Biol 1724: Lecture Notes
Specific Immunity to Genetics

Specific Resistance
(The Immune Response)

functionally, the third line of defense against infections

non innate, but adaptive:
- carefully targeted
  - → recognizes a specific foreign substance and acts to immobilize or neutralize it
- amplifies the immune response, complement reactions, etc

has the following characteristics:
1. Response to a Specific Antigen
   - protein or organic molecule,
   - free or attached to bacterial cell or other pathogen
2. Systemic Response
   - effective throughout the entire body
3. Has Memory
   - resistance lasts a long time

<u>Antigens</u>

any substance that can mobilize the immune system
- → ie. provoke an immune response

can be free molecules or attached to cells of bacteria, fungi, etc

the ability of a molecule to act as an antigen depends on its size and complexity

most are large complex organic molecules (MW >10,000), not normally found in the body
- ie. intruders = nonself

especially immunogenic:
- foreign proteins
- nucleic acids
- some lipids
- many large polysaccharides

but large simple molecules of many small repeating units (eg. plastics) have little or no immunogenicity

must be foreign to the host
- our body is programmed to recognize our own
  - proteins as "**self**" ie. not immunogenic

- but these same proteins may be strongly
  - immunogenic to others
    - eg. transfusions, transplants

microorganisms and pollen grains are immunogenic
- because their surface membranes have many such foreign molecules on them

- examples of antigen containing structures:
  - bacterial capsules
  - cell wall lipopolysaccharides of G- bacteria
  - glycoproteins in cell membranes
  - attachment sites for viruses
  - bacterial toxins and extracellular enzymes

small molecules such as peptides, nucleotides, and many hormones are NOT immunogenic
- →but may become so by attaching to the body's own proteins (=Haptens)

- eg. chemicals in poison ivy, animal dander, some detergents, cosmetics, etc

actually, only certain parts of an entire antigen are immunogenic
- usually a small sequence of amino acids (~10) that triggers an immune reactions
  - → = **antigenic determinants (=epitopes)**

most naturally occurring antigens have a variety of antigenic determinants
- eg. large proteins have 100's

specific immunity involves two different kinds of lymphocytes: T cells and B cells:
- both originate in bone marrow
- T cells move to thymus for further maturation
- B cells develop further in bone marrow
- after development both are dispersed to lymph nodes and spleen until needed

The immune response (specific immunity) involves the interaction of two major processes in the body, directed by two different kinds of **lymphocytes** (WBC's):

A. Antibody Mediated Immunity
(AMI; Humoral Immunity)

B. Cell Mediated Immunity
(CMI)

Antibody Mediated Immunity

=AMI; =Humoral Immunity

involves the release of proteins called antibodies

Mediated by B lymphocytes (B-cells)

B-Cell Development & Activation

1. by the time an infant is a few months old
   B lymphocytes (B cells) have completed the 1st stage of their development:
   manufactured in fetal liver
   they synthesize up to 100,000 antibody molecules that they hold in the cell membrane

2. The next stage of development occurs in lymph nodes and spleen and only occurs if B cell encounters an antigen it recognizes:

   a. specific B cells activated by exposure to an antigen
      →antigen binds to antibodies on cell membrane of B cell
   b. triggers clonal selection and multiplication
      → produces numerous copies of identical cells with identical antibodies on cell membranes
   c. differentiation into **plasma cells** and **memory cells**
   d. **plasma cells** secrete **antibodies**
      2,000 Ab/sec over few (4-5) days, then dies
   e. **memory cells** do not secrete antibodies
      but if later exposed to same antibody they can develop into plasma cells and secrete antibodies

ie. they "remember" an earlier encounter with the antigen

Antibodies

antibodies are proteins called immunoglobins
=gamma globulin of plasma proteins

each of us has ~ a billion different kinds of antibodies
and each of these has a unique shape

each immunoglobin molecule consists of 4 polypeptide chains joined together to form a "Y" shaped molecule

each antibody has 2 or more **combining sites**
→ small concave areas at tip of arms of "Y" that are uniquely shaped and complementary to the epitope

two long (=heavy, ~400 AA's) chains and two short (=light, ~200 AA's) chains linked by disulfide bonds
constant region → same AA sequence for all in same class
variable region → =antigen binding sites (tips of Y)
the body uses ~300 gene "pieces" to make >1 Billion different kinds of antibody molecules

the amino acid sequence determines the specific shape of these polypeptide chains

this unique shape allows a specific antibody to combine with specific antigen

Classes of Antibody Molecules:

