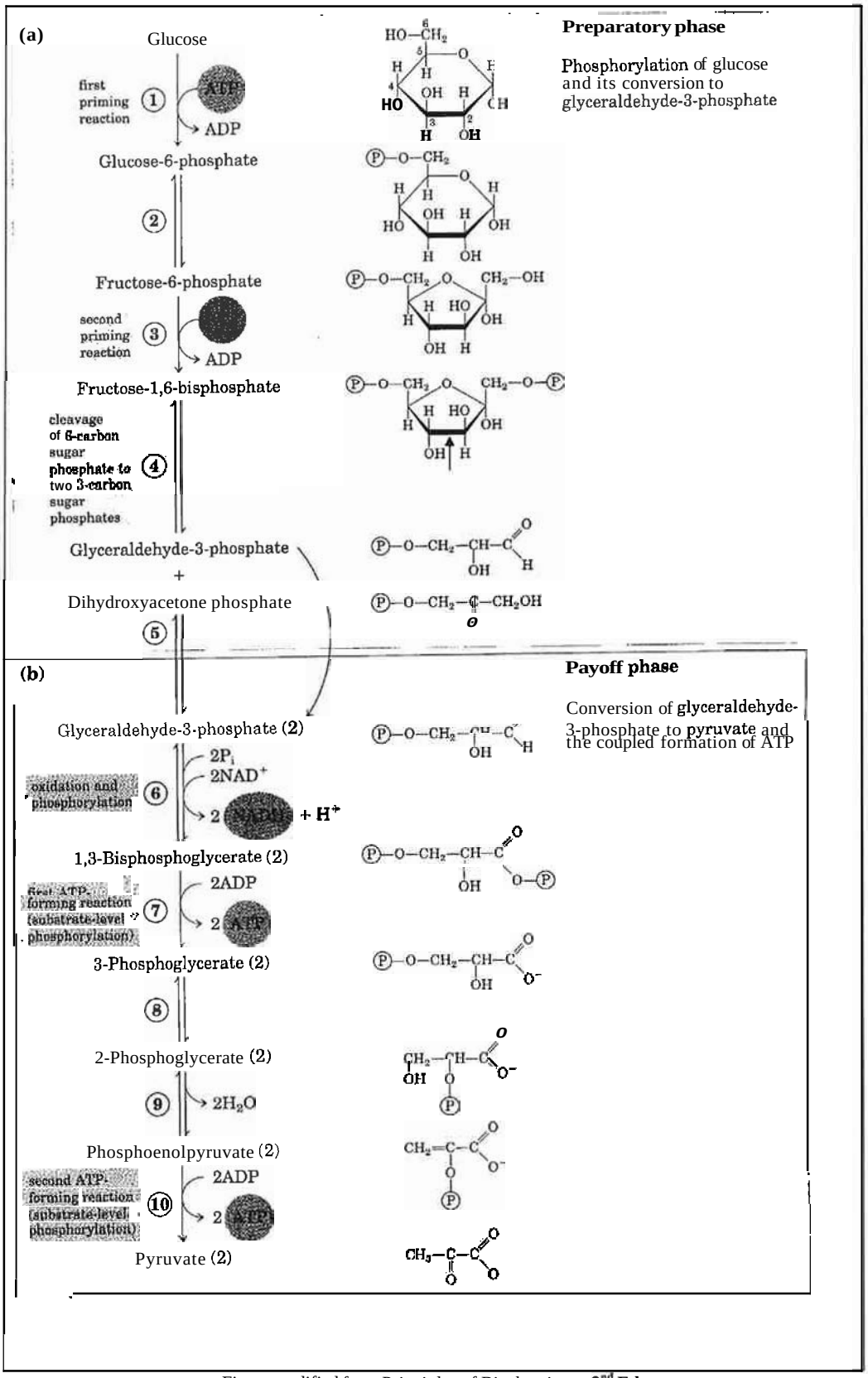


Figure modified from Principles of Biochemistry, **2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p402.

The first five steps are referred to as the "preparatory" phase, since no energy (ATP or NADH) is produced. The final five steps are called the "pay off' phase since they do produce energy and the final product: pyruvate. Once pyruvate has been produced, there are three possibilities for its use. The diagram below shows these possibilities:

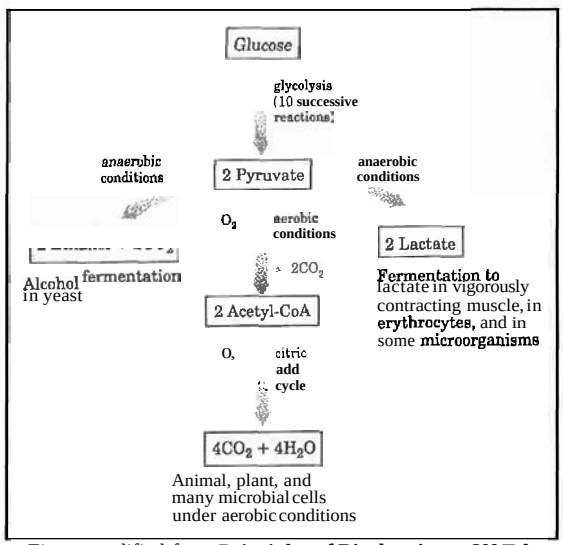


Figure modified from **Principles of Biochemistry,** 2'' **Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p403.

Normally, under aerobic conditions, pyruvate enters the Citric Acid (or Krebs) Cycle. Under anaerobic conditions, like overworked skeletal muscle, pyruvate is reduced to lactate. Certain tissues such as the retina, brain, and erythrocytes will convert glucose to lactate even under aerobic conditions. Finally, in plants, microorganisms, and some invertebrates, pyruvate is fermented to yield ethanol and CO_2 (i.e., beer).

3. TCA Cycle (Also known as: Krebs Cycle or Citric Acid Cycle)

This is the aerobic, catabolic mechanism that occurs in the mitochondria1matrix. Each glucose molecule causes 2 turns of the TCA cycle since 2 pyruvate molecules result from the breakdown of one glucose molecule. The total energy 1 glucose molecule can produce***from the*** TCA ***cycle*** is 20 ATP (10 ATP for each turn of the TCA cycle). If you also add the total energy produced from glycolysis, and the breakdown of pyruvate into Acetyl-CoA, each glucose molecule can yield 32 ATP!

Pyruvate is oxidized to Acetyl-CoA and enters the TCA cycle. Just be familiar with the 9 major compounds involved as products and/or reactants in the TCA cycle: Acetyl-CoA→ Oxaloacetate→ Citrate→ Isocitrate→ alpha-Ketoglutarate → Succinyl-CoA → Succinate → Fumarate → Malate. The full details to the cycle are shown on the next page for your viewing pleasure.

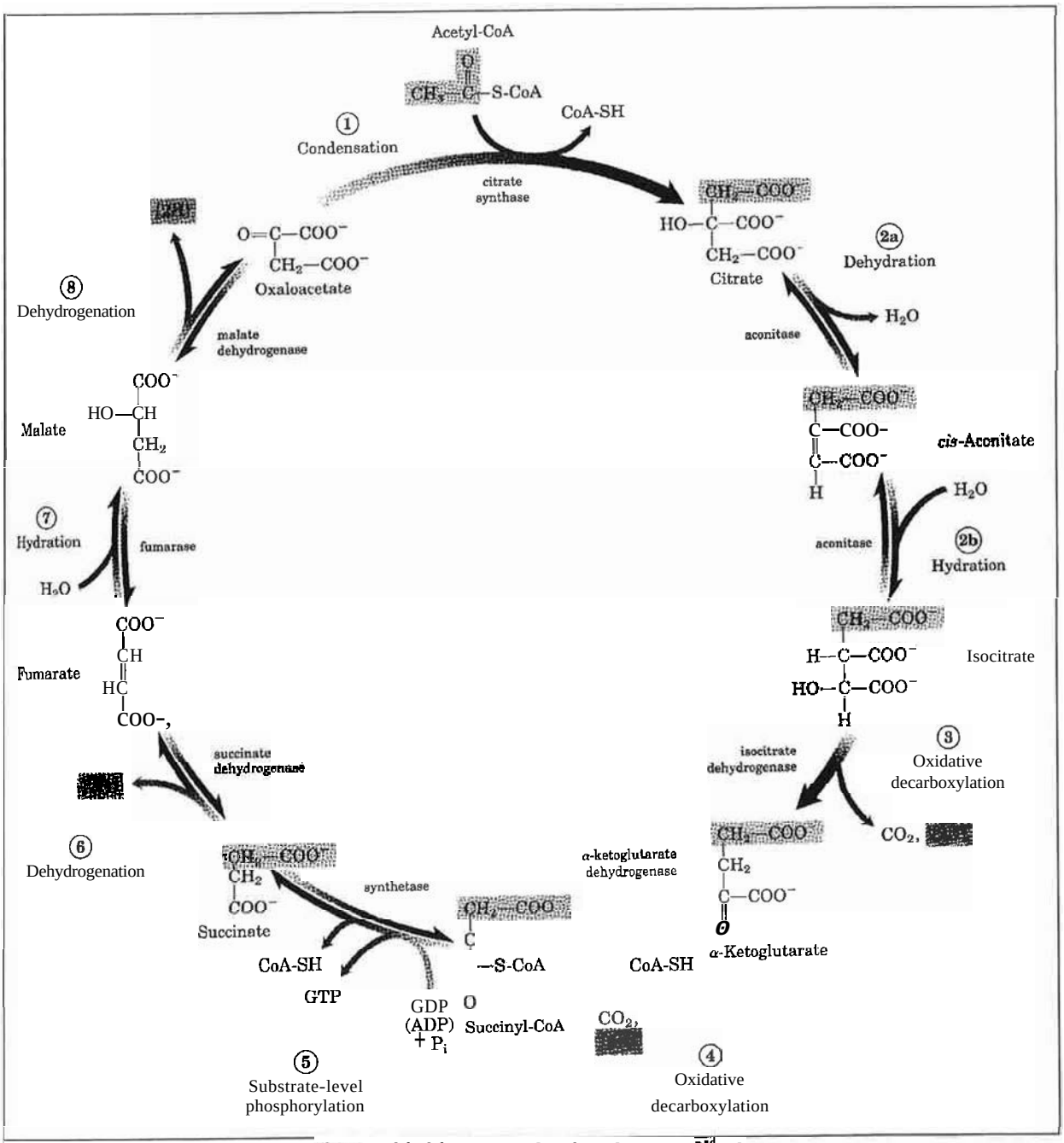


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p453.

4. Pentose phosphate pathway (PPP) (also known as the Phosphogluconate Pathway)

The PPP generates energy differently from glycolysis and the TCA cycle. Those two processes produce ATP, whereas the PPP yields NADPH. NADPH is an "energy-carrying" molecule because it can be used to "reduce" certain molecules (especially in the biosynthesis of fatty acids and steroids). A second product of the oxidative PPP is essential pentoses, which are required for synthesis of RNA, DNA and nucleotide coenzymes. For every glucose molecule that undergoes the PPP, 12 NADPH are formed and 6 Ribose-5-Phosphate molecules. See the diagram below for the details of this pathway:

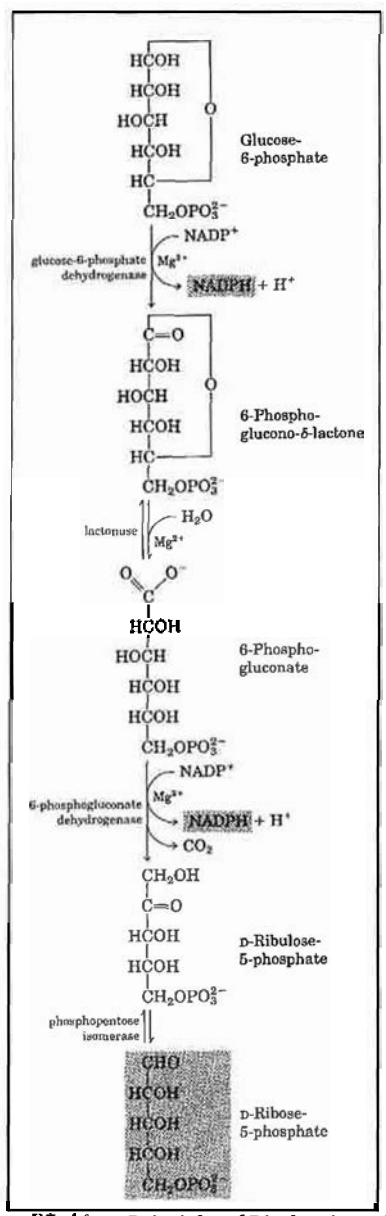


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p436.

5. Gluconeogenesis

In simple terms, this is the reversal of glycolysis. However, there are 3 reactions in glycolysis that are so exergonic (energy releasing) that they are essentially irreversible. Therefore, in gluconeogenesis (the synthesis of glucose), these 3 reactions are reciprocally regulated by utilizing allosteric inhibitors or potentiators to allow those reactions to run. For example, in glycolysis Fructose-6-Phosphate is converted to Fructose-1,6-bisphosphate by way of the enzyme phosphofructokinase 1 (PFK-1). In gluconeogenesis, the opposite reaction is catalyzed by Fructose-1,6-bisphosphatase (FBPase-1). See diagram below:

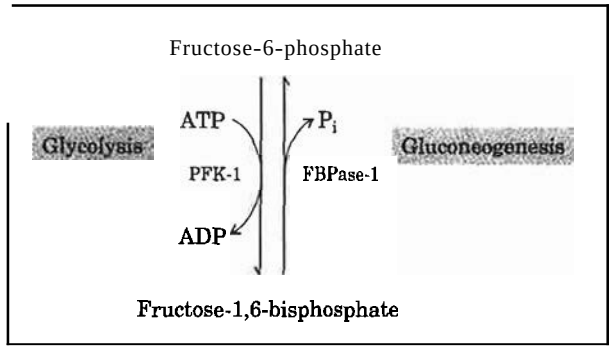


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p435.

The allosteric inhibitor of FBPase-1 is Fructose-2,6-bisphosphate, which also happens to be a potent activator of liver PFK-1.

Gluconeogenesis is basically the formation of glucose from simple molecules such as pyruvate or lactate. This process occurs primarily in the liver and sometimes in the kidneys. The role of gluconeogenesis is to maintain normal blood glucose levels (especially to brain and muscle) even when other sources of glucose have run out.

6. Glycogen synthesis/storage and breakdown/utilization

Glycogen is the storage form of glucose. The synthesis of glycogen occurs in nearly all tissues, but is mainly accomplished in the liver and skeletal muscles. Glycogen in the liver is stored as a reservoir for any tissue in the body that becomes depleted of glucose. The glycogen in muscle tissue however, is used as a quick resource of ATP, which can be rapidly obtained as glycogen is broken down into glucose and glycolysis yields the energy rich molecule: ATP.

Glycogen is basically a linear compound made up of glucose molecules strung together in a chain, linked via ***a-1***–4 bonds:

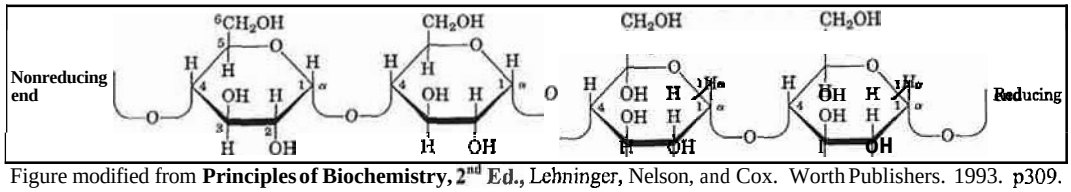


Figure modified from **Principles of Biochemistry, 2nd Ed.**, Lehninger, Nelson, and Cox. Worth Publishers. 1993. p309.

Free glucose is converted to glucose-6-phosphate by either hexokinase (in the liver) or by glucokinase (in muscle). Then, glucose-6-phosphateis reversibly **converted** to glucose-1-phophate by phosphoglucomutase. Next, glucose-1-phosphate is catalyzed to form UDP-glucose (uridine diphosphate glucose) by the enzyme UDP-glucose pyrophosphorylase. Finally, UDP-glucose is converted into chains of glycogen, by glycogen synthase. Glycogen is not however merely one long, straight chain. It is made up of many smaller chains connected together via branching points, as shown below:

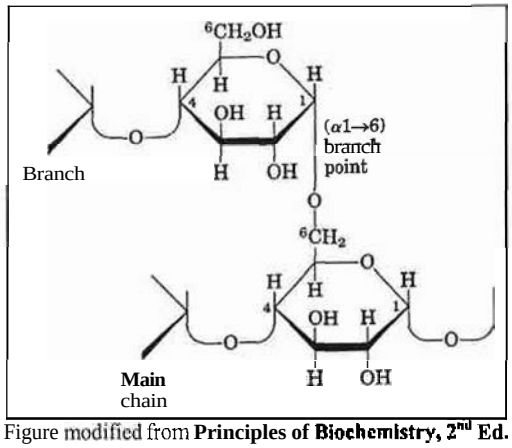


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p309.

The branches are created by *a* 1-6 linkages and are formed by the enzyme glycosyl-(4-6)-transferase. The biological reason for this branching structure is to make glycogen more soluble and more susceptible to reaction with the enzymes that build it and break it down, glycogen synthase and glycogen phosphorylase, respectively.

7. Electron transport system and oxidative phosphorylation

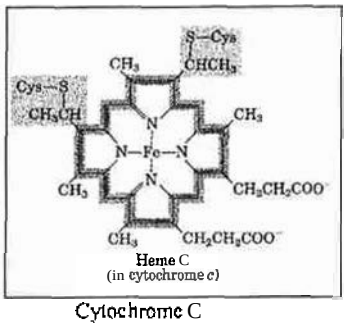
Oxidative phosphorylation is arguably the most important energy transfer reaction in animals. In a nutshell, it is the synthesis of ATP, driven by the reduction of oxygen (O_2) to water (H_2O). It is the culmination of all metabolic steps to break down carbohydrates, fats, and amino acids in aerobic cells, into usable energy (ATP).

a. Mitochondria1 structure/function/DNA

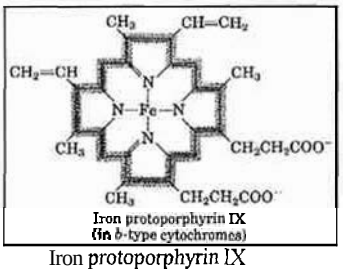
Oxidative phosphorylation occurs within the mitochondria of eukaryotic cells. Mitochondria are found inside eukaryotic cells and are hypothesized to be evolutionary remnants of an aerobic bacterium, capable of oxidative phosphorylation that formed a symbiotic relationship with a eukaryotic host cell. Mitochondria have an inner and an outer membrane. The outer membrane is very permeable to most molecules and ions. The inner membrane is highly impermeable, even to H^+ ions. This inner membrane holds the components of the respiratory chain (electron transport chain) and the enzyme complex that produces ATP. Mitochondria also have their own DNA within them and this is supportive evidence of their evolutionary origin.

b. Electron Transport/pH Coupling

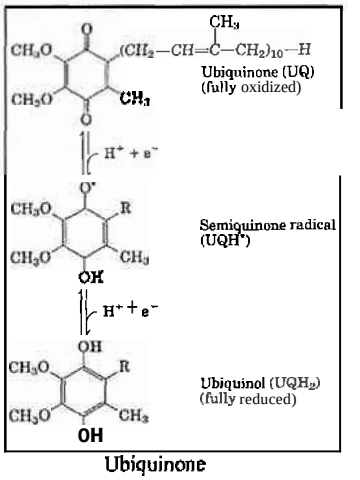
Within the inner membrane of mitochondria are integral proteins. These proteins contain prosthetic groups, which can transfer electrons to other proteins in a specific sequence. The prosthetic groups are a cytochrome, an iron-sulfur protein, or a ubiquinone.



Cytochrome C



Iron *protoporphyrin* IX



Ubiquinone

Figures modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p546.