IgG

most abundant antibody in plasma
75-80% of gamma globulin
also found in internal secretions
(synovial fluid, spinal fluid, peritoneal fluid)
effective against bacteria, viruses, and toxins
plasma levels increase dramatically during secondary responses
only Ig that can cross placenta

IgM

largest of the antibodies
only found in blood
5-10% of plasma immunoglobins

1st antibody released to blood by plasma cells
during primary response
attacks specific toxins eg. diptheria, tetanus,
botulism toxin
blood group antibodies belong to this group
→ cause agglutination

Ig A

dimer
10-25% in serum
also found in body secretions:
mucus, saliva, urine, milk, tears
active against bacterial and viral infections
inhibits attachment of parasites in gut
1st to encounter bacteria in GI tract
passed to nursing child in mothers milk

Ig E

associated with allergies
causes certain WBC's to release histamine
→ dilates capillaries
→ constricts bronchi

Ig D

very low concentrations in serum
levels increase during chronic infections

formation of the antigen/antibody complex by B-cell activity does not generally destroy the invader

→ it prepares it for destruction by
non-specific phagocytosis (WBC's)
triggering complement fixation
CMI (T-cell activity)

antibodies bind to antigens to cause a variety of possible effects:

1. **Agglutination**
bind to antigens on cells to cause them to
clump together
makes it easier for WBC's to remove
2. **Precipitation**
binds soluble antigens together causing them
to precipitate out of solution
makes it easier for WBC's to remove them
3. **Neutralization**
binds to bacterial toxins (esp. exotoxins) and

causes them to be nontoxic

4. **Prevents viral attachment**
   binds to viral receptor sites to prevent viral invasion of cells
   (doesn't work for latent viruses)
5. **Stimulates Natural Killer Cells**
   antibodies coat and mark a cell for destruction by the NK cells
   =antibody dependent cell mediated cytotoxicity
6. **Complement Fixation**
   triggers complement reactions
   especially against cellular antigens
   cascade reactions can cause:
   -cell lysis
   -opsonization
   -inflammatory enhancement

primary vs secondary response

primary

→ persons initial exposure to an antigen
lag of several days before antibodies begin being produced
peak production in ~10 days

secondary

→ reexposure to same pathogen triggers memory cell response
memory cells can persist for 20 years or more
much quicker response
much stronger response

natural vs acquired immunity

natural

→ immune response is triggered due to natural exposure to a pathogen

acquired (=artificial)

→ immune response is triggered by a medical procedure, eg vaccination

active vs passive immunity

active

→ exposure triggers body's own immune response including memory cells

passive

→ subject receives antibodies from another person or animal, rather than making them himself
offers immediate protection, short term

no active antibody production is stimulated
no memory develops

eg. fetus gets antibodies from mom
eg. gamma globulin to treat hepatitis, botulism, snake bites, etc

monoclonal antibodies

specific B cell (with desired antibodies) is fused to cancer cell
→ rapid production of large numbers of the same antibody

Cell Mediated Immunity

= CMI

Mediated by T lymphocytes (T-cells)

involves a more diverse group of cells than for B cell activation

usually, slower to respond

antigens are usually larger than in AMI

most active in:
bacterial infections
destruction of malignant tumor cells
transplant rejections

T-cells also contain antigen receptors on their cell membranes

<u>T-Cell Development & Activation</u>

1. probably also first develop in fetal liver from stem cells

2. then move to thymus where they develop and proliferate

3. move into lymph nodes and spleen as T- cells

T-cells cannot recognize *free* antigens in the blood
generally need cell to cell contact to work

a. specific T cells activated by exposure to a specific antigen (on a cell)

eg. viral infected cell, cancer cell
bacterial cell

b. initiate clonal selection and multiplication
c. differentiation into several cell types
d. various T-cells secrete immunoactive chemicals
=**lymphokines**, NOT antibodies
→which direct the activities of both B and T cells and phagocytes