The electron transfer occurs via one of three ways:

1. Reduction of the Fe^{3+} to Fe^{2+} (direct electron transfer)
2. Transfer of hydride ion
3. Transfer as a hydrogen atom

The cytochromes all contain a heme group, with Fe (an iron atom) in the center that performs the Fe^{3+} to Fe^{2+} reduction. See diagram below:

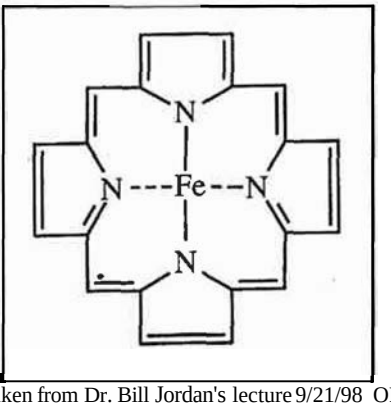


Figure taken from Dr. Bill Jordan's lecture 9/21/98 OPT 531

The Fe-S proteins have 1, 2 , or 4 Fe atoms bound to sulfur that can undergo reduction. See diagram below:

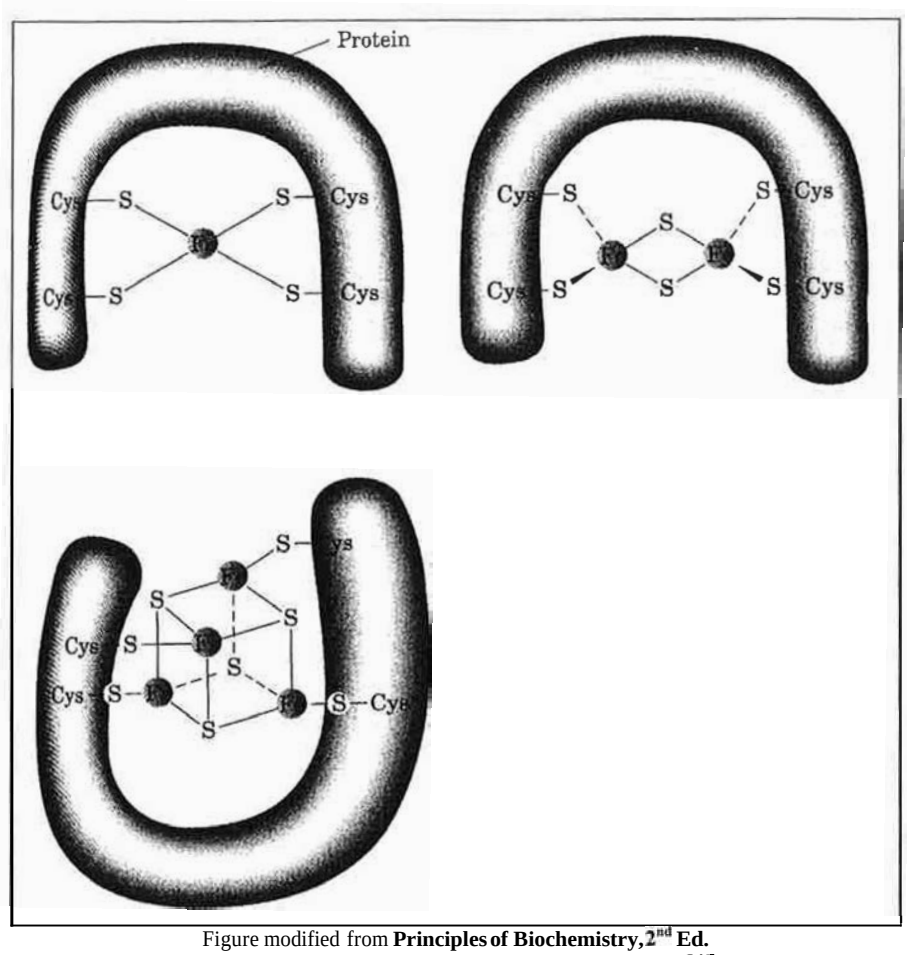


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p547.

And, finally, ubiquinone (AKA Coenzyme Q) can transfer electrons by accepting 1 or 2 electrons from donors. See figure on previous page showing ubiquinone.

The electron transport chain consists of 4 protein-enzyme complexes (I, 11,111, and IV). **Complexes** I, III, and IV are all within the mitochondria1 inner membrane and they all actively transport H^+ out of the mitochondrial matrix into the mitochondria1 interrnembrane space. This creates a proton gradient across the inner mitochondrion membrane, which drives the synthesis of ATP from ADP and P_i (inorganic phosphate). See figure below:

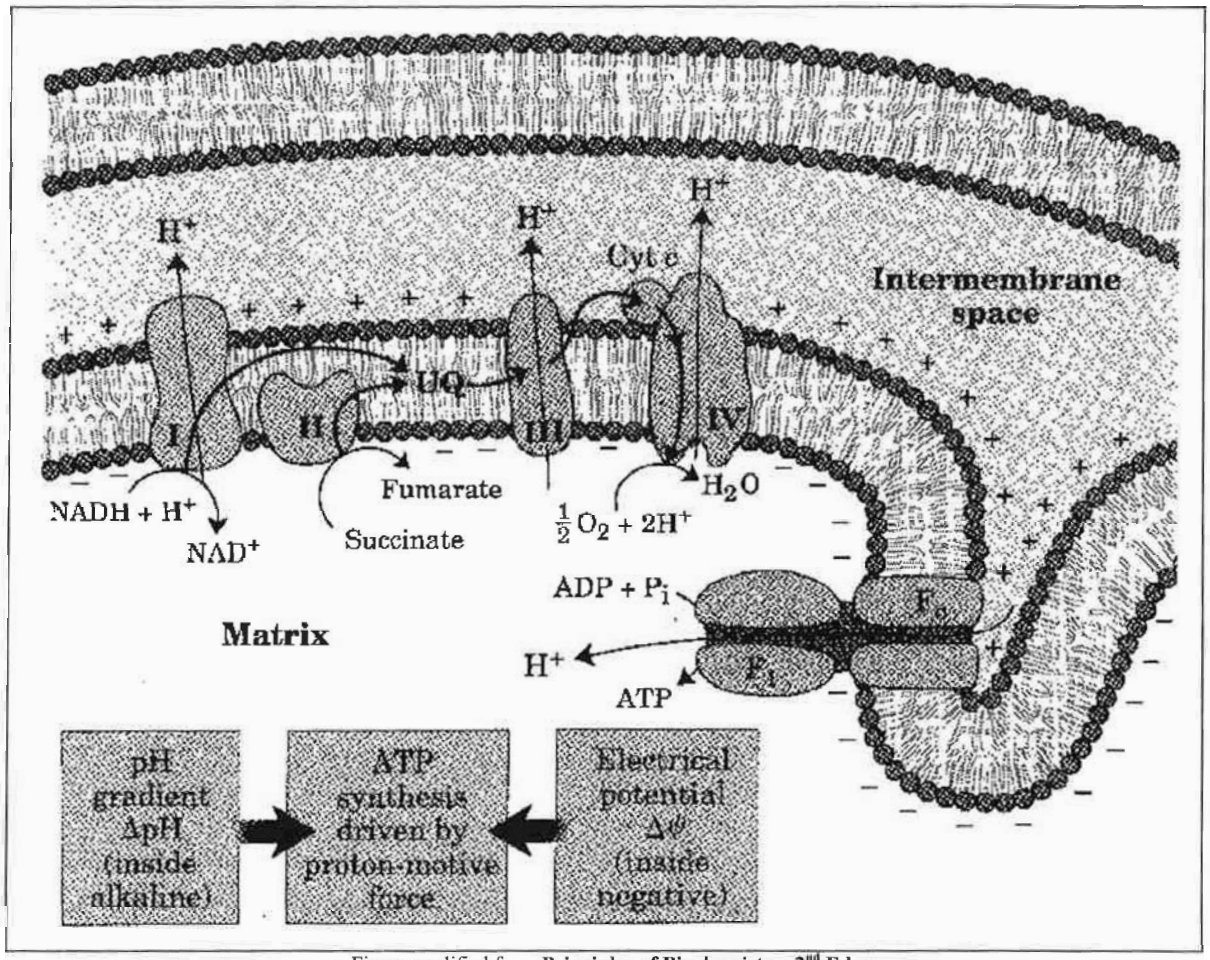


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p559.

E. Lipid Biochemistry

1. Structure and Function

a. Fatty Acids/Eicosanoids

Lipids found in biological systems all share one common trait: they are all insoluble in water. Fats and oils are the main storage forms of energy for many organisms. Phospholipids and sterols constitute roughly half the mass of membranes in living organisms. Many other lipids play important roles in the make up of compounds such as enzyme cofactors, electron carriers, pigments, hormones, and intracellular messengers.

Fatty acids are long, chain-like molecules made up mostly of hydrocarbon backbones and a carboxylic group on one end. Some fatty acids contain 3 carbon rings or hydroxyl groups. Below is the generic structure for a fully saturated fatty acid. Saturated means that there are no double bonds between carbon atoms.

$$CH_3(CH_2)_X\text{-}COOH$$

An unsaturated fatty acid contains one or more C=C double bond(s). These double bonds cause the fatty acid molecule to become "kinked" at the site of the double bond. See diagram below:

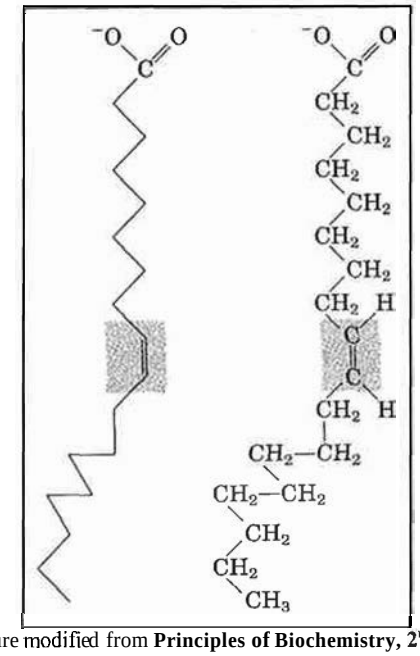


Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p242.

The long hydrocarbon chain is anywhere from 4 to 36 carbons in length. This portion is highly nonpolar and accounts for why fatty acids are water insoluble. The longer the hydrocarbon chain is in the fatty acid, and the fewer the double bonds, the lower the molecule's solubility in water. Fatty acids like to be packed next to one another, orderly, with their hydrocarbon chains running next to each other and their carboxylic groups lined up, as can be seen on the next page.

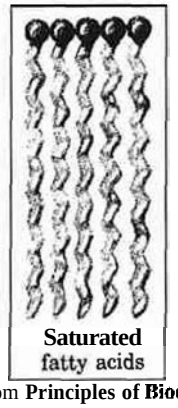


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p242.

Eicosanoids are a fatty acid derivative of arachidonic acid, which is a 20-carbon, polyunsaturated fatty acid. They act like hormones, but do not transport from tissue to tissue like hormones. They act upon the tissue in which they are produced. There are 3 classes of eicosanoids: prostaglandins, thromboxanes, and leukotrienes. The general structure of arachidonic acid and the three eicosanoids are shown below:

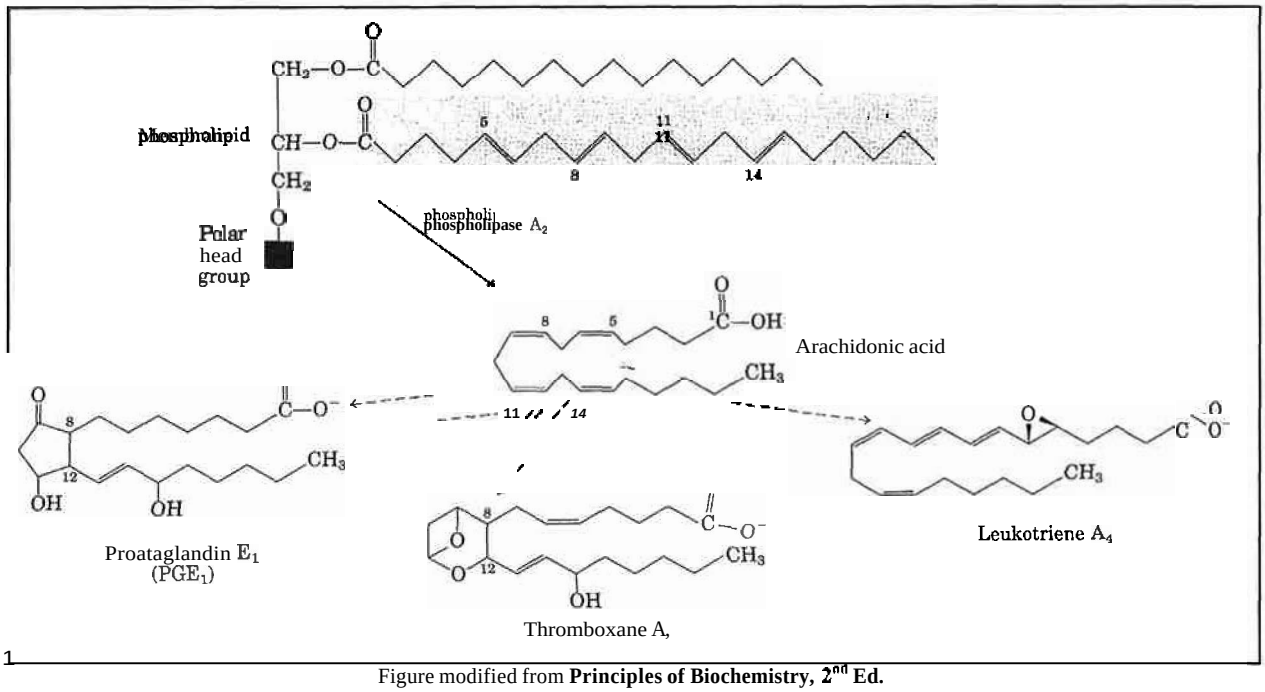


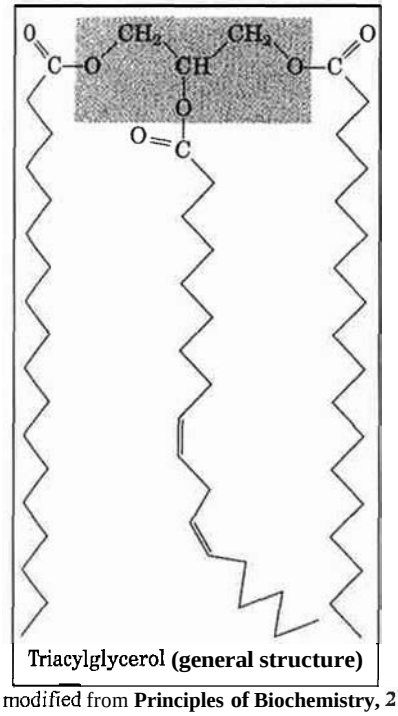
Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p258.

Prostaglandins act in most tissues by regulating the synthesis of cyclic AMP (cAMP). The function of prostaglandins ranges from stimulation of smooth muscle in the uterus during menstruation or labor, affecting blood flow to specific organs, the wake-sleep cycle, affecting the responsiveness to hormones (epinephrine or glucagons) in certain tissues, to elevating body temperature and causing inflammation resulting in the sensation of pain.

Thromboxanes are produced by blood platelets. They act in the formation of clots and reduce the flow of blood to the site of the clot.

Leukotrienes were first found in leukocytes. They act on muscle linings to induce strong contraction. Asthmatics have an overproduction of leukotrienes in the linings of their lungs. Leukotrienes account for the lung contractions found in anaphylactic shock and can be fatal, especially to those allergic to bee stings, penicillin, or other agents.

b. Triacylglycerols (Also known as triglycerides)
Triglycerides are the simplest of lipids formed from fatty acids. The basic structure is 3 fatty acids linked to one glycerol via ester linkage. See below:



Triacylglycerol **(general structure)**

Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p243.

The fatty acids can be all the same, or any mixture of different fatty acids. Triglycerides are *nonpolar*, hydrophobic molecules that are essentially water insoluble. The function of triglycerides is energy storage within cells. They form "oil droplets" within the cytosol, serving as metabolic fuel reservoirs. Specialized cells called adipose, or "fat cells," in vertebrates store large amounts of triglycerides. Can anyone say cellulite?

c. Phosphoglycerides (Also known as glycerophospholipids)
The basic structure of phosphoglycerides is shown on the following page.

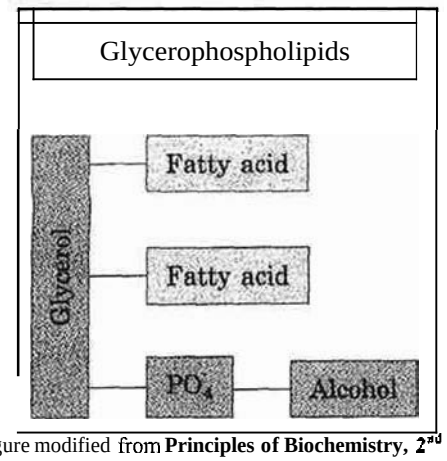


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p247.

A polar alcohol is linked to glycerol via a phosphodiester bond. And, similar to triglycerides, two fatty acids are ester linked to the glycerol. The fatty acids can be any combination, but the polar head group is always a derivative of phosphatidic acid. Phosphoglycerides function as membranes in the form of lipid bilayers. Lipid bilayers will be discussed in a later section.

d. Sphingolipids

A second class of membrane lipids is known as the sphingolipids. Unlike phosphoglycerides and triglycerides, sphingolipids do not contain glycerol. Sphingolipids *are* composed of the long-chain amino alcohol Sphingosine, or one of its derivatives. Attached to this are a fatty acid chain and either a polar head alcohol or a phosphoric acid in diester linkage to the polar head group. Shown below is the basic structure of sphingolipids:

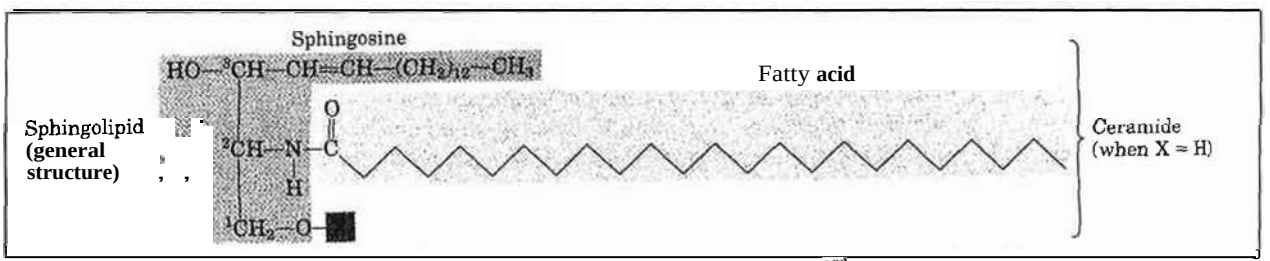
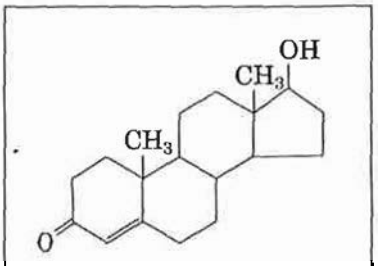


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p250.

e. Sterol derivatives

Sterols are compounds consisting of a characteristic backbone with 4 fused rings (3 have 6 carbons, 1 has 5 carbons). Testosterone is the example shown on the next page.



Testosterone

Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and **Cox.** Worth Publishers. 1993. p257.

Sterols are structural lipids within membranes of most eukaryotic cells. In addition to structural support, other sterols function as precursors for a wide range of compounds with specific biological activities. Examples are: cholesterol, bile acid, and sex hormones (progesterone and testosterone).

f. Isoprenoids
Isoprenoids are lipids synthesized from precursors related to isoprene:

Isoprene $CH_2=C(CH_3)-CH=CH_2$

A few examples of isoprenoids are the essential vitamins A, D, E, and K. Other isoprenoids act as enzymatic cofactors, electron carriers, or as intracellular signals.

2. Digestion, Absorption, and Transport of Lipids (e.g., types of lipoproteins)

Lipids are absorbed in the small intestine. They mostly come in the form of triglycerides. These simple lipids however, are still too large to be directly absorbed. Bile salts, like taurocholic acid, are released from the gallbladder after ingestion of a fatty meal. These salts act like detergent to break down the triglycerides into microscopic *micelles* (very tiny spherical oil droplets). The formation of micelles significantly increases the action of *lipases* **(enzymes that** break down lipids into monoglycerides, diglycerides, free fatty acids, and glycerol). These products can then diffuse into intestinal epithelial cells. At this point they are repackaged into lipoprotein aggregates called *chylomicrons* and **are now** in the form of triglycerides bound to cholesterol and specific proteins, called *apoproteins*. Different combinations of proteins and lipids produce particles with varying densities. They range from very Iow-density lipoproteins (VLDL), low-density lipoproteins (LDL), to high-density lipoproteins (HDL). Chylomicrons now move from intestinal cells into the lymphatic system, and then into the blood where they are carried to muscle and adipose tissue. Here they are broken down into fatty acids and glycerol by *lipoprotein lipase*. The cells *in* the muscle and/or fat tissue can **now** absorb them. In muscle, fatty acids are now oxidized for **energy, and** in **adipose** tissue they are re-esterified into triglycerides for storage.

3. Fatty Acid Metabolism (e.g., beta-oxidation, ketone bodies, gluconeogenesis)

Beta-oxidation of fatty acids occurs within the mitochondria. Remember that fatty acids are long chains of carbohydrates with a carboxyl group on one end. In β−oxidation, 2 carbon units are removed at a time from the fatty acid by an oxidation reaction catalyzed by dehydvogenases. Each 2-carbon unit then forms an acetyl-CoA. Beta-oxidation is the 1st of three steps in fatty acid oxidation. The 2nd step is when acetyl-CoA is oxidized to CO_2 in the Citric Acid Cycle, and the final step is the electron transfer/oxidative phosphorylation process, which yields ATP.