Kinds of T-Cells Produced:

i. **Helper T-cells** (esp CD4 cells)
most prevalent of all kinds of T cells, 65%
directly helps T and B cells to function
releases lymphokines:
→ recruit lymphocytes
→ stimulate differentiation of lymphocytes
→ help B cells recognize antigens
there can be no immune response without them

ii. **Cytotoxic T- cells** (CD8 cells)
directly kill specific target cells by lysis
especially effective against foreign cells, cancer cells, fungi , some protozoa and helminths
recognizes virally infected cells by viral antigens on cells surface

iii. **Suppressor T-cells** (CD8 cells)
restricts rampant uncontrolled immune response
dampens activity of T and B cells
brings immune response to an end

iv. **Delayed Hypersensitivity Cells**
chronic infections
cell mediated allergies

v. **Memory Cells**

Lymphokines:

various T-cells secrete immunoactive chemicals
= lymphokines = **cytokines**

soluble chemical messengers by which cells of the immune system communicate with each other

1. chemotactic factor

→ attracts macrophages to invaders

2. macrophage activating factor

→ tells macrophages to destroy antigen
gives them enhanced antibacterial activity:
increased metabolic activity
more lysosomes
increased phagocytosis

3. lymphotoxin

→ poison which kills any cell it contacts
requires direct cell contact

4. migration inhibition factor

→ halts macrophage migration

?????

lymphokines: soluble chemical messengers by which cells of the immune system communicate with each other

a. Interleukin 1

→ stimulates helper T-cells in presence of antigen
→ attracts macrophages in inflammatory resonse

b. Interleukin 2

→ proliferation of TH cells
→ proliferation and differentiation of B-cells
→ activation of Tc and NK cells

c. alpha interferon

→ inhibits intracellular viral replication
→ increases activity of macrophages against microbes and tumor cells

d. Tumor Necrosis Factor

→ toxic to tumor cells
→ enhances activity of phagocytic cells

e. GM-CSF (Granulocyte Macrophage -Colony Stimulating Factor)

→ stimulates the formation of RBC's and WBC's from stem cells

Interacations of AMI and CMI Systems:

both systems work together to increase the immune response against specific foreign antigens

eg. production of antibodies by B-cells often requires
helper T-cells
esp. "T-dependent antigens" – proteins such as viruses, bacteria, foreign RBC's, hapten–carrier combinations

eg. stimulate B-cells to differentiate into plasma cells and produce antibodies

Neuroendocrine-Immune Interactions

all three systems are interconnected
- neural links:
  - neurons innervate immune system organs such as spleen and lymph nodes
- chemical links:
  - all three produce active chemicals
    - neurotransmitters, hormones, lymphokines
  - sometimes one chemical can have effect in all three systems

all three coordinate and control the responses to the outside world

the immune system acts as a "diffuse sense organ"

relays data about inflammation or infections to brain

Examples of interactions:

eg. Brain might respond to an infection by causing fever and achy feeling (part of nonspecific defense)

eg. stress can activate parts of same pathway

eg. mental state can influence the body's resistance to disease: anxiety or psychological stress increased severity of a cold

hypothalamus→ pituitary→ adrenal→ stress

>bld sugar → reduced inflammatory response

eg. immune system can be taught to react to visual cue with an allergic reaction = conditioned response

Clinical Applications of Immunity

1. Vaccinations

based on primary vs secondary response

primary

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2. Monoclonal Antibodies

specific B cell (with desired antibodies) is fused to cancer cell

→ rapid production of large numbers of the same antibody

3. Organ Transplants and Rejections

same principle as blood transfusions

usually need immunosuppressive drug therapy

4. Allergies

immediate (acute) hypersensitivity

mediated by B cells

IGE → mast cells → histamine

anaphylactic shock

delayed hypersensitivities

mediated by T cells

antihistamines don't work

use corticosteroids

5. Immunodeficiencies

congenital

eg. SCID

acquired

eg. AIDS

6. Autoimmune Diseases

5% of adults in North America

→ 2/3rd of victims are women

normal state of self tolerance breaks down due to:

→ self reactive lymphocytes are normally silenced during development

in this case some escape and attack body

→ new self antigens (?antibodies) appear

due to gene mutation or hapten binding

→ foreign antigens resembling self antigens

trigger antibodies that not only attack foreign antigens but self antigens as well

autoantibodies & sensitized T-cells

some of most common autoimmune diseases:

eg. Multiple Sclerosis
destruction of myelin sheath of brain and spinal cord
especially in young adults
nerve fibers are severed
neurons short circuit
cycles of remission and relapse

eg. Myasthenia Gravis
destruction of neuromuscular junctions
→ Ach receptors
results in muscle weakness
typical symptom = droopy eyelids

eg. Graves Disease
increased thyroid activity
→ thyroid produces excessive amounts of thyroxine

eg. Juvenile Onset Diabetes Mellitis
destruction of beta cells in Islets of Pancreas
results in insulin deficiency

eg. Rheumatoid Arthritis
joint inflammation and destruction

eg. Lupus
attacks kidneys, heart, lungs, skin

The Respiratory System

Respiratory system functions as gas exchange system for oxygen and carbon dioxide
→ **cellular respiration** (energy production)

closely tied to circulatory system

Physiology of Respiration

External Respiration

= pulmonary ventilation

we move ~500 ml of air in and out of lungs with each breath

breathing involves 2 processes:
- inspiration
- expiration

involves moving air down a **pressure gradient**

Inspiration
- an active process
  - involves contraction of diaphragm
    - → innervated by phrenic nerve
  - may also involve external intercostals

  - contraction of diaphragm lowers pressure in thoracic cavity:
    - outside pressure > pressure in lungs → lungs inflate

  - outside: 760 mmHg ⟶ inside: 754 mmHg

Expiration
- mainly a passive process
  - relaxation of diaphragm
- volume of chest decreases, forcing air out of lungs
- may also involve contraction of internal
  - intercostals
  - inside: 763 mmHg ⟶ outside: 760 mmHg
    - (forced=up to 790 mmHg)

Factors that affect pulmonary ventilation:

1. Resistance to airflow
- in respiratory passages
- constriction increases resistance (=drag)
- mainly in bronchi and bronchioles

2. Compliance
- lungs are >100 x's more distendable than a balloon
- lungs increase in volume passively as chest cavity expands

- Pulmonary fibrosis reduces compliance

3. Elasticity of lungs
- elasticity = tendency of organ to return to normal position or shape
- lungs contain lots of elastin fibers

Emphysema = less elastic and more collagen fibers
→ requires 3-4x's more energy to breath
(15-20% vs 5% normal)

4. Surface Tension ⟶

outer surface of lungs and inner surface of alveoli
are covered with thin film of water
water has a high surface tension (very "sticky")

on outer surface of lungs:
→ visceral pleura tends to stick to parietal pleura
creates slight negative intrapleural pressure
helps to inflate lungs during inspiration

on inside of alveoli:
→ tends to cause the alveoli to collapse upon themselves

counteracted by:

a. lungs never completely deflated;
always contain some air

b. secrete **surfactant**
a lipoprotein
reduces surface tension in alveoli
not produced until 8th month of pregnancy
→ respiratory distress syndrome

pneumothorax
opening in chest cavity
eliminates pressure differential
causes lungs to collapse

<u>Respiratory Volumes</u>

the volume of air exchanged in breathing is measured with a **spirometer**

provides information on pulmonary functions

Tidal Volume (TV)
normal volume of air with each breath
small part of total lung capacity (~10%)

~500 ml

Expiratory Reserve Volume (ERV)

additional air one can expire after releaseing tidal volume
use internal intercostals to forcibly expire additional air
~1000-1200 ml

Inspiratory Reserve Volume (IRV)

additional amount of air that can be inspired in addition to tidal volume
use external intercostals to lift rib cage
~3300 ml

Residual Volume

air that cannot be removed from lungs
~1200 ml
removed in pneumothorax

Vital Capacity (VC)

largest volume of air that can be moved into or out of lungs
VC = IRV + TV + ERV

vital capacity is affected by:

a. overall size of individual, gender→ size of lungs
b. volume of blood in lungs → eg congestive heart failure
c. excess fluid in pleural or abdominal cavity
d. loss of lung elasticity → eg. emphysema
e. misc health related factors → eg. smoking, exercise, etc

Forced Expiratory Volume (FEV)

time required to exhale vital capacity

Total Lung Capacity (TLC)

maximum amount of air the lungs can hold
TLC = VC + RV
~5700-6200 ml

Minute Respiratory Volume (MRV)

amount of air that ventilates lungs each minute
index of respiratory efficiency
= TV x Breathing rate
= ~500 ml x 12

= ~6000 ml/min [6 l/min vs exercise = ~100-200 liters/min]

But of the Tidal Volume (~500 ml)
about 150 ml never gets to alveoli
remains in air passages

Alveolar Ventilation Rate
= ~350 ml x 12
= ~4200 ml/min (~70% of MRV)
= 63 gallons/hr
= 1512 gallons/day
a better index of effective ventilation
→ eliminates "dead space"
deeper breaths more effective than more frequent breaths

Disorders indicated with pulmonary functions tests:

Restrictive Disorders
diseases interfering with inspiration
pulmonary fibrosis → lowers VC
emphysema → lowers minute volume

Obstructive Disorders
diseases interfering with expiration
asthma (bronchiole constriction)
→ normal VC
→ but lower forced expiratory volume
emphysema

Alveolar Gas Exchange

composition of air:

air entering lungs	**air exiting lungs**
[78% N2]	
21% O2	14% O2
0.04% CO2	5.6% CO2

the exchange of gasses in the lungs takes place between alveolar air and venous blood

gas exchange occurs across the lining of the alveoli and capillaries (2 cell layers thick)
→ **respiratory membrane**

total surface area ~ 70 (60-80)M^2
(=760 ft^2 ~20'x38')

Gas exchange is the result of simple diffusion down oxygen and carbon dioxide concentration gradients:

concentrations of gasses usually measured in partial pressures
PO2 = 21% of 760 mmHg = 160 mmHg
PCO2 = 0.04% of 760 mmHg = 0.3 mmHg

	Alveoli		Blood Entering Lungs
PO2	105mmHg	←	40mmHg
PCO2	39mmHg	→	46mmHg

Amount of O2 diffusing into blood depends on:
1. **oxygen pressure gradient**
2. **surface area of lungs**
3. **respiratory rate**

Oxygen binds to hemoglobin inside RBC's
= oxyhemoglobin

The exchange of gasses in tissues is also by simple diffusion:

	Blood leaving lungs		Tissues
PO2	104mmHg	→	≤40mmHg
PCO2	40mmHg	←	≥45mmHg

The amount of oxygen delivered to tissue cells is affected by:
1. **rate of oxygen utilization**
   regulates the rate of delivery by controlling size of gradient
   as conc of O2 in tissues decreases; the bonds between O2 and Hb weaken
2. **Carbon Dioxide concentration**
   more CO2 → more O2 released
3. **pH**
   lower pH → more O2 released
4. **temperature**
   higher temp→ more O2 released

Dissociation Curve for Hemoglobin:

1st O2 on and off is hardest
other 3 are easier to bind or remove

eg. creates differential release of oxygen to cells needing it most

eg. More oxygen is released to active muscle cells

Myoglobin → has 1 heme group
holds onto O2 longer
accepts O2 from Hemoglobin
"middleman"

<u>Transport of Gasses in Blood</u>

Oxygen

almost all hemoglobin in blood going through lungs manages to pick up oxygen
→ 97-99% saturation
versus ~70% saturation in venous blood

→ hemoglobin has a very **high affinity** for O2

only ~1-1.5% of O2 is carried dissolved in plasma

Hyperventilation doesn't increase PO2 of blood
only slightly increases dissolved O2 concentrations
→ may deliver a little more O2 to tissues
but not much

the amount of oxygen carried in the blood then is mainly dependent on the amount of hemoglobin in blood

4 O2/hemoglobin → 250 Million Hb/RBC → 1 Billion O2/RBC

anemia decreases oxygen transport

Only 20-25% of oxygen is unloaded per circuit of bloodflow
→ venous reserve
"holding breath"