Ketone bodies are produced from acetyl-CoA when glucose levels in the blood are low (either during DM or starvation), or for transport to other tissues in the body. Low blood glucose causes oxaloacetate to be utilized in production of more glucose (gluconeogenesis), rather than to accept acetyl-CoA into the Citric Acid Cycle. Thus, a build up of excess acetyl-CoA occurs and its conversion to a "ketone body" is favored. The three types of ketone bodies that can be formed are acetoacetate, *D-β-hydroxybutyrate,* and acetone. Acetone is exhaled out the lungs, while the other 2 can be used as emergency energy sources by skeletal muscle, heart muscle, and the brain. See diagram below:

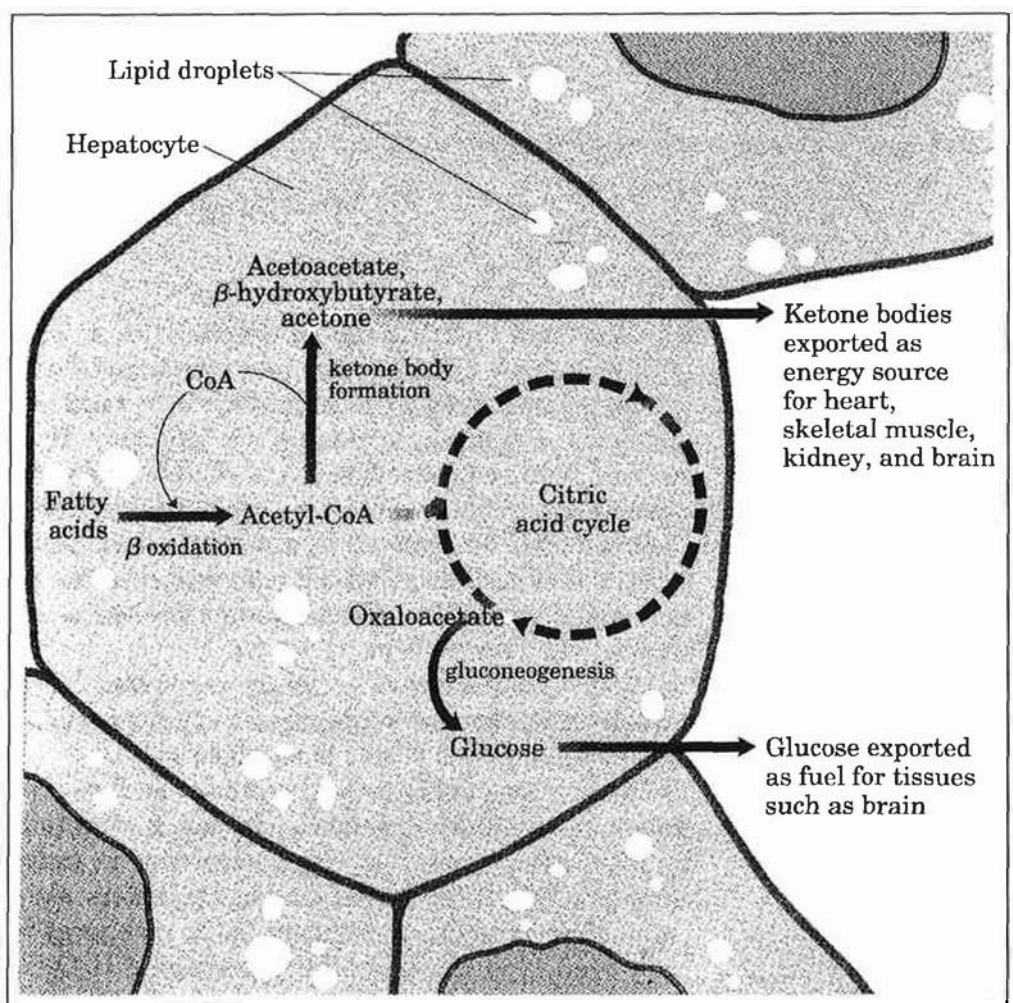
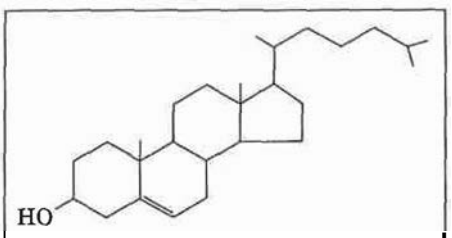


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p501.

4. Cholesterol and steroid metabolism

Cholesterol is the precursor molecule to many important compounds, including steroids, vitamin-D, and bile acids. Cholesterol is usually created in the liver from acetyl-CoA. It is a very complex set of reactions and I wouldn't bother trying to memorize the details. See pages 669-674 of Principles of Biochemistry 2nd Ed, (1993) in the library for the nit-picky details, if you feel the need to. Cholesterol has the classic sterol backbone as seen here:



Cholesterol

Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p674.

All steroid hormones come from cholesterol. These are synthesized in either the cortex of the adrenal gland (mineralocorticoids), by the kidney (glucocorticoids), or in the gonads/placenta (sex hormones: testosterone, estradiol, progesterone). Bile acids and their salts are created in the liver and function to aid in the digestion of lipids. Vitamin D (also known as cholecalciferol) is a cholesterol derivative and a precursor to the hormone 1,25-dihydroxycholecalciferol, which regulates calcium uptake in the intestines, as well as balancing the deposit and release of calcium and phosphate in bones.

5. Membrane biochemistry

a. Unit membrane/lipid bilayer

Biological membranes are mostly made up of polar lipids and proteins. The lipids are amphipathic in nature (they contain a polar hydrophilic head and a non-polar, hydrophobic tail). This characteristic is key to the role membranes play in cellular interactions.

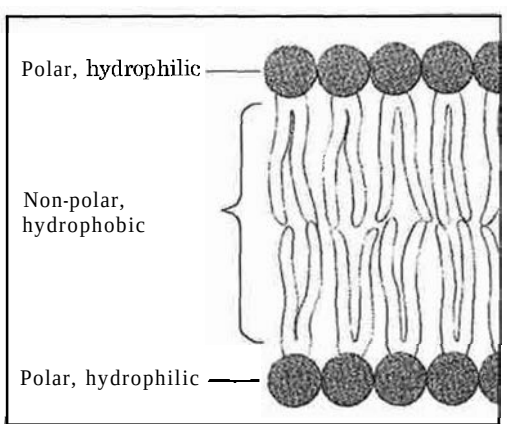


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p276.

They align as shown in the figure above creating a physiological barrier that is selectively permeable to polar solutes, yet permeable to non-polar ones, and is called a lipid bilayer.

b. Fluid mosaic model

The molecules in the membranes (lipids and proteins) are "fluid" because they interact with each other through non-covalent bonds. The exception is protein-to-protein interactions. See below for a typical rendition of the model:

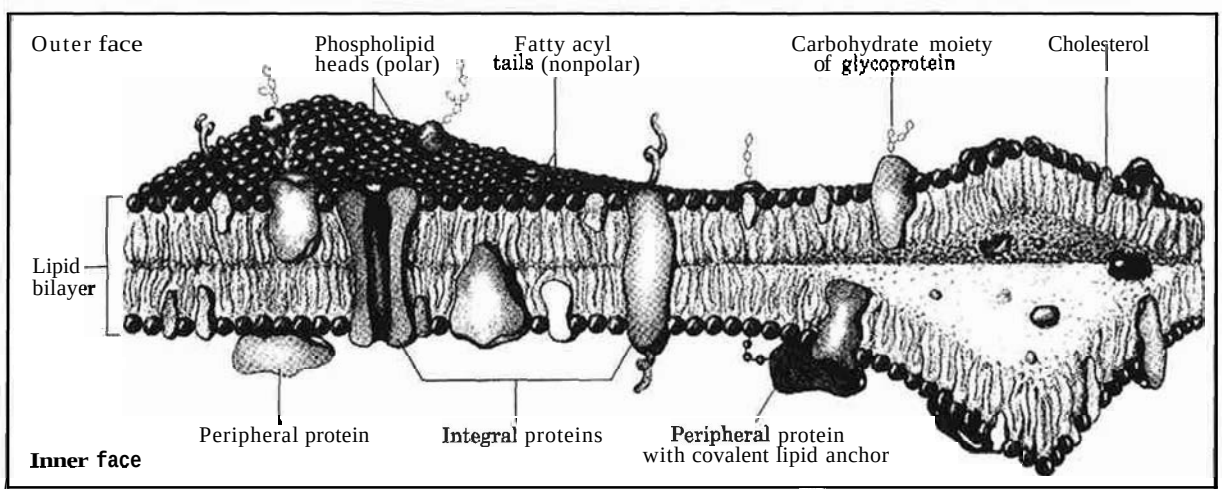


Figure modified from **Principles** of **Biochemistry, 2nd** Ed.
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p272.

c. Membrane proteins and lipids/structure and function

Lipid structure was noted above. Proteins associated with membranes are either peripheral or integral to the membrane. Peripheral proteins are bound loosely or at least reversibly to the membrane. Whereas, integral proteins are firmly bound and may even span the entire width of the membrane.

The function of membrane lipids is primarily as a barrier to polar solutes. The function of membrane proteins is much more diverse. These can vary from light absorption (as seen in rhodopsin in the membranes of rod cells) to simple transport conduits for specific solutes, as well as chemical receptors for hormones.

F. Molecular Biology

1. DNA structure and function

a. Deoxynucleotides and synthesis

Remember that nucleotides have a nitrogenous base, a pentose, and a phosphate group.

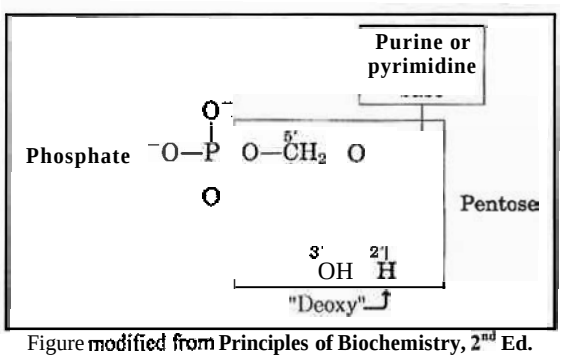


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p325.

The nitrogenous base is joined covalently to the pentose sugar, at the 1' carbon. The base can either be a purine or a pyrimidine. The purine bases found in DNA are adenine and guanine. The 2 types of pyrimidines are cytosine or thymine. The pentose in DNA is 2'-deoxy-.-ribose, and is shown in the figure above. Below are the structures of the nitrogenous bases found in DNA:

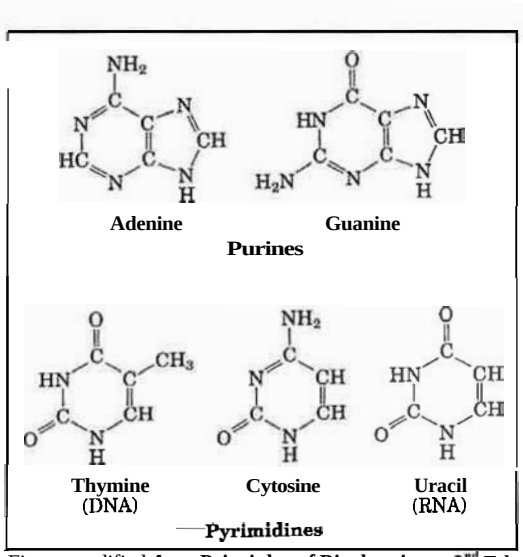


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p674.

b. Base pairing/double helix

DNA is made up of successive nucleotides, bound together by phosphodiester linkage between the 5'-hydroxyl group of one nucleotide and the 3'-hydroxyl group of the next nucleotide, as seen in diagram on the following page.

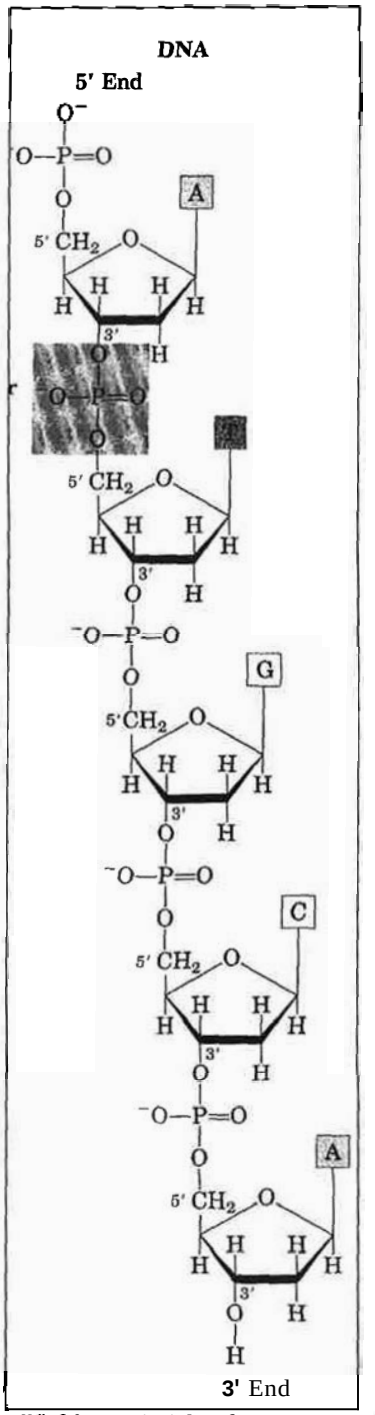


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p328.

Each strand of DNA is thus aligned in either a 5'→3' order. When two strands of DNA combine to form a DNA molecule, the classic, right-handed, double helix is formed. The strands must run in opposite polarity to each other (one runs 5'→3', the other runs 3'→5'). The negatively charged phosphate groups and the hydrophilic deoxyriboses all point toward the outside of the helix and interact with the surrounding environment. On the inside of the helix, the hydrophobic bases interact with each other as is seen in the figure on the next page.

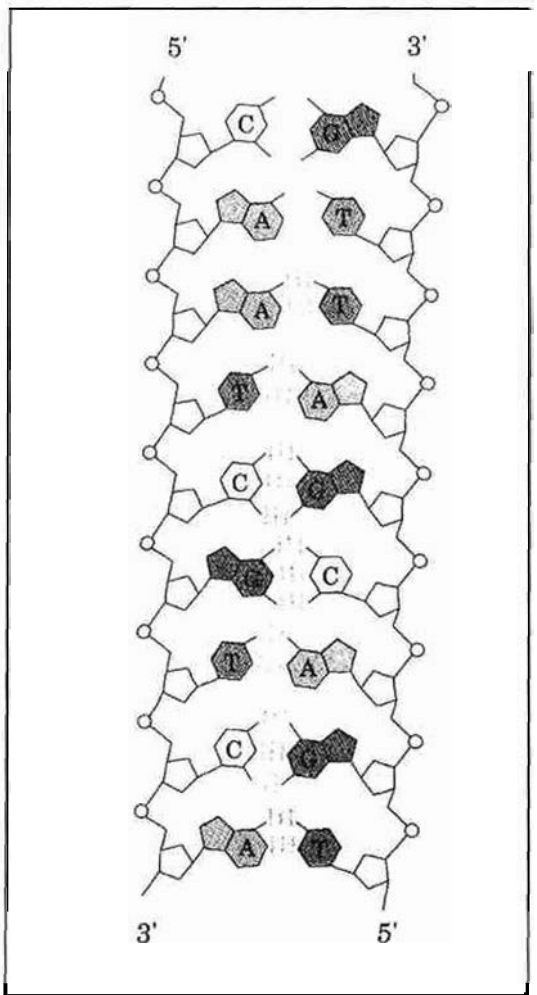


Figure **modified** from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p335.

Interestingly, James Watson and Francis Crick (DNA's discoverers) found that only thymine (T) will interact with adenine (A), and only cytosine (C) will interact with guanine (G). Thus, base pairs (A-T), (T-A), (G-C), and (C-G) are extremely important factors in keeping DNA's structure.

c. Genetic code/introns, exons

The genetic code is the specific set of triplet code in either **DNA** or mRNA that code for the amino acids of proteins. Introns are nsn-translated segments of DNA. In other words, these are nucleotide sequences within DNA that do not code for the amino acid sequence of the polypeptide formed from that DNA. Exons are the segments that do code for the amino acids. Remember, exons are "extremely" important. This will help you remember that they are the ones that actually code for proteins.

d. Chromosome structure

Chromosomes are the packaged form of all the cellular genes within a cell. Chromosomes are linear structures of DNA. At both ends of the chromosome are telomeres, which are long

sequences of base pairs that help stabilize the chromosome, Each chromosome also has one centromere, which also consists of a long sequence of highly repetitive DNA. The function of the centromere is an attachment point for the chromosome during cell division. The centromere attaches to proteins in the microtubules of the mitotic spindle. This attachment ensures proper segregation of chromosomes to daughter cells.

2. RNA structure and function

a. Ribonucleotides and synthesis

Ribonucleotides (RNA) differ from DNA by a few characteristics. The first difference is the hydrogen/hydroxyl group found on the pentose at the 2' position. Note the basic structure of a DNA molecule shown in the previous section covering DNA structure. Compare that figure to the one shown below of RNA:

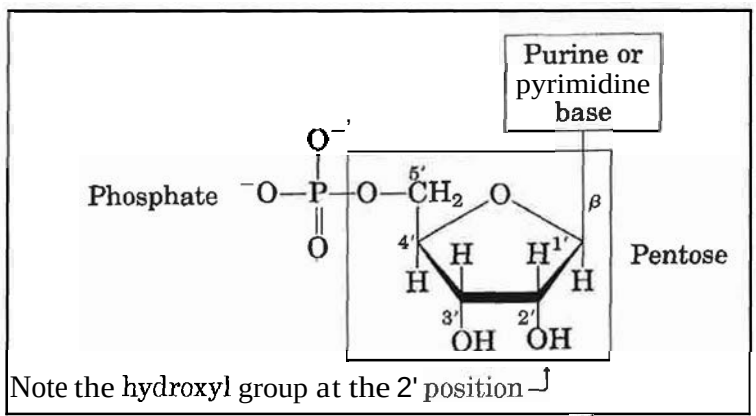


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p325.

The second difference between DNA and RNA has to do with the nitrogenous bases. RNA contains the bases adenine, cytosine and guanine, just as DNA. However, RNA contains little to no thymine, but instead has uracil. Finally, RNA is single stranded, and DNA is double stranded. RNA is much more versatile than DNA, as it can function as a catalyst and as an information molecule. Yet, nearly all RNA is obtained from DNA templates, through a process called ***Transcription.*** Three classes of RNA result from transcription: mRNA (Messenger RNA), tRNA (Transfer RNA), and rRNA (Ribosomal RNA). The specifics on their individual structure and function are covered in the next few sections.

Transcription differs from **DNA** replication in a few ways as well. First, it does not require a primer in order *to* initiate. Transcription begins with something called promoters, which are specific sequences on the DNA **template.** The second way transcription differs from replication is that it **does** not fully **copy** the entire DNA sequence. Promoters along the DNA template initiate fragmented synthesis allowing for more efficient **copying** rather than copying much unnecessary information. Transcription is similar ***to*** replication in that an enzyme is required for it to occur. This enzyme is called DNA-directed RNA Polymerase. It copies the DNA template in the 3'→5' direction, just as is done in DNA replication. Also, the same base pairings are created in transcription (with the exception that no thymine is used, and uracil takes its place).

In order to copy the DNA double strand, the RNA Polymerase must unwind a portion of the helix, forming a "transcription bubble" as seen below.

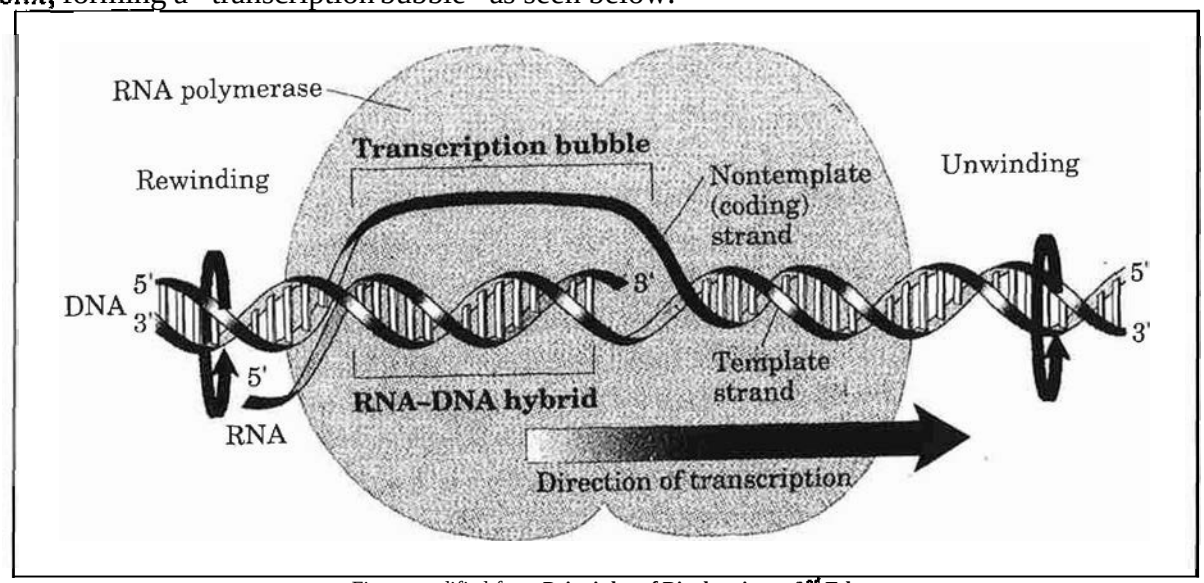


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p858.

b. Messenger RNA synthesis and function

Messenger RNA (mRNA) is one of three different classes of RNA (mRNA, tRNA, and rRNA). Its function is to take the genetic information from the chromosome to the ribosomes. Once transcription has yielded its product of RNA (called a primary transcript at this point), it is full of unnecessary information known as introns. This useless information is excised by a process called "splicing," and the result is Messenger RNA. After the splicing is complete, a protective cap is placed on the 5' end of the mRNA. It is made up of a modified guanosine triphosphate and not only protects the mRNA from hydrolytic enzymes, but also may signal where the ribosome should attach for protein synthesis. On the 3' end, a polymer of adenylate residues is attached. They also function to reduce the likelihood of degradation.

c. Ribosomal RNA synthesis and function

Ribosomal RNA begins as a Preribosomal RNA transcript (designated as 45S). This transcript contains many introns (shown in white in figure below) and is thus cleaved into smaller, more useful pieces (exons – the black areas in figure below) by enzymes and produces the 18S rRNA, the 5.8S rRNA, and the 28S rRNA. There is another Preribosomal RNA transcript, which produces the 16S rRNA, the 23S rRNA, and the 5S rRNA, and it is called 30S. See figure on next page.

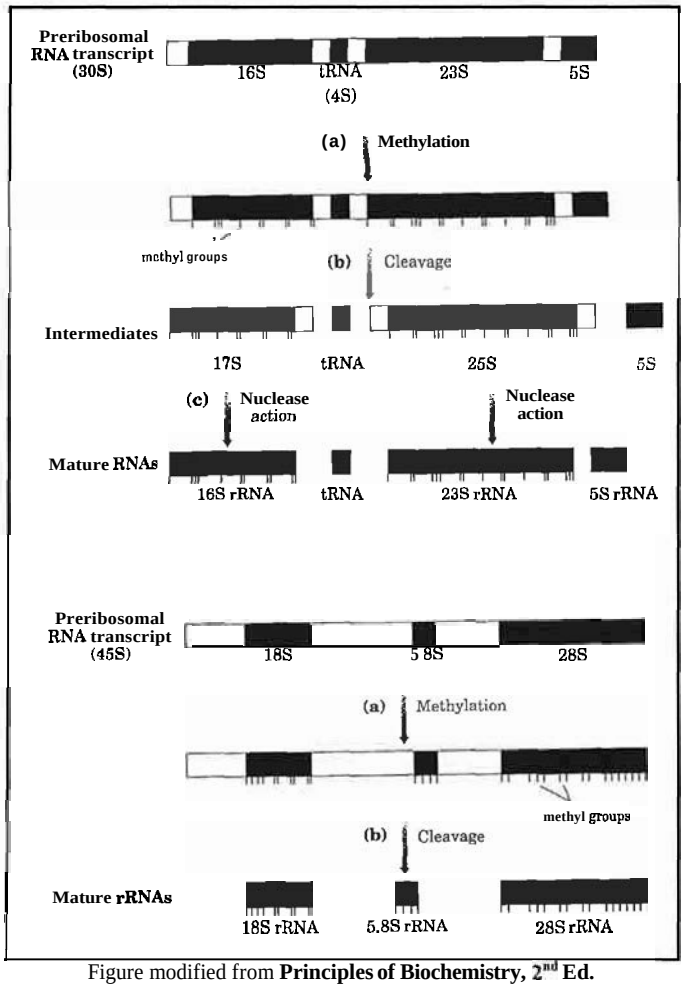


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and **Cox.** Worth Publishers. 1993. p875.

These fragments of RNA then associate with proteins and form the mechanical feature known as a Ribosome. Ribosomes are the site of protein synthesis. Ribosome function will be covered in more detail in a later section.

d. Transfer RNA synthesis and function
Transfer RNA (tRNA) is an adapter molecule in protein synthesis. It reads the code on the mRNA and also helps direct the correct amino acid into place on the growing polypeptide during protein synthesis. Similar to rRNA, tRNA begins as a Preribosomal RNA transcript and its introns are cleaved forming tRNA. See the figure above.

3. *DNA replication*

DNA replication is the means by which genetic information is passed on from cell to cell, or parent to offspring. The process is governed by a few rules. First, DNA replication is ***semiconservative.*** This means that when one DNA molecule is synthesized, it contains one strand from the "old" DNA strand, and one from the "new" strand. A once popular theory was that DNA synthesis was ***conservative.*** This would mean that each molecule of DNA was produced by: either two strands of parental DNA, or two strands of "new" DNA. However, this

hypothesis would never yield hybrid forms of DNA, which we now know exist. Below shows pictorial examples of both conservative and semiconservative replication:

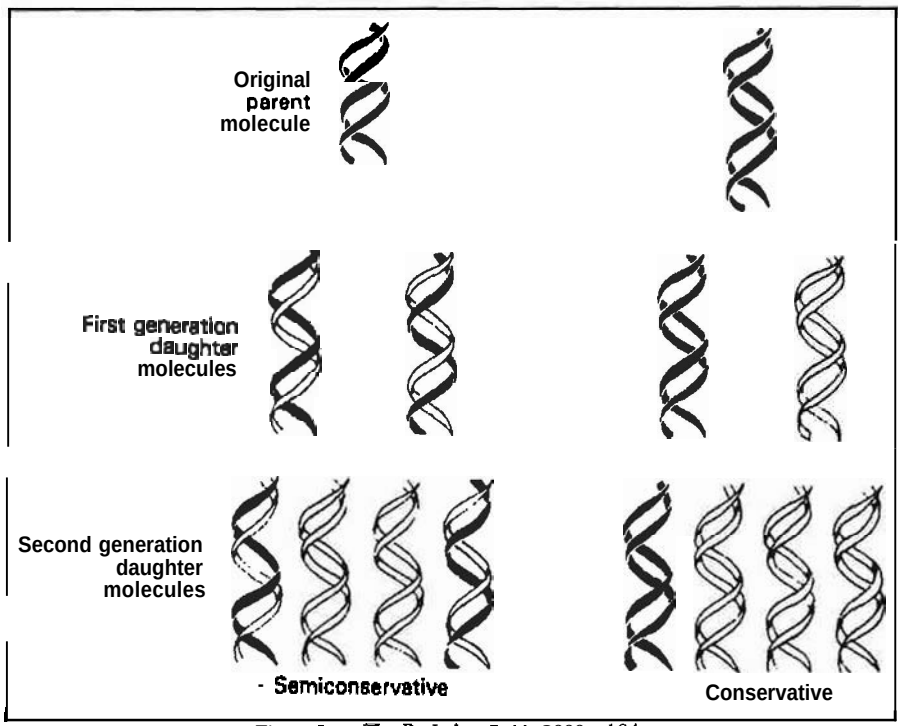


Figure from The Berkeley Guide 2000, p194.

The second rule is that replication begins at an origin and usually proceeds bi-directionally. Finally, DNA synthesis always occurs in the **5'→3'** direction and is semi-discontinuous. This means that as the Leading strand is synthesizing continuously, the Lagging strand must produce fragments. Note in the figure below, if both strands were to continuously synthesize, the Lagging strand would have to work in the 3'→5' direction. The result of this discontinuous type of synthesis produces *Okazaki Fragments*.

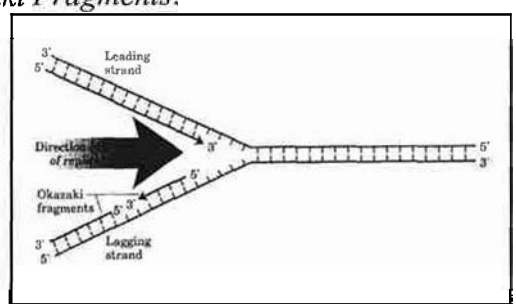


Figure modified from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and **Cox.** Worth Publishers. 1993. p819.

Replication is a process involving three steps: ***initiation, elongation, and termination.*** The steps differ from each other by the enzymes that perpetuate them and the products produced. The details of these steps are identical to that of protein synthesis and will be discussed in the section on "Protein Synthesis."

4. Protein Synthesis

a. Ribosome function

In eukaryotic cells, ribosomes function as the place where protein translation (synthesis) occurs. Three subunits make up the ribosome. One is labeled the 80S subunit and is the largest of the three. The "S" refers to the molecule's sedimentation coefficient. The other two subunits are labeled 60S and 40S. When these three subunits are fit together to form a ribosome, there is a cleft formed between them. Within this cleft is where the mRNA molecule passes through during translation.

b. Initiation, elongation, and termination

Initiation, elongation, and termination are common steps in the synthesis of: proteins, DNA, and RNA. In protein synthesis, a mRNA molecule, which contains the code for the polypeptide to be made, will bind to the ribosome's 40S subunit. Then, a tRNA molecule, which is bound to its amino acid will also combine with the ribosome. The first amino acid-tRNA complex is always MET-tRNA. Once these three (ribosome, tRNA complex, and mRNA) have combined, along with initiator proteins, the structure formed is called an initiation complex. The aminoacyl tRNA (MET-tRNA) then base-pairs with the initiation codon on the mRNA (AUG), which signifies the beginning of protein synthesis. See diagram below:

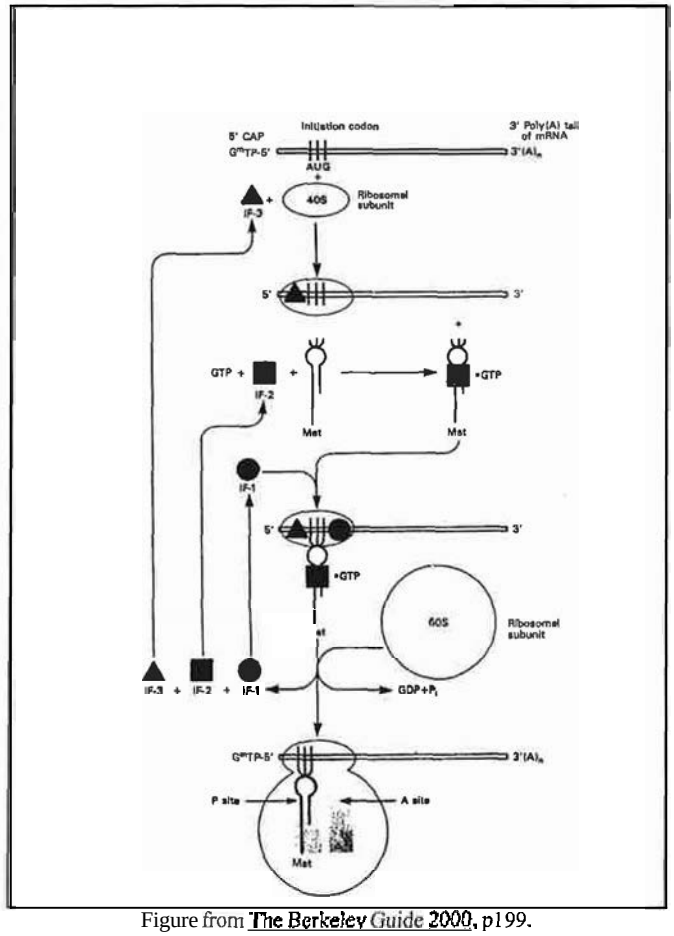


Figure from The Berkeley Guide 2000, p199.

Elongation of the polypeptide occurs as each new codon from the mRNA approaches the ribosome. As this happens, its complementary aminoacyl-tRNA base-pairs to it. The amino acids are then covalently attached to lengthen the polypeptide. Elongation is propagated by cytosolic proteins called elongation factors. Every time a new aminoacyl-tRNA binds to the ribosome, as well as every time the ribosome moves along the mRNA, a price must be paid. This price comes in the form of GTP hydrolysis. Therefore, every amino acid added to the polypeptide costs 2 GTP.

Termination of protein synthesis occurs when the termination codon from the mRNA reaches the ribosome. This causes the release of the polypeptide from the ribosome, as well as the break up of the ribosomal subunits. This entire termination process is aided by non-ribosomal proteins called release factors.

c. Post-translational modification/protein sorting
Few polypeptides are fully functional when just synthesized. They may require the addition of acetyl, phosphate, methyl, carboxyl, or other groups to certain amino acid residues; attachment of prosthetic groups or oligosaccharides; need to be folded; may need to have one or more amino acid residues removed; or it may even need to be proteolytically cleaved.

5. Gene expression and regulation

It is estimated that there are over 100,000 genes in the human genome. Of these, few are expressed at any one time. This must therefore be a regulated system. Regulation of gene expression is a critical component for cellular metabolism as well as during development. Also, since protein synthesis has such a high energetic cost, gene expression regulation is utilized here as well. There are 6 main ways to regulate the amount of a protein formed. The diagram below shows these 6 processes:

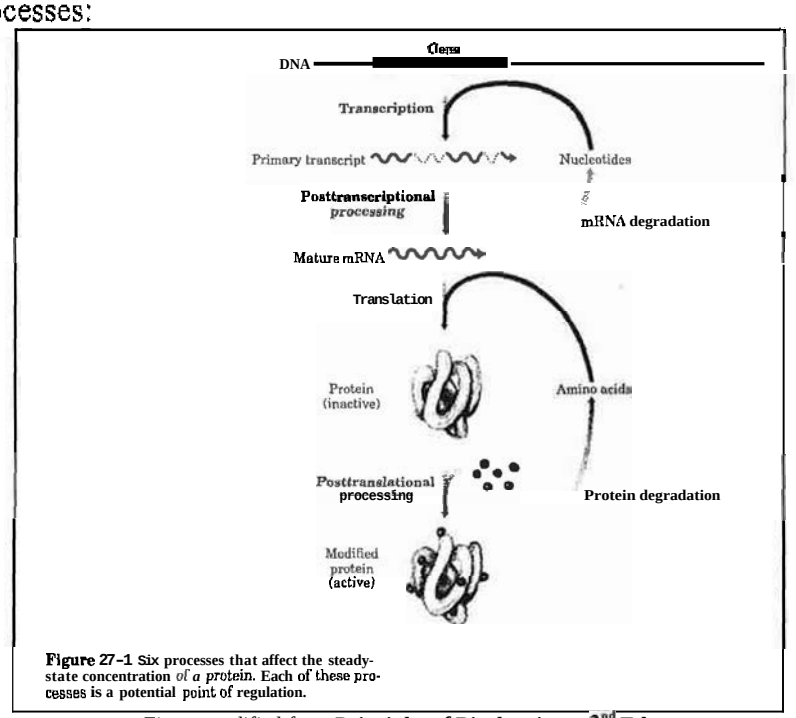


Figure 27-1 Six processes that affect the steady-state concentration of a protein. Each of these processes is a potential point of regulation.

Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p942.

Gene regulation is the most efficient way of doing this since it is the first step in the pathway.

6. Mutations and repair

Damage to the base pair sequence of DNA that is not repaired is called a lesion. If this unrepaired DNA is replicated and transmitted to future generations, it becomes permanent. At this point it is called a "mutation." A mutation can be a simple replacement of one base pair for another, or an addition or deletion of one or more base pairs. Since there are so many genes in the human genome, it is not always bad when a mutation occurs. If no harmful effects result, the mutation is said to be "silent." Even favorable mutations can occur, although they are quite rare.

Every cell has multiple DNA repair systems. There are repair systems for base-pair mismatches, base-excisions, nucleotide-excisions, and direct repairs of the main sequence. Sometimes the damage is too **extensive** and can result in what is known as error-prone repair. The typical mammalian cell accumulates thousands of lesions in a 24-hour period, but thanks to DNA repair systems, only 111,000 will result in a mutation.

7. Oncogenes/proto-oncogenes/tumor suppressor genes

Oncogenes are cancer-causing genes. They may be any of several mutant genes that cause cells to exhibit rapid, uncontrolled proliferation. Cellular genes, usually ones that code for regulatory proteins, that are converted into oncogenes are referred to as proto-oncogenes. These proto-oncogenes usually encode for proteins involved in cellular growth, cell division, development, or gene regulation.

Tumor suppressor genes behave in the opposite manner. They inhibit the formation of tumors within cells. They are even sometimes referred to as "anti-oncogenes." They act like recessive alleles; as long as the cell has at least one normal allele, then the tumor suppression continues. This is in contrast to the oncogene, which acts as a dominant allele; just one allele will predispose the cell to tumor formation.

8. Tools of Recombinant DNA Technology

a. DNA mapping/cloning

The techniques of locating, isolating, preparing, and studying small segments of DNA, derived from much larger chromosomes, is commonly referred to as "DNA cloning." Recombinant DNA technology, also known as genetic engineering, involves the use of five basic procedures. First, a method for cutting DNA at exact locations. This is accomplished via sequence specific endonucleases. Secondly, a method for binding two pieces of DNA together covalently, using DNA ligase. The third procedure involves the selection of a small, self-replicating molecule of DNA. Fourth, a method is needed to move recombinant DNA into a host cell that can provide the recombinant DNA with replication "machinery." Finally, a method is needed to select host cells that contain recombinant DNA. DNA mapping involves the identification of relative positions of genes on a DNA molecule and of the distance between them.

b. Polymerase chain reaction

Polymerase chain reaction (PCR) is a process utilized to amplify DNA segments. It was invented by Kary Mullis in 1984. DNA strands are first heated to separate them, and then annealed with short synthetic primers of target DNA. The four deoxynucleotide triphosphates are added, and the primed DNA is then selectively replicated. This process is repeated about 25 times to produce an amplification of the original DNA sample by about 10^6-fold. See the figure below for details.

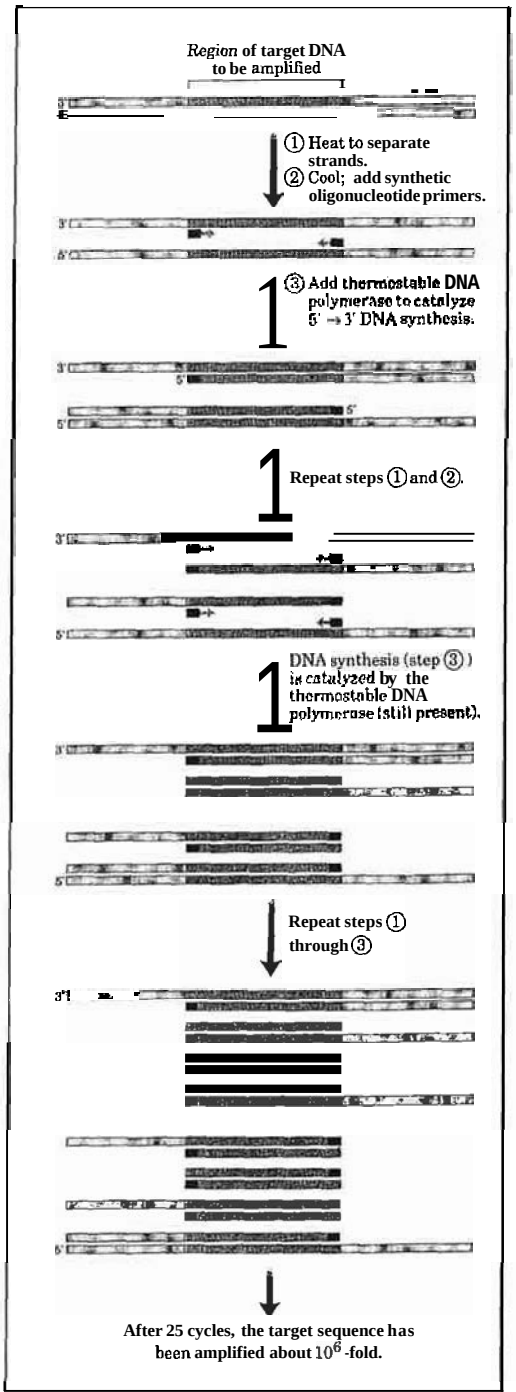


Figure taken from **Principles of Biochemistry, 2nd Ed.** Lehninger, Nelson, and Cox. Worth Publishers. 1993. p998.

c. Chromosome analysis

Since a single gene is only a very small portion of a chromosome, it is difficult to find the segment of DNA that contains a particular gene. Biochemists have devised a method for finding genes that involves two steps. The first step is to build a DNA library made up of thousands of DNA fragments. These fragments are derived from the cellular chromosome. Next, the specific gene that is desired is located by its one distinguishing feature; its DNA sequence. Forensic specialists utilize these techniques to identify suspects by DNA samples collected at crime scenes. This is referred to as DNA fingerprinting. You do not need to know the nitty-gritty details for boards though.