Hemoglobin saturation reduced to ~70%:
high altitudes
CV disease

CO binds to Hemoglobin even more strongly than does oxygen
→ CO poisoning (takes very little, but continuous

exposure)

Carbon Dioxide

transported in blood three major ways:

1. **7% dissolved in plasma**
   → >20x's more soluble than O2
2. **20-23% bound to hemoglobin**
   CO2 binds to amino group of hemoglobin
   (O2 binds to heme portion)
   =carbaminohemoglobin
3. **70% converted to bicarbonate ions**

$$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

this reaction occurs mainly inside RBC's
bicarbonate ions are then released into the plasma

oxygen release is enhanced by CO2 loading

<u>Regulation of Respiration</u>

normal breathing is automatic, rhythmic

Skeletal muscles of diaphragm and intercostals are innervated by somatic motor neurons

controlled by respiratory reflex centers in brainstem

Three reflex centers in brain that regulate breathing:

1. **respiratory center: medulla**

   (medullary rhythmicity area)

   establishes basic rhythm of breathing

   maintains automatic breathing rate
   → 12-15 breaths/min

   a. contain chemoreceptors that are sensitive to changes in CO2
   b. chemoreceptors in aorta and carotid sinus also monitor CO2 levels in arterial blood

elevated blood CO_2 → faster breathing

c. other chemoreceptors in aorta and carotid sinus also monitor pH

more acidic → faster breathing

d. O_2 sensors in aorta and carotid sinus detect slight reductions in O_2 and cause reflex stimulation of respiratory center

more of a backup system
→ rarely is the most important control

if cells in respiratory become hypoxic they may fail

Hypoxic drive: people with respiratory disease these O_2 receptors become more important

2. apneustic: pons

promotes inspiration, breath holding
forceful, prolonged inspiration

3. pneumotaxic center: pons

antagonist to apneustic
inhibits inspiration
fine tunes, prevents overinflation

the two centers in pons insure a smooth transition between inspiration and expiration

helps maintains rhythmicity of breathing

when connection between medulla and pons are cut breathing becomes abnormal
→ gasps

"inflation & deflation reflexes" alternate activity

helps regulate depth of breathing

occurs when stretch receptors in pleura, bronchioles and alveoli are stimulated during inspiration

→ prevents overinflation

when stretch receptors are no longer stimulated
→ prevents further expiration

Hypothalamus

irritant receptors trigger bronchiole constriction, coughing etc

Cerebrum

emotional state, eg fear, pain, can speed up breathing

can voluntarily speed up or slow down breathing
→ but can't overpower reflex controls

Pulmonary Blood Pressure

heart pumps ~5l of blood per minute
→ 5 liters in systemic circuit
→ 5 liters in pulmonary circuit

change in pressure:

systemic circuit:

averages 100 ⟶ 0
→difference = **100 mmHg**

high resistance

pulmonary circuit:

averages 15 ⟶ 5
→ difference = **10 mmHg**

low resistance
→ no pulmonary edema

alveolar airflow – blood flow coupling

if low O2/high CO2 get
→arterial constriction
→bronchial dilation
improves gas exchange in alveoli

Digestive System

We need food for cellular utilization:
- nutrients as **building blocks** for synthesis
- sugars, etc to break down for **energy**

most food that we eat cannot be directly used by the body
- →too large and complex to be absorbed
- →chemical composition must be modified to be useable by cells

digestive system functions to altered the chemical and physical composition of food so that it can be absorbed and used by the body; ie
- **→physical and chemical digestion**
- **→absorption**
- **→collect & eliminate nonuseable components**

Digestive Physiology

lumen of GI tract is continuous with outside of body
- → food being digested must be isolated from body cells since it's the same composition as rest of body
- → digestion occurs OUTSIDE the internal environment of cells and tissues

digestive system functions to
- digest or break down food
- absorb nutrients

as materials are being processed they are moved through alimentary canal by:
- **peristalsis**
- **segmentation**