G. Nutrition

1. Digestion of proteins, carbohydrates and lipids

The digestion of protein begins in the stomach. First, mucosal cells, within the stomach lining, produce the hormone gastrin. This stimulates the secretion of HCl (Hydrochloric acid) by the Parietal cells within the gastric glands as well as pepsinogen by the Chief cells. Both Parietal cells and Chief cells are located within the stomach lining. Pepsinogen is an inactive form of the enzyme pepsin. Once secreted into the gastric juices, pepsin then activates pepsinogen into pepsin. Pepsin cleaves the protein molecules by hydrolyzing peptide bonds. This breaks down the larger polypeptide into many smaller ones. Next, the now acidic stomach contents dump into the small intestine. Once here, the low pH causes the secretion of the hormone Secretin into the bloodstream. Secretin then goes to the pancreas and perpetuates the release of bicarbonate into the small intestine. The bicarbonate helps to raise the pH by neutralizing the HCl. When the amino acids reach the duodenum, the hormone cholecystokinin is released into the bloodstream and stimulates the pancreas to secrete the precursors for the enzymes trypsin, chymotrypsin, and carboxypeptidase. The pancreas protects itself from being digested by releasing these enzymes in their inactive, or zymogenic, form. Enteropeptidase then activates trypsinogen (trypsin's inactive form) into trypsin. Activated trypsin can then catalyze the inactive forms of both trypsinogen and chymotrypsinogen into their respective active forms; trypsin and chymotrypsin. These active forms will hydrolyze the amino acid chains further into smaller and smaller pieces. A further use for trypsin is to activate the zymogenic form of carboxypeptidase called procarboxypeptidase. Carboxypeptidase is a zinc-containing enzyme that also breaks down the now smaller peptide molecules. A final peptidase is released by the small intestine, called aminopeptidase. This completes the break down process of the protein into free amino acids. The free amino acids are now small enough to be transported across the epithelial lining of the small intestine and into the bloodstream. See figure on next page.

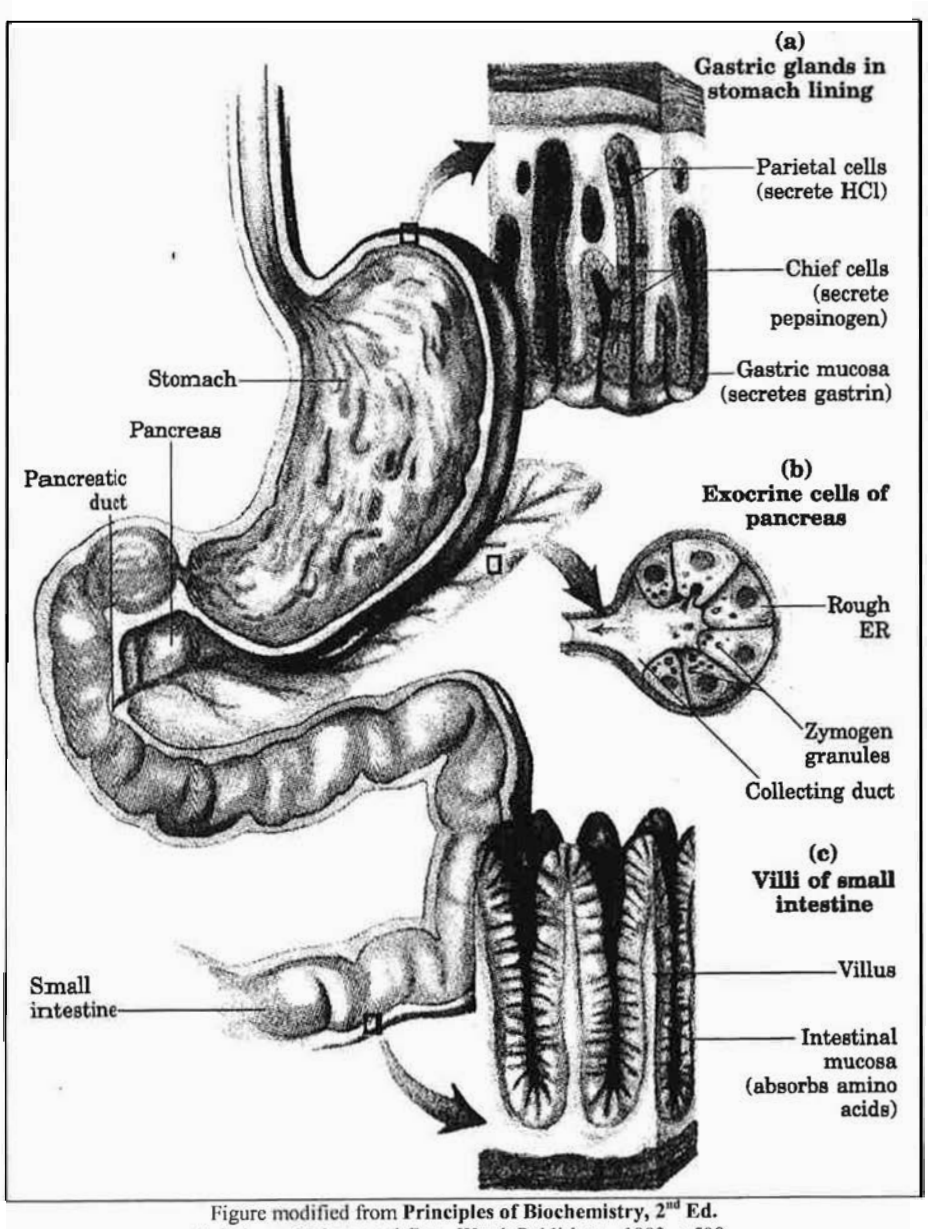


Figure modified from **Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. Worth Publishers. 1993. p509.

Dietary disaccharides (examples include maltose, lactose and sucrose) are hydrolyzed in the small intestine into monosaccharides by specific enzymes for each different disaccharide. Examples of monosaccharides include glucose, fructose and ribose. See figure below for the specific reactions.

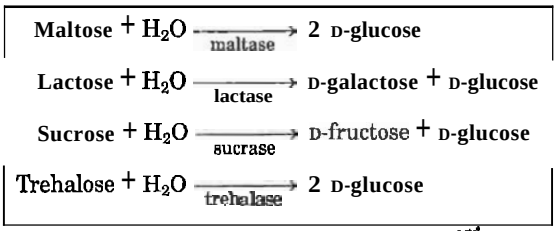


Figure taken **from Principles of Biochemistry, 2nd Ed.**
Lehninger, Nelson, and Cox. **Worth** Publishers. 1993. p424.

These monosaccharides are then transported across the epithelium of the cells lining the small intestine and enter the bloodstream. Next, they are carried to the liver and are subsequently phosphorylated and enter the glycolytic pathway.

Enzymes in the intestine help to hydrolyze triacylglycerols (lipids) to ease their absorption and digestion. These enzymes are generally referred to as lipases. Adipocytes (fat cells to you and me) contain Iipases that help break down stored lipids, releasing fatty acids to be exported to other tissues in the body for use as fuel.

2. Essential Amino Acids

Essential amino acids are those that cannot be produced by the human body itself. In other words, you must eat it. Current theory says that there are eight essential amino acids for an adult, and one extra one for young children. The list includes:

- Histidine
- Isoleucine
- Leucine
- Lysine
- Methionine
- Phenylalanine
- Threonine
- Tryptophan
- Valine
- and the one needed by children is Arginine

3. Vitamins

a. Classification
Vitamins are classified based upon their solubility. They are either water-soluble or fat-soluble.
The fat-soluble vitamins are: K, A, D, and E. Remember, "KADE is fat"
The water-solublevitamins are: C (ascorbic acid), Niacin, folacin (folate), riboflavin (B_{12}), thiamin (B_1), and pyridoxine (B_6).

b. Function
Vitamins are essential micronutrients taken in through the diet.

Vitamin K is utilized as a cofactor and is required for normal blood clotting. Deficiency leads to slow blood clotting. Warfarin is a synthetic form of vitamin K and is used both as rat poison and an anticoagulant medication in humans.

Vitamin A (Retinol) is required for vision. Deficiency in vitamin A can lead to: night blindness, dry eye, dry skin, retarded growth, and sterility in males.

Vitamin D is a precursor to the hormone 1,25-dihydroxycholecalciferol. This hormone regulates the uptake of calcium in the intestine. It also regulates the release and deposition of both calcium

and phosphate in bones, keeping these two balanced. Deficiency leads to Ricket's Disease, a defective bone formation disorder.

Vitamin E is a potent antioxidant. This will be covered in the next section. Deficiency in humans is extremely rare but could cause scaly skin, muscular weakness, wasting and sterility.

Vitamin C's primary function is to assist in the production of collagen. It is also an antioxidant, which again will be covered below. Deficiency in this vitamin can lead to scurvy, a disease that causes rotten teeth and gums.

Niacin is used by the metabolic machinery of our bodies to produce derivatives such as NAD, and NADP, which are coenzymes in oxidation-reduction reactions. Deficiency of niacin leads to a disease called pellagra. Pellagra causes cutaneous, mucous membrane, CNS, and GI symptoms. **Advanced** deficiency includes symmetric photosensitive rash, scarlet stomatitis, glossitis, diarrhea, and mental aberrations.

Folacin is used by the body to form red blood cells and also helps in the formation of genetic material within cells. Deficiency can cause anemia, weight loss, weakness, and the birth defect known as spina bifida.

Riboflavin (vitamin B_2), acts as an essential coenzyme in many oxidation-reduction reactions involved with carbohydrate metabolism. Deficiency results in oral, ocular, cutaneous, and genital lesions.

Thiamin (vitamin B_1), participates in carbohydrate metabolism through decarboxylation of α-keto acids. Thiamine also acts as coenzyme to the apoenzyme transketolase in the pentose monophosphate pathway for glucose. Deficiency causes Beriberi with peripheral neurologic, cerebral, cardiovascular, and GI symptomatology.

Pyridoxine (vitamin B_6), functions as a coenzyme in many reactions. Consequently, the vitamin B_6 group is important in blood, CNS, and skin metabolism. Primary deficiency is rare, because most foods contain vitamin B_6. Secondary deficiency can result from malabsorption, alcoholism, oral contraceptive use, chemical inactivation by drugs (i.e., isonicotinic acid hydrazide, cycloserine, hydralazine, penicillamine), excessive loss, and increased metabolic activity. Deficiency in adults is usually anemia and in children it can cause convulsions.

4. Minerals

Minerals are the inorganic nutrients that we must have in our diets. There are six macrominerals and nine trace minerals that are considered to be essential to humans. These are the minerals that we need daily in order to function. The macrominerals function as electrolytes, and as essential components of bones and teeth. Trace minerals act as components of enzymes or as part of the endocrine system.

The macrominerals are: sodium, potassium, calcium, magnesium, phosphate, and chloride. The nine trace minerals are: iron, iodine, fluorine, zinc, chromium, selenium, manganese, molybdenum, and copper.

5. Oxygen toxicity/antioxidants/control of free radical, peroxide, and superoxide

Oxygen toxicity occurs with the administration of oxygen at concentrations greater than 60% for periods of time greater than 12-24 hours. Oxygen produces free radical toxic metabolites that can damage pulmonary cell membranes. Alveolar capillary endothelial damage results, leading to pulmonary edema from increased capillary permeability. Impaired gas exchange occurs, inflammatory cells congregate, and pulmonary fibrosis is the end result.

Antioxidants are chemical protectors against free radicals within living organisms. Examples of antioxidants are: glutathione, vitamin C, carotenoids, and vitamin E. Free radicals result when oxidation-reduction reactions go awry. Usually these reactions produce a net exchange of electrons that is balanced (i.e., one molecule is oxidized and one is reduced). However, some highly reactive molecules can oxidize stable molecules and cause them to become unstable species, which we know as free radicals.

A free radical is a molecule with an unpaired electron that can be positive, negative or not charged at all. Some are stable, but most are highly reactive. Free radicals can cause chain reactions that perpetuate themselves and can cause major damage, on a molecular and cellular scale.

In a free radical chain reaction, there are three steps. First, the initiation step, free radicals are formed by molecules that easily give up electrons, like hydrogen peroxide. In the next step, calledpropagation, the "chain-carrying radicals" are alternately consumed and produced. In the final step, termination, the radicals are destroyed. Therefore, unless a molecule comes along that can bring about the termination step, the free radical will damage any and all accepting molecules. Antioxidants play the role of terminator!

Within biological systems there are four common oxygen metabolites that are free radicals: hydrogen peroxide (H_2O_2), superoxide ($O_2^{-}\bullet$), hydroxyl radical ($OH\bullet$), and singlet oxygen ($^1O_2$). Free radicals can induce local injury by reacting with lipids, proteins, and nucleic acids. The interaction of free radicals with cellular lipids leads to membrane damage and the generation of lipid peroxide byproducts. Despite the actions of antioxidant nutrients, some oxidative damage will occur, and accumulation of this damage throughout life is believed to be a major contributing factor to aging and disease.

General Physiology

Pertinent Classes: Opt 531 Ocular Anatomy, Physiology, and Biochemistry
Useful Text: **Human Physiology, 3rd Ed.** Rhoades, Rodney & Pflanzer, Richard Sanders College Publishing, 1996

A. Cellular Functions

1. Cytoplasm and Cytoskeleton:

Cytoplasm is a substance with a complex internal structure, in which cellular components are found. The internal structure is made up of cytoskeleton.
The cytoskeleton is composed of specialized proteins in the cytosol, which maintain the cell shape and positions of organelles. It also mediates movement of the cell and movement of the organelles within the cell. It is made up of different types of protein fibers:

i. Microtubules and Intermediate Filaments – Found in deeper regions of the cell. They influence the distribution of microfilaments and, therefore, influence the overall cytoskeleton design.
ii. Microfilaments – Just below the plasma membrane and extend into cell processes.
iii. Myosin Filaments

Microtubules and microfilaments are dynamic structures. Their formation is readily reversed and their distribution is subject to change as the physiological conditions of the cell change. Intermediate filaments are much more stable – formation may be irreversible.

	Diameter (nM)	Structure	Protein Subunit
Microtubules	24	Hollow	Tubulin
Intermediate Filaments	10	Hollow	Several types
Microfilaments	6	Solid	Actin
Myosin Filaments	15	Solid	Myosin

2. Functions of Organelles

Nucleus: Contains almost all the cell's DNA. Separated from the cytoplasm by the nuclear membrane, a double membrane. Minute pores in the membrane allow for communication with the endoplasmic reticulum.

Nucleoli: Found in the nuclear membrane and it the site for ribosomal RNA synthesis.

Endoplasmic Reticulum: A network of tubes running throughout the cytoplasm. It is continuous with the plasma and nuclear membranes. It provides a surface area for chemical reactions and is a pathway for transportation of molecules within the cell. It also stores synthesized molecules. It plays a role in both lipid and protein synthesis.

Ribosomes: Are located on the outer surface of the ER, some are found free in the cytoplasm. They are used in protein synthesis.

Golgi Complex: Consists of 4-8 flattened sacs called Cisternae. The ends expand and separate from the complex and are known as secretory vesicles. They package and secrete certain proteins and lipids, synthesis carbohydrates, and combines carbohydrates and proteins to form glycoproteins.

Mitochondria: Found throughout the cytoplasm. Has a double membrane in which the outer is portion is smooth and the inner is arranged in a series of folds called Cristae, because of these folds there is a large surface area in which chemical reactions occur. They produce ATP.

Lysosomes: Has a single membrane and they contain powerful digestive enzymes.

Centrioles: Play a role in cell division and as basal bodies in the formation of cilia and flagella.

3. Intracellular and Extracellular Environment:

Intracellular: The fluid within the cells. It has a relatively low concentration of sodium ions and a high concentration of potassium ions.

Extracellular: The fluid outside of the cells. Contains a high concentration of sodium ions and a low concentration of potassium ions. It is the medium of exchange between cells and the external environment.

There are 4 types of external fluid:

i. Interstitial fluid: between cells
ii. Plasma: fluid portion of blood
iii. Lymph: fluid in the lymphatic vessels
iv. Cerebrospinal fluid: an ultrafiltrate of plasma.

4. Membrane Potential and Transport Mechanisms:

Membrane potential: an electrical potential is established when there is a difference in the net charge between the inside and outside of a cell. In many nerve cells the electrical potential across the membrane is –60 mV. Voltage differences across the membrane are measured with extracellular voltage as a reference a minus sign, therefore, indicates that the cell is more negative than the extracellular fluid. Cells are more negative due to the presence of large negatively charged organic anions, these are charged amino acids and proteins that are too large to pass through the ion channels of the membrane.

Transport Mechanisms: There are two types of movement across a plasma membrane.

i. Passive movement - occurs due to concentration gradients and results in a less concentrated state overall
ii. Active movement – oppose gradients and produce a more concentrated sate overall. Requires carrier proteins and energy.

Passive Transport includes:

i. Simple Diffusion: Usually involves lipid soluble substances that pass directly through the lipid interior of the plasma membrane.
ii. Facilitated Diffusion: Uses a protein that enables the passage of the substance.

Active transport includes:

i. Primary Active Transport: the movement of the solute is directly linked to an energy yielding reaction. (Ex. Na^+/K^+ ATPase pump)
ii. Secondary Active Transport: active transport is not linked directly to the energy yielding reactions.

5. Membrane Receptors and Post Receptor Events

A receptor is a protein to which a signal molecule can bind with high specificity and affinity. Signal molecules bind to membrane receptors and produce a response without gaining entry to the cell. They do this via second messengers.

Second messengers amplify the signal molecules signal because multiple second messengers are produced by one bound signal molecule.

Three examples of second messengers:

i. Cyclic AMP: The binding of the signal molecule activates Adenylate Cyclase, which generates cyclic AMP that, in turn, acts as a second messenger
ii. Calcium Ions: binding of signal molecule causes a membrane channel to open allowing for: a. Influx of ions into electrically excitable nerve or muscle cell triggering an
action potential or

b. Influx of ion (ex. Ca^{2+}) to such a point that concentration is high enough such
that the ion acts as a second messenger

iii. Inositoltriphosphate and Diacylglycerol: Binding of signal molecule activates Phospholipase C which catalyzes the breakdown of Phosphatidylinositol Biphosphate into Inositol Triphosphate and Diaclyglycerol which act as second messengers.

B. Respiration

1. Mechanisms of Breathing:

The diaphragm contracts and pushes the abdominal contents down and, therefore, enlarges the plural space. At the same time the ribcage is pushed outward which also increases the pleural space. The increase in pleural space volume decreases the pleural space pressure, which causes the lungs to expand and fill with air.

Muscular movements during inspiration:

Normal inspiration: Diaphragm is the only respiratory muscle used.
Forced inspiration: External intercostals muscles are recruited to pull the rib cage up and out to increase the thoracic cavity. Accessory muscles can also be used during deep and heavy breathing, such as during intense exercise.

Expiration: Diaphragm relaxes, the thoracic cavity decreases and the lungs deflate. During normal breathing expiration is a passive process but with forced expiration expiratory muscles are activated. Expiratory muscles include muscles of the abdominal walls and the internal intercostals muscles. Abdominal muscles help push the diaphragm up and the internal intercostals muscles pull the rib cage down.

2. Gas Exchange in the Lungs:

Gas exchange occurs in the alveoli, microscopic air sacs that are surrounded by a network of capillaries that allow blood and air within the alveolus to be brought into close contact. Oxygen diffuses across the walls of the alveolus into the blood while carbon dioxide diffuses from the blood into the alveolus.

3. Diffusion of O_2 and CO_2

As inspired air reaches the Alveoli its speed approaches zero. Primary movement of air, now becomes diffusion rather than bulk flow. The partial pressure of oxygen in the Alveoli is sufficient to drive oxygen into the capillaries. Carbon Dioxide in venous blood also has correct partial pressure to move CO_2 in the opposite direction to O_2 (i.e. from capillaries into Alveoli).

4. Oxygen Transport and Hypoxia, Carbon Dioxide Transport

Most Oxygen is transported to the body via Red Blood Cells. Hemoglobin allows for the efficient transport of large amounts of Oxygen. Each Hemoglobin molecule contains four heme molecules which each contain an iron atom. Each iron atom is capable of binding with an O_2 molecule. If partial pressure of Oxygen is high (like in the lungs) it binds with a heme, however, when partial pressure of Oxygen is low (like in the tissues) Hemoglobin releases the oxygen.

Hypoxia is the condition of low Oxygen (ex. as in high altitudes). The chief immediate response to hypoxia is hyperventilation. The long terms effects of hypoxia are an increase in Red Blood Cells. This allows more Oxygen to be carried to the body but causes blood to become more viscous and, therefore, increases the workload on the heart.

Carbon Dioxide Transport: Carbon Dioxide is transported to the lungs in three different ways:

i. 60% of CO_2 is transported as Bicarbonate ions
ii. CO_2 can combine loosely to some amino groups of Hemoglobin to form Carbaminohemoglobin. Hemoglobin has higher affinity for CO_2 when Hemoglobin is deoxygenated.
iii. A small amount (7-10%) of CO_2 is transported in a dissolved state in the plasma and Red Blood Cells.

All three transportation methods are readily reversible in the lungs. The blood never completely empties of Oxygen in the tissues or Carbon Dioxide in the lungs, that is, some O_2 and some CO_2 always remains in the blood.

5. Regulation of the Respiratory Rate:

Oxygen, Carbon Dioxide, and Hydrogen ions can all change alveolar ventilation by changing rate and depth of breathing.

There are two sets of chemoreceptors in the body that monitor levels of O_2, CO_2, and H^+. One set is in the Medulla and they are known as the Central Chemoreceptors. They only monitor levels of cerebral spinal fluid Hydrogen ions. The second set, the peripheral chemoreceptors, are located in the arch of the aorta (the aortic bodies) and in the neck at the bifurcation of the common carotid artery (the carotid bodies). These receptors respond mainly to changes in oxygen tension but are also stimulated by changes in carbon dioxide tensions and hydrogen ion concentration. Carbon dioxide is most influential on alveolar ventilation, followed by pH and then oxygen levels. If CO_2 levels increase alveolar ventilation is increased to blow-off excess CO_2. That is hyperventilation occurs.

6. Acid Base Balance

Carbon dioxide is transported as bicarbonate ions:

$$CO_2 + H_2O \leftarrow \rightarrow H_2CO_3 \leftarrow \rightarrow H^+ + HCO_3^-$$

If Hypoventilation occurs CO_2 is not removed as quickly as it is produced, therefore, as is seen in the above equation H^+ concentration also rises and blood becomes more acidic. The respiratory system acts to minimize pH changes in blood. This can be done by adding a fixed acid or base to the blood or by adding or removing CO_2.

A free acid is any acid other than carbonic acid. The concentration of fixed acids is not affected by lung function. If blood is made more acidic by addition of a fixed acid the decrease in pH reflexively increases ventilation. The respiratory system brings blood pH closer to normal, but it cannot eliminate a fixed acid or base from the body, therefore, a normal pH cannot be restored.

C. Gastrointestinal Activity

1. Absorption:

The major function of the gastrointestinal system is to absorb water and dissolved materials. Absorption is to a large degree, accomplished by epithelial cells lining the surface of the small intestine. Significant amounts of water and inorganic salts are, however, absorbed in the proximal large intestine.

Absorption is via active transport and diffusion. Most absorption of organic constituents of the contents of the small intestine occurs midway through the small intestine. However, the lower small intestine can also absorb digestive products and, therefore, acts as a reserve absorptive area if some food escapes prior absorption. The small intestine has a very large surface area due to numerous infoldings and the presence of villi and microvilli it is, therefore, well suited for absorption.

Water is absorbed via osmosis. A gradient is created via the transport of sugars, amino acids, and other molecules into the blood. Active transport of sodium ions from the colon is the primary absorptive process that occurs in the large intestine. This creates a gradient by which water is also absorbed. The large intestine does not absorb carbohydrates, proteins, or fat digestion products.

2. Motility:

There are two basic types of motor activity:

1) Mixing movements: Mix digestive secretions with food, thereby, aiding digestion. This movement also aids absorption by bringing contents into contact with absorptive surfaces.

2) Propulsive movements: The rate of propulsion varies with each organ and depends on the organ's function. (ex, movement form mouth through pharynx and esophagus is very

rapid, whereas movement from the stomach through the small and large intestine is very slow to allow time for digestion and absorption.)

Motility in the digestive tract is via peristalsis, a contractile wave that propels the digestive contents down the digestive tract.

3. Nervous and Hormonal Regulation:

There is very little regulation of digestion and absorption motility and secretion are, however, regulated by both neural and hormonal mechanisms. Receptors of the tract include sensory nerve receptors (ex. chemoreceptors which respond to chemical agents in the contents of the tract and mechanoreceptors that respond to the distention of the tract.)

The Vagus nerve, which is a parasympathetic preganglionic nerve, is the major motor and secretory external nerve of the digestive tract. Most of the vagal efferent fibers are cholinergic and excitatory, however, the splanchnic nerves are sympathetic and adrenergic and they depress the excitability of the system.

There is also regulation by short reflexes, nerve plexuses present in the wall of the digestive tract. These short reflexes can be excitatory or inhibitory.

Hormonal Control: There are four hormones of gastrointestinal origin:

i. Gastrin
ii. Cholecystokinin (CCK)
iii. Secretin
iv. Gastric Inhibitory Peptide (GIP)

They are all important in the control of motility and secretion. These hormones are released from cells found throughout the epithelial lining of certain regions of the tract. The hormones are released into the blood where they travel to target organs and exert their effect.

4. Associated Structures:

Salivary glands: Saliva softens and lubricates food and neutralizes acidic products produced by oral bacteria. Saliva is produced in the acinar cells of the parotid, submaxillary, and sublingual glands.

Parotid glands contain serous cells that produce amylase, a digestive enzyme that helps break down starch. The submaxillary and sublingual glands contain serous cells and mucous cells that secrete mucin, which when combined with the watery secretion of serous cells forms mucous. Parasympathetic cholinergic and sympathetic adrenergic stimulation both excite salivary secretion. The parasympathetic nerves are, however, more important.

Pancreas: Delivers an exocrine secretion to the duodenum. The secretion contains digestive enzymes as well as a high concentration of sodium bicarbonate, which neutralizes acid from the stomach.

Pancreatic juice is capable of nearly completing digestion in the absence of all other digestive secretions. Secretion by the pancreas is controlled by the hormones secretin and cholecystokinin.

Liver: Liver cells, hepatocytes, secrete bile, which is stored in the gallbladder. With food present bile is moved through the common bile duct into the small intestine. It plays a role in the digestion and absorption of fat. Bile is composed of bile salts, bile pigments, cholesterol, lecithin, chloride, bicarbonate, and sodium. Cholecystokinin stimulates the release of bile.

D. Muscle

1. Neuromuscular Junctions:

Alpha motor neurons are nerve cells in the spinal cord that control the contraction of skeletal muscles. Synaptic connections are formed with skeletal muscles at neuromuscular junctions. Acetylcholine is the neurotransmitter that is used; it binds to nicotinic receptors, which causes depolarization of the membrane and from this contraction of the muscle.

2. Conduction and Contraction

The tension of a muscle can be controlled in two ways:

1) a motor neuron can control the tension developed by a single muscle fiber with the frequency of action potentials it generates. This is the frequency code of contractile force.

2) More motor neurons and, therefore, more motor units can be recruited to increase the force of contraction. This is known as the motor system's population code.

The cells of muscles are surrounded by electrically excitable plasma membrane. The surface membrane can then be excited to produce an action potential. These action potentials are caused by time and voltage dependent changes in permeability of the membrane to sodium and potassium ions.

The action potential spreads throughout the large muscle cell via the transverse tubular system. The T-tubules are an inward extension of the plasma membrane – the interior of the T-tubules is continuous with extracellular space. This allows for rapid activation of skeletal muscle.

The Sarcoplasmic Reticulum stores and releases ionized calcium, which is the substance that controls muscle contraction. Upon activation by an action potential the sarcoplasmic

reticulum releases a large amount of Ca^{2+} into the cytoplasm near the myofilaments. The myofilaments are then freed from their resting state and contraction occurs. With the movement of Ca^{2+} back into the sarcoplasmic reticulum relaxation occurs.

In the presence of calcium the troponin molecule undergoes a conformational change, thereby, allowing actin and myosin to interact.

Prior to calcium being released each myosin head has an ATP bound to it, when myosin and actin are able to interact the myosin head attaches to the actin filament at approximately 90 degrees and ATP loses a phosphate ion. The energy created brings the angle of attachment closer to 45 degrees. This pulls the actin filaments in toward the center of the sarcomere. The ADP molecule is released from the myosin. With the reattachment of an ATP molecule the myosin head detaches and readies itself for another cycle.

Structure of Skeletal Muscle

There are two types of protein filaments that make up skeletal muscle. When viewed with an electron microscope they appear as a repeating pattern of dark and light cross banding. These protein filaments are called myofilaments and they are organized into a sarcomere. The center portion of the sarcomere is made up of thick filaments (called the A band) composed of myosin. The outer regions are composed of thin filaments called actin.

The M-lines run across the middle of the A band and hold the thick filaments in side-by-side alignment. The region that contains only thin filaments is called the I-band.

The Z-line marks the center of each I-band and serves to mark the boundary of the sarcomere.

The H-zone is the center region of the A-band where the thin filaments of the I-band have not penetrated.

Contraction occurs, not due to length change of thick or thin filaments, but by a change in the amount of their overlap. i.e. the length of the A-band stays constant but with contraction the length of the I-band decreases.

The thin filaments are associated with a molecule called tropomyosin that in turn is composed of a protein complex called troponin.

3. Types of Contraction:

Isometric contraction: the muscle does not do any external shortening; rather, it develops force/tension while pulling against immovable attachments.

Isotonic contraction: Force in the muscle remains constant while the muscle shortens.

Auxotonic contraction:	The force continually increases as the muscle shortens.
Meiotonic contraction:	The force lessons as the muscle shortens.

Real life contractions usually involve a combination of the above types of contraction.

4. Reflex Arc:

There are sensory neurons that have fiber processes within skeletal muscles. These neurons convey information to the CNS regarding the state of contraction and tension in muscle fibers. Some sensory neurons innervate intrafusal muscle fibers and form the muscle spindle, while others innervate tendons to form the Golgi tendon organs.

Muscle Spindles detect the length of the muscle and its velocity of contraction. It acts as a stretch receptor and increases its action potentials when the intrafusal fibers stretch.

Golgi Tendon Organs transmit information about the force or tension produced by the contraction of the muscle. With an increase in tension from the muscle contraction, the Golgi tendon organ increases its action potentials.

Information from both the muscle spindles and Golgi tendon organs is sent to the spinal cord where it is forwarded to somatic sensory cortex or is used within the spinal cord for reflex action.

Stretch Reflex (aka: Knee Jerk Reflex):

Tapping the patellar tendon, below the knee, stretches muscle spindles, which causes action potentials to move along the muscle spindle sensory neurons. The sensory neurons form a synaptic connection with motor neurons that cause the leg to extend. In order for this to occur, however, antagonistic muscles must be inhibited. Inhibition occurs due to activation of inhibitory interneurons within the spinal cord.

5. Smooth Muscle (aka Visceral Muscle):

Smooth muscle has involuntary action and is under control of the autonomic nervous system. It is found in internal organs such as the stomach and intestines. Smooth muscle is also composed of thick and thin filaments, however, they are not organized into ordered sarcomeres. In general smooth muscle is involved in homeostasis.

E. Body Fluids

1. Composition of Body Fluids:

There are two categories of fluids in the body, which differ in both composition and volume but have the same solute concentration. These two categories are:

i. Intracellular: Contains more potassium, magnesium, and protein then does the extracellular fluid. Contains approximately two thirds of body water.
ii. Extracellular: Contains approximately one third of body water. Can be subdivided into
a. interstitial fluid and Lymph
b. Blood plasma: nearly identical to Interstitial fluid and Lymph but with a higher protein content. Sodium is the major cation, with chloride and bicarbonate the major anions.

2. Control Systems of the Body:

Cell membranes are highly permeable to water; this allows an osmotic equilibrium between extracellular and intracellular fluids to exist. Cells can regulate and preserve their volumes and, thereby, maintain or change electrolyte balance through diffusion. (Either passive or facilitated diffusion, or osmosis, or active transport.)

The distribution of water between blood plasma and interstitial fluid is determined by hydrostatic and colloid osmotic pressures. Hydrostatic pressure tends to push fluid out of capillaries while colloid osmotic pressure, which is due to plasma proteins, tends to retain fluid in vascular system.

3. Regulation of Volume and Osmolarity of Extracellular Fluid.

In most vascular beds, there is a net force moving fluid outward at the arterial end of the capillaries. This is countered, roughly, by the same net force favoring inward movement of fluid at the venous end.

F. Renal System and Body Fluids

I. Nephron, Tubular Reabsorption, and Secretion

The nephron is the basic unit of kidney structure and function. It is composed of a renal corpuscle and a renal tubule.

The renal corpuscle is itself composed of a group of capillaries called the glomerulus and Bowman's capsule.

The renal tubule is divided up into several distinct segments:

The fist is the proximal tubule that begins as the proximal convoluted tubule and becomes the proximal straight tubule. Next comes the Loop of Henle and then the thin limb, which has both an ascending and a descending part. This is followed by the thick ascending limb. After the thick ascending limb is the distal convoluted tubule that joins connecting tubules, which in turn lead to cortical and collecting ducts. These lead to outer medullary connecting ducts. Collecting ducts are not really a part of the nephron as they have have a different embryological origin and there are more nephrons than collecting ducts.

There are two types of nephron:

1) Coritical: whose renal corpuscles are in the outer cortex
2) Juxtamedullary: whose renal corpuscles are in the inner cortex

Tubular Reabsorption and Secretion:

There is a very high hydrostatic pressure in the glomerular capillaries; this causes a filtrate of plasma to be pushed out of the capillaries into the urinary space of Bowman's capsule. Glomerular filtration is non-selective both useful substances and waste products are, therefore, filtered.

Tubular reabsorption: the process by which substances are transferred from the tubular fluid to the capillaries surrounding the tubules. Most useful substances are returned to the capillaries.

Tubular secretion: Substances are transferred to tubular fluid from capillaries surrounding the tubules.

Tubular reabsorption can be active or passive. Active requires energy and can work against a concentration gradient and passive works with the concentration gradient and does not require energy.

2. Regulation of Glomerular Filtration:

The glomerular filtration barrier has high permeability to small molecules and water, but restricts the movement of large molecules. Electrical charge is also an important determinant of filtration. Negatively charged structural elements impede filtration of negatively charged plasma proteins such as albumin.

Filtration rate is dependent on glomerular hydrostatic pressure, which is high because of low resistance of wide upstream vessels and high resistance of narrower downstream blood vessels.

There is a high rate of glomerular filtration due to: a highly fluid permeable filtration barrier, and large surface area of filtration bamer. There is also an unusually high hydrostatic pressure in the glomerulus compared to other capillary beds; the last reason is that there is a very high rate of renal blood flow, which allows for rapid filtration rate.

Glomerular hydrostatic pressure is very dependent on arterial blood pressure and resistance of upstream blood vessels and downstream blood vessels. With severely decreased blood pressure glomerular filtration rate decreases substantially. Glomerulus hydrostatic pressure can also be affected by changing the diameter of afferent and efferent arterioles. If afferent blood vessels are constricted the glomerular filtration rate will decrease due to the decreased downstream glomerular pressure and decreased blood flow. Constriction of efferent arterioles causes an increase in upstream glomerular

pressure and blood flow decreases. These effects counter act one another on effect on their effect on glomerular filtration rate, therefore, constriction of efferent arterioles can either increase or decrease glomerular filtration rate.

With efferent arteriolar dilation glomerular filtration rate decreases due to the decrease in glomerular pressure and increase in blood flow.

3. Functional Characteristics of Renal Blood Vessels:

Glomerular capillaries re-form the efferent arteriole, that is, they end in an arteriole and not a venule.

Renal circulation has two capillary beds in series with blood pressure being high in glomeruli and low in peritubular capillaries – to allow for reuptake of fluid reabsorbed in tubules.

4. Renal Regulatory Mechanisms:

Renal Autoregulation: Renal blood flow and glomerular filtration change very little over a wide range of arterial blood pressure. This is thought to be due to changes in the caliber of blood vessels upstream from the glomerulus. If blood pressure increases, these vessels constrict, thereby, increasing renal vascular resistance and minimizing an increase in blood flow. If blood pressure decreases the vessels dilate. This autoregulation is not dependent on extrinsic nerves or hormones.

5. Renal Control of Blood Pressure and Water Balance:

The kidneys participate in water balance in two ways:

1) By adjusting water output,
2) By affecting water intake

A key hormone in controlling water excretion is Antidiuretic Hormone (ADH).

ADH is produced in the Hypothalamus and released from the posterior pituitary. The main stimulus for ADH release is cellular dehydration, however, extracellular dehydration (hypovolemia or a decrease in effective arterial blood volume) also stimulates ADH release. The collecting duct epithelium in the kidney is the primary target for ADH. The final effect of ADH stimulation is an increased in water permeability of the luminal cell membrane.

Renal excretion of water is continuously adjusted by changes in plasma ADH levels. This keeps plasma osmolarity and extracellular fluid volume at normal levels. If there is excess water plasma levels of ADH decrease and water excretion increases.

Kidneys release renin in response to decreased blood volume. Renin results in the production of Angiotensin II, which acts on neurons in the third ventricle of the brain to stimulate thirst.

6. Renal Control of Plasma Sodium and Potassium Levels:

Retention or loss of sodium from the body will be paralleled by changes in the amount of water in the extracellular fluid.

The regulated variable is extracellular fluid volume, that is, sodium excretion is controlled to maintain extracellular fluid volume. Changes in extracellular fluid volume are sensed by cardiovascular volume receptors and by the kidneys.

Increases or decreases in glomerular filtration rate lead to directionally similar changes in sodium excretion. Increase in glomerular filtration rate, however, leads to only a slight increase in sodium excretion due to glomerulotubular balance. The proximal convoluted tubule and the loop of Henle increase their rates of sodium reabsorption in response to increased glomerular filtration rates.

Aldosterone: increases reabsorption of sodium by acting on the collecting ducts. A decrease in extracellular fluid volume stimulates Renin release. Renin is an enzyme that acts on Angiontensinogen.

Angiotensiongen + Renin → Angiotensin I + Angiotensin Converting Enzyme→ Angiotensin II

Angiotensin II is a vasoconstrictor and it, therefore, increases blood pressure. It also stimulates synthesis and release of aldosterone. Angiotensin II also directly stimulates sodium reabsorption by the kidney proximal tubule. Angiontensin II stimulates thirst centers and may also stimulate ADH release.

Stimulation of renal sympathetic nerves result in a decrease in sodium excretion by decreasing glomerular filtration rate and renal blood flow (with high levels of stimulation) or by direct stimulation of tubular cells so that they reabsorb more sodium (for low levels of stimulation).

Atrial Natriuretic Peptide is released by the Atria due to mechanical stretch caused by an increase in blood volume. This causes an increase in sodium excretion aid a decrease in blood volume.

With increase potassium levels aldosterone is released by direct stimulation of Adrenal cortex and it causes an increase in potassium excretion.

Note that more sodium than water is reabsorbed in the loop of Henle because the ascending limb is impermeable to water bur reabsorbs sodium.

Potassium is reabsorbed by the proximal convoluted tubule and the loop of Henle. Under normal conditions, potassium is secreted by the collecting ducts.

7. Regulation of Acid-Base Balance:

Kidneys rid the body of acid or base when there is an excess or deficit of hydrogen ions in the body. Urine is acidified by secretion of hydrogen ions by the tubular epithelium.

Three processes are involved in the acidification of urine:

1) Reabsorption of filtered bicarbonate in the proximal convoluted tubule.
2) Excretion of titratable acid. Hydrogen ions combine with filtered phosphate that acts as a buffer.
3) Excretion of Ammonia. Ammonia is synthesized by kidney tubule cells. Once in the urine combines with a Hydrogen ion to form an ammonium ion, which does not readily diffuse through the lipid layer of the plasma membrane. It is, therefore, trapped in the acidic urine.

G. Circulatory System

1. Mechanical Events of Cardiac Cycle:

The ventricles are the main pumping chambers of the heart. While the atria do contract their contraction adds very little to ventricle filling under normal resting conditions.

Diastole refers to the period of the cardiac cycle during which the ventricles are filling with blood. Systole, on the other hand, refers to the portion of the cycle in which the ventricles are actively contracting and pumping blood out of the heart.

As ventricles relax the pressure inside them is decreasing. When ventricular pressure decreases below atrial there is a forward pressure gradient and the AV valves are forced open and ventricular filling begins. As the heart rate increases, atrial contraction becomes more important in ventricular filling.

With ventricular muscle contraction, ventricular pressure increases. It is soon greater than atrial pressure and the AV valves are forced closed. When ventricular pressure exceeds pressure in the aorta blood flows from the ventricle into the Aorta. Ventricles begin to relax and pressure falls below that of the aorta, which causes a reversal in blood, flow in the region of the aortic valve. This causes the closure of the semilunar valve.

2. Electrical Activity of the Heart

The pacemaker is the single location from which the stimulus for the heart action arises. The pacemaker is the Sinoatrial Node (SA node), which is a specialized region of the muscle cells in the right atrium. After repolarization the membrane begins a slow depolarization that quickly brings the membrane potential to its threshold, and another

action potential takes place. Heart rate is regulated by the rate at which the diastolic potential (the value at which the cells repolarize) reaches threshold. The rate of the SA node pacemaker is controlled by the autonomic nervous system. The parasympathetic system decreases rate.

Brachycardia = Resting heart rate<60bpm
Tachycardia= Resting heart rate>100bpm

SA node pacemaker exerts its effect first in the musculature of the right atrium followed by the left atrium. In the lower region of the right atrium is a region of specialized cells called the atrioventricular node (AV node). They slow and weaken action potentials causing a delay in the spread of action potentials to the ventricles. This delay ensures that the atria finish their contraction prior to the ventricles beginning theirs. After the AV node the impulse enters the Bundle of His – muscle cells specialized for rapid contraction. The bundle of His divides into two bundle branches – one for each ventricle. The bundle branches further divide to form Purkinje Fibers. From the Purkinje fibers, the impulse passes into the ventricle wall, causing contraction. This arrangement causes a nearly simultaneous activation of all ventricular muscle.

3. Significance of EKG:

The principal features of an Electrocardiogram (EKG or ECG) are labeled P, Q, R, S, and T.

P Wave: Caused by depolarization of atrial muscle.
QRS Complex: Caused by depolarization of the ventricles
T Wave: Caused by repolarization of the ventricles.
Isoelectric Line: A line of no deflection that occurs when the entire heart is depolarized or resting.

Atrial repolarization is weak and occurs during ventricular depolarization and is, therefore, hidden.
EKG shows electrical events and you can only infer that muscular contraction has occurred. Also activity of conduction system and nodal tissues can be inferred. Example: if P wave is not followed by QRS complex you can assume that conduction was blocked somewhere between the atria and ventricular muscle. If QRS complex is very broad you should assume that some ventricular muscle was activated later than it should have been.

4. Hemodynamics:

Blood Flow – the volume of blood that moves past a particular point in the cardiovascular system during a given period of time. Since the cardiovascular system is a closed system and is, for the most part, arranged in series flow measured at the aorta will be the same as the total blood flow through the lungs, systemic circulation, etc. However, individual vascular beds that make up systemic circulation are arranged in parallel and, therefore, only a portion of total systemic blood goes through them.

Blood is caused to flow through vessels by a force, which can be measured as blood pressure. What causes blood to flow is not the pressure at any given point, rather it is the pressure gradient between two points.

Frictional forces tend to impede blood flow. Resistance is a quantity that summarizes all frictional components that oppose blood flow in a particular situation. Diameter of blood vessels is an important constituting factor to the resistance of blood flow. The smaller the vessel is the greater the resistance. Viscosity of blood is also an important factor in resistance, the more viscous the blood the greater is the resistance.

5. Regulation of Blood Flow and Pressure:

The ultimate goal of the body is to maintain blood flow not blood pressure.
Bar receptors function as stretch receptors within the wall of the elastic arteries. They are located in the wall of the arch of the aorta and in the carotid sinus. Baroreceptors monitor mean arterial pressure. They increase the rate of firing in response to stretch. Afferent nerves from the baroreceptors synapse with nerves that make up the cardiovascular control centers in the medulla.

Efferent nerve fibers from the cardiovascular control centers synapse with cell bodies of the parasympathetic and sympathetic neurons that innervate the heart and blood vessels. With a change in baroreceptor activity reciprocal changes in parasympathetic and sympathetic activity to the heart and blood vessels is produced. That is increased nerve activity from the baroreceptors causes a decrease in the rate of stimulation of sympathetic nerves and an increase in parasympathetic nerve stimulation.

In response to sympathetic stimulation the venous smooth muscle contracts. So with an increase in arterial pressure, there is a decrease in sympathetic activity to veins resulting in venodilation, this results in a shift of blood volume from the heart and arteries to the veins and a resultant decrease in end diastolic volume that decreases blood volume. Decreased sympathetic nerve stimulation to blood vessels causes dilation of vascular beds, therefore, a decrease in peripheral resistance. Increased parasympathetic causes a decrease in heart rate and contractility.

6. Lymph Formation and Function:

Lymphatic vessels function to return fluid and plasma proteins that have leaked out of capillaries into interstitial spaces back into the circulating blood. The lymphatic system is the only route by which plasma proteins can be returned to the blood. The lymphatics also transport substances absorbed from the gastrointestinal tract, fat and fat-soluble vitamins, to the blood. As the lymph flows trough the lymph nodes microorganisms and other foreign material are removed via phagocytosis by lymphocytes and phagocytes.

7. Blood and its Functions:

Blood is a connective tissue. Blood is a vehicle that moves many different substances to various areas within the body for a variety of purposes. Blood also conducts heat from the body's core to the respiratory passageways and skin to allow for its dissipation.

Some blood cells defend against foreign agents and injury. Blood also plays a role in maintaining normal extracellular pH. Chemical buffers in blood convert strong acids and bases into weak acids and bases and, therefore, minimize large pH shifts.

Whole blood consists of red corpuscles (erythrocytes), white corpuscles (leukocytes), and platelets (thrombocytes) that are suspended in intracellular fluid called plasma.

Erythrocytes: primarily function to transport oxygen, and carbon dioxide.

Leukocytes: function to combat foreign substances that enter the body. Include Granulocytes like neutrophils, eosinophil, and the basophil as well as agranulocytes like the monocyte and lymphocyte.

Platelet (thrombocyte) – is a fragment of a megakarocyte. Have an important role in hemostasis (mechanisms that minimize or prevent the loss of blood when a blood vessel is opened.) Hemostasis involves:

i. Local vasoconstriction
ii. Formation of platelet aggregate (clump)
iii. Formation of blood clot and
iv. Clot retraction and dissolution.

Platelet aggregation provides a framework for coagulation. Damaged cells of an injured blood vessel release adeonosin diphosphate (ADP), which attracts platelets and causes them to clump. Platelets that come in contact with the collagen of the vascular wall degranulate (release stored chemicals) releasing ADP, serotonin (a vasoconstrictor) and platelet factors necessary for blood coagulation. The released ADP attracts even more platelets and causes them to swell and become sticky. They thus adhere to the damaged site and form a plug. In the formation of a clot fibrin is formed when thrombin, an enzyme, converts fibrinogen to fibrin. Fibrin forms a mesh like network at the damaged site trapping red blood cells to form a clot.

H. Endocrine System

I. Hormones:

Feedback regulation: Endocrine cells detect or monitor the effect that the hormone they release has. The rate of hormone release can, therefore, be adjusted in an appropriate manner.

Hormones can be classified intone of three chemical classifications:

i. Amino Acid derivatives: With just a few chemical changes an amino acid can be converted to a hormone.

ii. Peptides or Proteins: Hormones can range anywhere from very small to very large proteins. Synthesized on ribosomes of rough ER and are packaged into vesicles to by secreted by the Golgi complex.

iii. Steroids: The precursor for all steroid hormones is cholesterol. There are five classes of steroids (glucocorticoids, mineralocorticoids, androgens, estrogens, progestins), which share common synthesis steps. The type of steroid produced by any particular endocrine cell is determined by relative amounts of enzymes present. They are not stored; rather they are synthesized and secreted on demand.

Methods of Action: Amine and peptide hormones exert their effect by binding to a membrane receptor, which causes the generation of intracellular second messengers. An effect is exerted by altering the activity of proteins that already exist in the cell.
Steroid hormones bind to intracellular receptors and alter gene expression within the cell nucleus. That is, an effect is exerted through the production of new proteins.

2. Hypothalamic Control of Pituitary Gland:

The pituitary gland is composed of 3 lobes, two of which serve an endocrine function. While the pituitary gland secretes at least nine different hormones, it does not itself synthesize all nine.

The anterior pituitary is a true endocrine gland in that they receive signals via the blood and respond by releasing their hormones into the blood. The posterior pituitary acts like a group of neuroendocrine cells (a cell which is directly innervated by nerve cells and releases a hormone in response to stimulation).

The posterior pituitary gland secretes two hormones, oxytocin and antidiuretic hormone. These hormones are synthesized in cell bodies located in the hypothalamus. They are transported to the posterior pituitary through axons of the neurons that produced them. Generation of action potentials in these neurons cause hormone release.

The anterior pituitary synthesizes six hormones. Their secretion is controlled by several different releasing/inhibiting hormones produced in the hypothalamus. Generation of action potential in the neuroendocrine cells of the hypothalamus, which produces the releasing/inhibiting hormones, causes their release into the blood. They then travel to the pituitary and exert their effect.

3. Pituitary Control of Endocrine Glands:

Luteininzing hormone and follicle stimulating hormone stimulate production of sex steroid hormones by the gonads.

LH: Stimulates Leydig cells to synthesize and secrete testosterone.
FSH: In females stimulates follicular growth. Stimulates granulosa cells to synthesize estrogen.

Adrenocorticotropic Hormone: Regulates the synthesis and secretion of cortisol from the adrenal cortex.
Thyroid Stimulating Hormone: Stimulates cell growth in the thyroid and the release of thyroid hormones.

4. Functions and Regulations of Adrenal Cortex:

Cells in the adrenal cortex secrete glucocorticoids. Their secretion is controlled via a cascade of hormones.

Corticotropin-releasing hormone (CRH) is released from the hypothalamus. Its release is controlled by inputs from higher brain centers. It causes the release of adrenocorticotropic hormone (ACTH), which causes the release of glucocorticoids.

Hypothalamus releases CRH → Pituitary releases ACTH → Adrenal cortex → Glucocorticoid (cortisol)

Three main steroids are produced by the adrenal cortex:

i. Cortisol: A glucocorticoid. Effects liver, skeletal muscle, and adipose tissue. Can be considered catabolic, that is, it promotes protein breakdown.
ii. Aldosterone: a mineralocorticoid. Increases the retention of sodium by kidneys, therefore, increasing water retention.
iii. Dehydroepiandrosterone (DHEA) – an androgen. Converted to testosterone.

5. Functions and Regulation of Adrenal Medulla:

The adrenal medulla secretes epinephnne and norepinephrine. Chromaffin cells are the functional unit of the adrenal medulla. Chromaffin cells are directly innervated by preganglionic fibers; in response to stimulation epinephrine is released into the blood.

Epinephrine synthesis:

Tyrosine + Tyrosine Hydroxylase → Dopa → Dopamine → Norepinephrine + PNMT → Epinephrine

Epinephrine produces the same results as direct sympathetic stimulation of the tissue except epinephrine stimulation is longer lasting.

6. Functions and Regulation of Thyroid Gland:

T_4 Thyroxine is a major hormone produced by the thyroid gland.
T_3 Triiodothronine is also produced by the thyroid but to lesser amounts.

Thyroid hormones require iodine to be produced but it is not always available in a diet, therefore, mechanisms of storage of iodine have developed. Thyroid hormone secretion is regulated by TSH and the effects of the thyroid hormones are widespread.

7. Functions and Regulation of Pancreatic Insulin and Glucagon:

Glucagon is produced in the pancreas alpha cells whereas insulin is produced in the beta. Together they are know as the Islets of Langerhans.

Insulin release is stimulated most importantly by an increase in blood glucose but also due to amino acid levels, fatty acids, gastrointestinal hormones, neural and pharmacological stimuli and other pancreatic hormones. Glucagon, on the other hand, is released in response to a decrease in blood glucose levels.

8. Regulation of Blood Glucose Levels:

An increase in blood glucose levels leads to an increase in insulin secretion from the pancreas beta cells. Most tissues in the body depend on insulin to take up glucose. By promoting the uptake of glucose by cells insulin also stimulates glucose metabolism. Insulin stimulates glycogen synthesis while decreasing glycogen breakdown. Glucagon works in the opposite fashion.

9. Functions and Regulation of Vitamin D, Parathyroid Hormone, and Calcitonin:

Three hormones are involved in moving calcium ions between extracellular fluid and bone. This is an important way to maintain constant extracellular fluid calcium ion concentration.

i. Parathyroid hormone is produced by the parathyroid glands and is primarily stimulated by a decrease in plasma calcium concentration. The net effect of parathyroid hormone is to increase plasma calcium concentration.
ii. Calcitonin is produced by the thyroid gland. An increase in plasma calcium causes secretion of calcitonin. Calcitonin causes an increase deposition of calcium in bones, which is accompanied by a decrease in plasma calcium.
iii. Vitamin D is obtained in the diet or formed in the skin by the action of UV light from a precursor derived from cholesterol. Vitamin D must be made hormonally active in the liver and kidney.

10. Functions and Regulation of Endorphin, Enkephalin, and Growth Hormone Blood Levels:

Growth hormone secretion is under control of two hormones produced by the hypothalamus: Growth hormone releasing hormone and Somatostatin. Growth hormone release is not a constant release; rather there are pulses of release at different times of the day. About one hour after the onset of deep sleep growth hormone is at its most consistent level. A series of growth hormone release pulses occurs from 2-4 hours after a meal.

Endorphins and enkephalins are released by the brain's analgesic system.

I. Reproductive System

1. Functions and Regulation of Reproductive Hormones:

The hypothalamus secretes gonadotropin-releasing hormone, which causes leutinizing hormone and follicle stimulating hormone to be released by the anterior pituitary in males. Lutenizing hormone is transported to the testes where it stimulates the production and release of testosterone.

FSH stimulates the conversion of sperrnatogonin into spermatocytes in the seminiferous tubules.

GnRH, LH, and FSH are released in a constant manner in males due to the presence of a feedback loop between the hypothalamus, pituitary, and testes. The hypothalamus monitors levels of sex hormones and adjust its release of GnRH correspondingly.

A main difference between the hormonal control of reproduction in the male and the female is the cyclic nature of hormone secretion in females. In the female LH and FSH stimulate immature germ cell development and hormone secretion in the ovaries.

2. Pregnancy, Birth, and Lactation:

High levels of circulating estrogen and progesterone in maternal plasma during pregnancy inhibit GnRH release from the hypothalamus. Without GnRH the release of LH and FSH are not released from the pituitary. Without LH, and FSH stimulation no new follicles are formed. Prolactin levels rise progressively throughout the pregnancy resulting in breast growth. Insulin, aldosterone, cortisol, and thyroxin levels also increase during pregnancy. These hormones control metabolic rates as well as levels of fluid, salt and glucose.

A number of hormones stimulate breast development during pregnancy to prepare for nursing. These hormones include: prolactin, estrogen, progesterone human chorionic goandotropin, and Human chorionic somatomammotropin. After birth the production and release of milk from the breasts is controlled by prolactin and oxytocin. Where prolactin stimulates the production of milk and its secretion into the breast aveoli and oxytocin stimulates the release of milk from the breasts. Both hormones are released due to neuronal stimulation during nursing.

Psychology

Pertinent Classes:

Opt 562 Behavioral Optometric Science
Opt 661 Physiological, Psychological and Cognitive Changes During the Lifespan
Opt 724 Pediatric and Developmental Optometry,
Opt 726 Normal and Abnormal Visual Perception,
Opt 727 Evaluation and Management of Patients with Perceptual Problems

Pertinent Textbooks: Visual Perception: A Clinical Orientation. Schwartz, S. Appleton and Lange. 1994, Changes During the Lifespan (class notes packet)

1. Psychophysical Methodology

2. Human Development

A. Normal Vision Development in the Infant and Child

1. SPATIAL VISION

i. The ability to understand directional concepts that organize internal and external visual space.
ii. Knowledge of visual space develops in the following order: UP/DOWN → FRONT/BACK → LEFT/RIGHT.
iii. There are several ideas concerning how visual spatial skills develop. Here are some of the highlights:
    a) Suchoff - There are three components in the development of visual space.
        - THE INVARIANT (aka zero point, reference point, or self): Critical because space is always described in relative terms. It's important for a child to know that they are a unique entity in the environment so they can describe where things are relative to themselves.
        - BILATERALITY (lateralization of self): Developing a set of internal coordinates based on the knowledge that the human body has two sides, and being able to differentiate these two sides from one another. Development of this concept is a prerequisite for the next stage, which is…
        - SPATIAL ORGANIZATION AND MANIPULATION. This stage involves taking the internal coordinates that have been established and projecting it into external space. This concept is important in

the organization and manipulation of the environment, as well as being an important step in making children less dependent on motor interaction and more dependent on vision.

b) Gessel - Describes the development of visual space in terms similar to those of Suchoff. Believes the infant's initial space is very egocentric and broadens with age. According to Gessel, the various stages of development occur in the following order:

i. Child operates in near space only
ii. Can shift attention to distance, but has difficulty shifting it back to near
iii. Can go near to far & vice versa, but has trouble with intermediate distances
iv. Begins to sense height, width, and depth in space
v. Understands their entire surroundings, but has a hard time orienting themselves within the environment
vi. Senses new objects and positions in space in context with each other and themselves
vii. Realization that a scene must appear different to another person from another angle

c) SUNY Battery - a series of tests used to evaluate the level of development of certain traits in a child.
   i. One of the traits measured in the SUNY Battery is SPATIAL VISION.
   ii. In evaluating the development of SPATIAL VISION, certain factors are considered by the SUNY Battery
      - Body Knowledge and Control – relative maturity of the concept that the child is the reference point/zero point
      - Bi-manual Integration and/or Ability to Cross the Midline – relative maturity of the individual's knowledge of him/herself as a bilateral being
      - Visualized Reversals – relative ability of the child to organize and manipulate space from another viewpoint
      - Note how these factors are also the basis of both Suchoff and Gessel's ideas on how SPATIAL VISION develops.
   iii. Body Knowledge and Control
      - Evaluated most commonly by observing if a child is able to move specific parts of their body upon request.
      - At 4 years old, child succeeds in homologous body movements (i.e., can raise both arms at the same time)
      - At 5 years old, the child starts being able to perform monolateral body movements (i.e., can raise either one a m or one leg at a time).

- At 6 years old, ipsilateral body movements are achieved (i.e. moving the right arm and right leg simultaneously).
- At 7 years old, the child is somewhat competent at performing contralateral body movements (i.e. moving the right arm and left leg simultaneously).
- Prior to age 8, all the above movements are performed successfully

iv. Bimanual Integration

- Evaluated most commonly by observing a child's behavior as they are asked to copy certain figures onto a blank sheet of paper
- At 3 years old, child writes with either hand and may switch hands when writing. They show no preference/dominance.
- At 4 years old, no consistent hand preference, but doesn't switch hands once writing or drawing is started with a certain hand.
- At 5 years old, consistent use of writing with one hand but the other hand provides no support of paper (either holding it down or orienting it)
- At 6 years old, non writing hand provides some degree of support and orientation of paper
- At 7-8 years old, writing hand is free to draw with paper fully supported by non-writing hand

2. REFRACTIVE ERROR

a) Emmetropization

i. An *active* feedback mechanism resulting in the coordinated growth of optical components of the eye so that a state of near emmetropia is reached.

ii. Evidence for emmetropization

- There is great change in axial length early in life, but there is little to no change in refractive error (RE). Therefore, there must be a change in other optical components to accommodate for the change in axial length.
- At birth there is a wide distribution of RE's in a given population, but at 6 years old this distribution becomes narrower, indicating a coordinated growth of optical elements towards emmetropia.
- In emmetropic eyes, there is an inverse relationship between corneal curvature and axial length. Changes in one feature are offset, so to speak, by changes in the other feature. This indicates that the growth of optical elements is aimed at attaining emmetropia.
- Animal studies have shown that RE's can be induced and then reversed if the causative agent is removed. Ex: Minus lenses were placed in front of a chick's eyes (i.e. baby chickens, not pretty girls!) → when the minus lens was removed, it was discovered that the chick was now myopic, as if the eye had made changes to

create an entire optical system that was emmetropic. Similar results have been found in humans.

b) General Trends in the Development of Refractive Error
   i. From birth to 6 yrs old, there is a wider spread of refractive errors than in the adult population.
   ii. General trend is to be born hyperopic with the amount decreasing as we age. By adulthood most people are slightly hyperopic or myopic.
   iii. Various sources list a range of +2.00 D to +3.20 D at birth.
   iv. Decrease in hyperopia begins at 12 to 15 months of age.
   v. In terms of ***moderate*** ametropia, the further the eyes have to go to reach emmetropia, the faster emrnetropization will occur.

c) Myopia
   i. 25% of pre-term babies are born myopic
   ii. 90% of newborns are between – 0.50 and +5.00 D
   iii. Low hyperopia at birth is a predictive sign of impending myopia
   iv. Myopia before 9 years old seldom progresses to less than 2 D and has a mean of – 4.00 D.
   v. Myopia after age 10 seldom progresses more than 3 D
   vi. Myopia that develops in first 15 years of life is called juvenile onset (JM) or early onset myopia
      - For JM, progression is constant about 0.5 D/year, stopping at age 15
      - Incidence of myopia is greatest in 8-13 year-old males and 10-13 year-old females.

d) Predictive trends seen at age 6
   i. 1.50 D hyperopia → child is likely to remain hyperopic, and may even become more so later on
   ii. 0.50 to 1.25 D hyperopia → child is likely to be emmetropic in adulthood
   iii. pl to 0.50 D → child will likely progress to myopia, especially if accompanied with ATR astigmatism
   iv. ≤ 0.50 D hyperopia → likely to become myopic in late teens if placed in a visually stressful environment
   v. ≥ 1.00 D myopia → by 13-14 years of age, 2.50 D or more myopia likely
   vi. ≥ 1.25 D → by 13-14 years of age, 4.25 D or more myopia is likely

e) Astigmatism
   i. Common in newborns...less common at 12-18 months old
      - Highest between 3-5 months
      - Declines by 5-6 months
   ii. Atkinson: By 18 months, most infants have no more astigmatism than the average in adults (0.75 D).
   iii. Prevalence of all types of astigmatism is high in early life

iii. Prevalence of all types of astigmatism is high in early life
- ~ 10% don't lose it or show it into adulthood

iv. Tendency to shift from ATR to WTR within the first 2 years of life

v. 40% of juvenile myopes have ATR astigmatism.
- If at 4-5 years old child doesn't have myopia, but has ATR astigmatsm, they will likely be myopic later in life.

vi. Most pre-term babies have ATR

vii. 80% of 6 year olds have WTR astigmatism

viii. Kids with uncorrected anisometropia are more likely to develop astigmatism. Uncorrected astigmatism can cause meridional amblyopia later in life.

ix. Major contributor to astigmatism is the cornea

f) Anisometropia
i. From birth to 3.5 years old, more common in children than in adults.
ii. 17% of newborns have > 1D of aniso
iii. 7-11 % of 1-4 year olds have > 1D of aniso

g) Amblyopia
i. Risk factors **(monocular** or binocular)
1 y.o. with ≥ 3.5 D antimetropia in one meridian
- **4** y.o. with more than **2D astigmatism** in that **eye**
- **4** y.o. with ATR or oblique astigmatism
- **increasing** *or* **unchanged refractive** error between 1 and 4 years old
- persisting anisometropia

ii. Partial correction of med-high hyperopia (≥ 3.5 D in one meridian) reduces the incidence of strabismus and amblyopia

h) Cambridge Study - For children with more than 4D of hyperopia at 6-8 months old:
- Give a partial prescription with:
  - Sphere → 1D LESS than the most myopic meridian
  - Cylinder
    < 2 years old – 50% of cylinder IF > 2.5 D
    2 – 3.5 years old – 50% of any cylinder
    3.5 years old – FULL Rx
- Uncorrected hyperopia > 3.5 D correlates with amyblopia after age 4
- Early spec Rx significantly decreases risk for strabismus and amblyopia

3. COLOR VISION

i. Review rod and cone morphology, and then review the section on normal and abnormal color vision in SCHWARTZ. If this sounds like a cop-out, well, that's

because it is!!! Honestly, though, I can't cover this section nearly as well as it's already covered in SCHWARTZ.

ii. 2-month old children are dichromats…some may be trichromats

iii. 3-month old children are definitely trichomats

iv. The *shape* of the infant spectral sensitivity curve is the same as in adults. Their spectral sensitivity is relatively more sensitive to shorter wavelengths (blue/green)

4. SPECTRAL TRANSMISSION OF THE OCULAR MEDIA

5. ACCOMODATION AND CONVERGENCE

a) Accommodation

i. Obviously difficult to measure in infants using traditional means because they can't say the target is "getting blurry". Also difficult to measure in someone with a visual impairment who hasn't seen blur before.

ii. Increased likelihood of decreased accommodation in Down's Syndrome and Cerebral Palsy patients.

iii. Normal accommodative response in infants is measured in 2 ways

- Photorefraction– A flash photo of the eyes is taken with a camera at a distance of 0.75 m or 1.5 m as the infant fixates the same distance. The pattern and size of the reflected light indicates whether the child is myopic or hyperopic relative to the camera.
- Dynamic Retinoscopy

iv. Recent studies by Brockrnan, Howland et al, and Cuiffreda indicate that babies can make accommodative changes, and sometimes with accuracy.

v. At 1 month old, accommodation is more consistent and accurate to near than distance stimuli.

vi. The overall tendency is to under-accommodate and near and to over-accommodate at distance.

vii. Adult accommodation has a stimuli-response curve of 0.8.

- Accommodation in infants improves until 5-6 months, at which point their accommodation is nearly adult-like in slope (0.8).

b) Convergence

i. At birth: Infants can perform vergence eye movements in the correct direction, but with very poor accuracy.

ii. 1 month: Can converge and diverge in response to targets moved along the midline.

iii. 2-3 months: Vergence responses are faster and more accurate. Also, there is a greater probability that some form of binocular fusion is present.

iv. The infant vergence system is not comparable to the adult system until 3 months of age. Before this age, convergence in infants is slower, less consistent, and less accurate.

v. Prevailing theory is that tonic and proximal accommodation are the stimuli which evoke convergence, because they don't require retinal feedback.

Vergence eye movements stimulated by image disparity develop later (at 3-4 months).

7. STEREOPSIS

a) Sensory Fusion
- Researched through electrophysiological testing, such as Visually Evoked Potentials (VEPs)
- Infants don't respond to tests until 8 wks. Avg. age of onset is about 10 wks.

b) Development of Stereopsis
- At 3 ½ months, most children can give stereo response to 45'
- At 6-7 months, all should be able to give a stereo response
- At 20 months, children have stereoacuity of 216''
- At 55 months, children have stereoacuity of 60”
- Stereopsis continues to increase the first 4-5 years of life
- The most sensitive period for binocularity is the first 2 years of life
- Children are born with the ability to achieve binocularity, but will lose this ability of it isn't exercised.

8. FORM REPRODUCTION AND PERCEPTION

a) Relates to the relative maturity of the individual's ability regarding an aspect of spatial orpanization and manipulation

b) Again, the SUNY Battery is a series of tests used to evaluate the level of development of certain factors in a child, *one* of which is FORM REPRODUCTION.

i. The specific tests used to evaluate a child's ability to perceive and reproduce specific form are the ''Winterhaven Copy Forms'' test and the “Pegboard” test
- NOTE: In studying the following information, DO NOT try to memorize the exact patterns that are expected at certain ages. Rather, try to remember the trends we expect to see in normal development. For example, do not memorize the fact that normal children will draw a circle before a triangle. Instead, note that the ability to draw oblique lines comes later in a child's development.

ii. Winterhaven Copy Forms
- Consists of seven figures: circle, cross, square, equilateral triangle, segmented rectangle, horizontal diamond, vertical diamond
- 2 years old: circular or vertical scribbles are evident
- 3 years old: circle and cross are reproduced with some success
- 4 years old: circle, cross, and square should be completed. Other figures are completed with some success
- 5 years old: equilateral triangle distorted vertically, with one side usually drawn vertically

- 5 years old: in reproducing the segmented rectangle, the lines that divide the rectangle aren't drawn from comer to corner, but rather, they are drawn such that individual lines meet in the middle.
- 5 years old: cannot draw diamonds
- 6 years old: circle, cross, square and triangle drawn with improved proportions. Segmentation of rectangle may still exist. Diamonds still cannot be drawn.
- 7 years old: rectangle should be drawn without using segments at all. Can draw diamonds, but they are distorted.
- 8 years old: All figures can be drawn at this age

iii. Pegboard

- Doctor and child each have a pegboard and pegs. The doctor creates specific patterns on is/her board and the child has to re-create the pattern of their own board.
- 2 years old: Child usually can't reproduce any of the patterns. May just place the pegs in a straight horizontal or vertical line.
- 3-4 years old: May be able to reproduce patterns 1 or 2, but may show spontaneous lateral reversals
- 5-6 years old: Child can usually reproduce the first three patterns. There will usually be some trouble with the oblique aspects of patterns 2 and 3, but will be able to correct them. Will tend to ''horizontalize'' or ''verticalize'' the oblique features.
- 6 years old: Spontaneous lateral reversals are still common at this age, but by this age children should be able to recognize the error and correct it by themselves.
- 7-8 years old: Can reproduce all of the figures, but may have to fix one or two of them along the way (usually patterns 4 or 5).
- 8 years old: Should be able to reproduce all the patterns without having to go back and make corrections.

9. TEMPORAL VISION

Again, this particular topic is explained very well and in great detail in Schwartz. The pages that pertain to this particular subject are 205-222

10. VISUAL FIELDS

Study by Schwartz, Dobson, and Sanstrom, 1987

- Birth – 2 months: only slight increase in the extent of VF
- 2-8 months: relatively rapid increase in extent of VF
- Infant VF at 8 weeks is smaller than adult in extent, but similar in shape (vertical extent > horizontal extent)
- 6 months – 1 year: return to a slower increase in VF size
- 1 year old: VF is adult-like

- Nasal VF (temporal retina) matures more slowly than temporal VF, especially in the first 3 months of life

Normal Motor Development in the Infant and Child

I. GROSS MOTOR/LANGUAGE DEVELOPMENT MILESTONES

a) Milestones in Motor Behavior
   i. Summary of notes given in Pediatric Optometry course
      - 1 week: Hands are idle and useless
      - 6 weeks: Outer fingers are the strongest
      - 8 weeks: Able to life head while on stomach
      - 12 weeks: Able to support a steady and erect position of head whem being held; trunk is also more rigid when being held
      - 16 weeks: Can present the "swimmer's" position
      - 20 weeks: Hand grasp becomes a squeeze and, when held upright, can support own weight
      - 24 weeks: Can grasp objects with both hands and places objects in mouth; grasp is a crude palmer grasp
      - 28 weeks: Able to sit while leaning on hands; hands discover feet; able to transfer objects between hands; can roll from back to stomach; can sit alone erect
      - 32 weeks: Inside fingers become more important in the grasp; can sit alone for a brief moment
      - 36 weeks: Can sometimes roll and pull himself/herself up into a free-sitting position
      - 40 weeks: Alternates hands and knees in true creeping fashion; can turn side-to-side while sitting; can grasp a cube deftly
      - 44 weeks: Can attain sitting position with very little resistance; balances momentarily in standing position; uses thumb and forefinger to grasp a pellet
      - 48 weeks: Takes short and unsteady walks
      - 52 weeks: Sitting is mastered; able to walk across room, rise and lower to/from standing position unaided; thumb opposes forefinger at adult skill level
      - 68 weeks: Walks
      - 15 months: Begins to throw things; can stack blocks one atop the other
      - 18 months: Can tower/build three cubes; bowel sphincters are becoming controlled
      - 2 years: Can run without falling; can turn single pages in a book; can insert upright spoon into mouth; uses 2-3 word sentences; can tower 5-6 cubes
      - 3 years: Can dodge, throw, stop/go, and turn sharp comers

ii. For more detailed milestones, review the handouts given out by Dr. Erickson in his Changes Through the Lifespan course, especially the following handout: "A Visual Handicap Affects the Infant, Sitter-Upper, Creeper-Crawler, Toddler, and Pre-Schooler"

b) Language Milestones – Again, Changes Through the Lifespan packet

2. REFLEXES IN THE INFANT

a) Blinking Reflex
   i. Bright light flashed in infant's eyes causes closing of both eyelids
   ii. Present at 6 months
b) McCarthy Reflex
   i. When tapped on the supraorbital area, a blink reflex on the same side that is tapped should be present
   ii. Disappears at 2-4 months of age
c) Nasopalpebral Reflex
   i. Tapping of bridge of nose causes blinking of both eyes
d) Ciliary Reflex
   i. Touching of the eyelashes causes a homolateral or bilateral blinking Absence is associated with lesion of the 5^{th} nerve
e) Cochleopalpebral Reflex
   i. Loud noise produces a blink and sometimes startle reaction
   ii. Only consistent auditory reflex found in newborns
   iii. Dependent on a normal auditory conduction and neuronal system
f) Doll's Eye Phenomenon
   i. When infant's head is rotated (while keeping the body still) the eyes are observed to stay fixed and do not move with the head
   ii. Usually present for first ten days of life and disappears when good visual fixation is achieved.

3. OCULOMOTOR SYSTEM

a) Pursuits
   i. Tested using 2 types of targets – constant velocity targets (aka simple ramp motion) and pendular motion (self-explanatory)
      - Constant Velocity Targets: target moves in an unpredictable manner but with constant speed
      - Pendular Motion: sinusoidal motion
   ii. Development of Response to Constant Velocity Targets
      - In early infancy smooth pursuits have been measured, but they are very unstable
      - Infants 4-6 weeks old exhibit smooth pursuit movements using slow constant velocity targets (5-15 degrees/second)

- By 10-12 weeks, infants exhibit smooth pursuit movements to targets moving ≥ 15 degreeslsecond

iii. Development of Response to Pendular Motion

Pursuit eye movements to these targets are brief and intermittent

- 2 months old: Can't follow these targets with a smooth pursuit. Rather, the infant attempts to follow these targets using a series of saccades
- 8-12 weeks: Earliest demonstration of pursuit eye movements to these targets. However, still likely to have these pursuits interrupted by an occasional saccade

iv. Conclusion: Infants are better at following slow-moving constant velocity targets than pendular motion targets

v. By 3 months old, velocity of pursuits starts to increase

vi. Horizontal pursuits develop faster than vertical pursuits

b) Saccades

i. Very fast, conjugate eye movements used to center gaze on object of interest rapidly and accurately

ii. Present at birth. Involuntary in nature. Have been recorded in 1-2 month olds.

iii. MOST mature of eye movements at birth

iv. Infant saccades are usually too small (undershoot targets), i.e. *hypometric.* Thus, more saccades are required to reach target in periphery (Saccadic Steps).

- 1-2 months old: requires 3 to 4 equal amplitude saccades to reach a peripheral target
- < 2 months old: start of saccade comes ½ second after the introduction of peripheral target. ~ 2 seconds are required to move to the target.
- Compared to adults, the speed (800 degrees/second) of the saccade is the same in infants, but the latency is greater in infants (112 to 1 second for infants vs 200 ms for adults)

  Accuracy of saccades increases within first year of life; 1st saccade covers ~ 90% of the target distance, with the 2nd and 3rd mainly for fine-tuning.
- By age 6 saccades should be nearly adult-like

c) Opto-Kinetic Nystagmus (OKN) – involuntary following

i. Slow eye movements in same direction of visual field motion that alternates with quick return saccades

ii. Purpose: to minimize the motion of a moving environment upon the retina in order to maintain a clear image

iii. Development of OKN

- OKN response in infants is more easily evoked when following large, moving, patterned fields as opposed to small, isolated targets

- < 3 months old, OKN is asymmetric between the two eyes
- OKN response starts becoming more symmetric at 5 months old (about the same time stereopsis begins to emerge)
- Overall, OKN is immature in infants. OKN response to a "20/20" target is not achieved until 3 years old

iv. Deprivation affects OKN development
- Monocular OKN response is asymmetric in adults with amblyopia
- OKN and pursuits are asymmetric in early onset strabismus and early onset monocular or binocular cataracts

d) Vestibular-Ocular Reflex (VOR)
i. Eye movement in response to head acceleration. Stimulus for this movement isn't from retinal feedback, but from the semi-circular canals in the middle of the ear
ii. Purpose: to minimize the movement of the eyes relative to visual environment in order to create a clear image
iii. Development of VOR
- Slow eye movement in the same direction of head turn, followed by a fast eye movement opposite to the direction of the head turn
- Relatively mature at birth compared to other eye movements
- 1 month old: Slow-phase eye movements in response to head acceleration are greater in amplitude and velocity than are found later in life
- 1-4 months old: ratio of eye velocity to head velocity is 1:1. In adults, that ration decreases to 0.6
- VOR in adults is greatly diminished (even gone) in adults blinded early in life, but not in adults blinded later in life

4. Visual-Perceptual Motor Skills

a) Perception is *learned*. Vision is the most important of perceptions
b) The development of motor skills is a pre-requisite for emerging perceptual and cognitive development
c) Child advances through the Visual-Motor hierarchy of developmental stages in the following order: almost exclusively motor → motor > visual → visual > motor → visual skills predominate
d) Skeffington: "Vision" is the outcome result of the integration of four systems that operate at all times, to varying degrees
i. Anti-gravity: movement of the whole person that provides information about where the person is in space. Through movement, the infant becomes aware of his/her body scheme and where they are.
ii. Centering: area of attention that utilizes the five senses to tell where object are in **space**
iii. Identification: integration of the five senses to determine what things are in space

iv. Speech-Auditory: allows child to feel or see an object and describe it, or to visualize it from name or description

e) Reading and writing skills emerge after satisfactory development of gross motor control

f) The use of the motor system to gain information about the environment means that vision has not emerged as the dominant processing system

B. Normal Cognitive and Social Development in the Infant and Child

Review Dr. Erickson's Changes Through the Lifespan Class

D. Effects of Early Environmental Restrictions

This is a summary of the main points in Schwartz starting from pg 355 of the text.

1. Deprivation Studies
    a) Although most newons in the visual cortex receive input from both eyes (i.e. they are binocular cells), they don't receive equal input from both eyes.
    b) Refer to ocular dominance histogram, Fig 17-1, pg 356
    c) Cat Models/Experiments
        i. The effects of visual deprivation on the development of ocular dominance were investigated
        ii. One eye of a cat was sutured at birth. The activity of the adult striate cortex of the same cat was later recorded.
        iii. Conclusion: Input from both eyes during development is necessary for the cortex to develop the normal complement of "binocular" cells, otherwise there is no stereopsis
        iv. Theory: If the cat is older (7-8 years old) and deprivation occurs for 1 year, there is no adverse effect because the cat has already had the chance to develop the normal complement of "binocular" cells.
    d) Plasticity of the system: The visual system is "plastic" early in life, but hard-wired later in life
    e) Critical or Sensitive Period: The period during which the visual system can be influenced by environmental manipulation
        i. For cats, the experiment showed that their critical period is 6 months

        If the occlusion is stopped within the critical period, then it has no effect on the development of the normal complement of "binocular" cells
    a) The human visual system is most sensitive to environmental manipulation during the first 2 years of life
    b) The human critical period is over by ~ 7-9 years of life

2. Amblyopia

a) Reduction in best corrected visual acuity secondary to monocular deprivation during the critical period
b) Forms of monocular deprivation
   i. Occlusion Amblyopia
      - Results when the eye is occluded during the critical period. For example, congenital cataract, monocular lid ptosis
      - The faster the treatment, the better then chances for attaining good vision
   ii. Anisometropia Amblyopia
      - When the two eyes have unequal refractive error
      - Amblyopia develops when one eye has a blurred retinal image at all distances during the critical period and the other eye has a clearer retinal image at some distances
      - Ex 1: OD +6.00, OS +1.00 → In this case, during the critical period, the right eye is always 5D out of focus. In effect, it loses the competition for cortical neurons and never develops fully
      - Ex 2: OD –3.00, OS –1.00 → In this case, during the critical period, one eye is focused at 33 cm while the other is focused at 100 cm. Each eye has a clear retinal image at some distance so neither eye becomes amblyopic
      - Monocular acuities are normal, but most likely stereopsis is decreased
      - Because the retinal images of the two eyes is never simultaneously focused, the patient presumably developed few "binocular" cortical neurons
      - Prevention is best attained by having an eye exam early in life, especially during the critical period
   iii. Strabismus Amblyopia
      - Caused by constant unilateral eye turn during the critical period, which leads to amblyopia in the deviated eye
      - Mechanism: deviated eye doesn't see same object that falls onto the fovea of the good eye, causing confusion (2 separate images in the same space) → to avoid this confusion, the patient suppresses the image of the deviated eye → suppression leads to amblyopia
      - Amblyopia doesn't develop in alternating or intermittent strabismics because each eye has the opportunity to view objects. BUT, there is a profound loss of binocular vision.
   iv. Meridional Amblyopia
      - Theory: the development of sensitivity to certain orientations is influenced by visual experience
      - Experiment: Animals raised in an environment consisting of only one orientation have a disproportionately large number of cortical cells sensitive to that orientation, and total opposite number of neurons sensitive to other orientations

- If a large astigmatism is present during the critical period, the patient's visual system may develop with one meridian more in focus than other meridians. As such, it is expected that the patient will manifest better vision in certain meridians than in other meridians
- When child progresses through critical period with one clear meridian and the other out of focus, it leads to meridional amblyopia. The clear meridian wins the competition for cortical cells.

3. Development of Refractive Error
   a) Myopia
      i. Nature vs Nurture
      ii. Nature
         - Myopia is an inherited condition
         - Identical twins, when mature, tend to have highly correlated refractive errors
         - Myopic parents are more likely to have myopic children
      iii. Nurture
         - Myopia is relatively uncommon when children enter school, but increases in frequency throughout the school years. (Near work correlation is the key, although there is no definite research to support this idea)
         - In animals, suturing the eyelids shut at birth (optically blurring the retinal image early in life) leads to development axial myopia.
         - Monkeys are raised with either a minus or plus lens in place. A minus lens elongates the eye, causing it to be myopic when the lens is removed. A plus lens results in an eye with a shorter axial length, so that when the lens is removed, the eye is now hyperopic.
         - Conclusion: Emmetropization is an active process
   b) Grating Acuity
      i. OKN
         - Presumably OKN is dependent on the ability to resolve the grating. If the grating can't be resolved, OKN response is presumably not elicited. BUT, is this truly reliable?
         - OKN has 2 response pathways: through the striate cortex and the optic tract nucleus
         - Some patients who are "cortically blind" can still show and OKN response due to the fibers going through the optic tract nucleus/pathway. Thus, OKN isn't 100% reliable.
      ii. Preferential Looking
         - When given a choice, infants prefer to view patterned stimulus rather than non-patterned stimulus.
         - With PL cards, stimuli are of the same luminance, so it is the actual pattern that attracts the child

- 1 month old: 201600 (1 cycle/degree)
- 1 year old: 201100 (6 cycles/degree)
- 3-5 years old: 20120

iii. Visually Evoked Potentials (VEPs)

- Studies indicate that adult level reached at 6-8 months old

E. Normal Changes in Vision with Aging

1. Contrast Sensitivity

a) Compared to a 20 year old, a 60 year old experiences decreased contrast sensitivity at the moderate and high spatial frequencies
b) Factors: reduction in retinal illumination due to decreased pupil size, nuclear sclerosis that causes increased light scatter, aging of neural elements
c) Senile Miosis: 20 year old pupil = 5.3 mm, 60 year old pupil = 3.2 mm
d) A 60 year old receives 113 the retinal illumination as a 20 year old.
   i. Leads to a decrease in contrast sensitivity and impaired color vision
   ii. Advantage: acts as a pinhole, leading to a decreased dependence of spectacles

2. Nuclear Sclerosis

a) Yellowing of the crystalline lens
b) Increases the absorption of blue light

3. Resolution Acuity

a) Age-related reduction in high spatial frequency sensitivity is seen clinically as a reduction in visual acuity

4. Useful Field of View

a) Attention-based measure of visual function
b) How well can a patient divide their attention between two stimuli. Can they identify a foveally-fixated target while also identifying a target presented in peripheral visual field?

5. Color Vision

a) Tritan (blue-yellow) defects become more prevalent
b) Thought to be due to decreased retinal illumination and the yellowing of the crystalline lens

6. Temporal and Motion Aspects

a) Sensitivity to temporal modulations decreases with age for ALL temporal frequencies
b) The ability to detect motion diminishes with age

7. Astigmatism

a) There is a gradual shift from WTR to ATR astigmatism.
b) Probably due to changes in the crystalline lens. It increases in dioptric power in the horizontal meridian relative to the vertical meridian.

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