Digestion

digestion = all food changes that occur in the alimentary canal

need to convert food into a form that can be absorbed and used by body cells

two types of digestion:
- **physical digestion**
  - breaking large pieces down into smaller pieces
- **chemical digestion**
  - breaking large molecules

(proteins, fats, starches, etc)
into small molecules
(amino acids, fatty acids, sugars, etc)

Mouth

food entering mouth is physically broken down
teeth
mixed with saliva
lubricant
enzyme = amylase
→ begins carbohydrate digestion
most (60%) of starch digestion by amylase from saliva occurs in stomach after swallowing bolus
at end of digestion in mouth food = bolus

Pharynx

bolus is swallowed
on swallowing
uvula closes off nares
epiglottis closes off glottis of larynx

Esophagus

wave of reflex contractions = peristalsis

Stomach

muscular contractions separate and mix food particles

in stomach bolus is mixed with gastric juices
gastric juices low pH ~2
hydrochloric acid
pepsin
→ ideal for breaking proteins into smaller fragments

body must be protected from harsh pH of gastric juices:

a. thick coating of bicarbonate rich mucous
b. tight junctions join epithelial cells to help prevent leakage
c. pepsin and HCl are secreted in inactive forms
d. stomach lining is rapidly replaced
→ renewed every 3-6 days

heartburn = cardiac valve doesn't close completely

vomiting = medullary reflex:
triggered by irritants in stomach
closing nose and glottis
relaxes cardiac sphincter
spasm of diaphragm

gastric ulcers: *Helicobacter pylori*
part of normal flora of stomach
can neutralize stomach acids
excessive growth can irritate stomach lining to produce ulcers

physical digestion is completed in stomach

once digestion in stomach is competed have a white milky liquid = **chyme**

stomach takes about 2-6 hours to empty after a meal

gastric emptying is controlled by
enterogastric reflex:
periodic opening/ closing of pyloric valve
prevents overburdening smaller duodenum

Duodenum

all physical digestion has been completed

Completes chemical digestion of food

most chemical digestion occurs here

enzymes secreted from pancreas and gall bladder

intestinal and pancreatic juices are alkaline
→ neutralize acidity of chyme

presence of chyme in duodenum triggers:
release of bile from liver & gall bladder
release of pancreatic secretions
release of duodenal secretions

1. Bile

contains no enzymes

contains
bile salts – made from cholesterol in liver
bile pigments (bilirubin, biliverdin)
cholesterol – normally remains in solution
may precipitate out as **gall stones**
is a surfactant → emulsifies fats into smaller fat droplets to speed their digestion

2. Pancreatic Juices

pancreas is an endocrine gland (insulin, glucagon)
but 98% of its tissues make and secrete digestive juices through ducts to the duodenum
include:
bicarbonates – to neutralize gastric acids
proteinases (esp trypsin and chymotrypsin)
- breaks proteins into peptides and amino acids
lipases – fats to fatty acids and glycerol
amylase – starches to mono & disaccharides
nucleases – nucleic acids into nucleotides

3. Duodenal Secretions

include:
peptidases – breaks polypeptides into amino acids
disaccharidases – disaccharides into monosaccharides
nucleosidases & phosphatases – break nucleotides into component parts

Large Intestine

some digestion occurs here due to bacteria
esp in caecum
esp herbivores → large caecum
carnivores → small or no caecum

<u>Control of Digestive Secretions</u>

secretions from digestive glands is under nervous and hormonal control

digestion begins as mainly an autonomic nervous reflex

digestion is completed due mainly to hormonal controls

1. Saliva

strictly a nervous reflex

reflex is triggered by:
- mechanical and chemical presence of food in mouth
- olfactory stimulation
- visual stimulation

salivation can also be a learned response
→ learned by association: eg. Pavlov's dog

2. Gastric Secretions

A. secretions occur in three separate phases:

cephalic phase
- secretions first activated by sight, smell, taste and thoughts of food

gastric phase
- continued secretion is triggered by presence of polypeptides in pyloric region of stomach
- stimulates parietal cells to secrete hormone = **gastrin**
- gastrin circulates within capillaries of stomach and enhance secretions from gastric glands in stomach wall
- gastrin is secreted as long as there is food in stomach

Intestinal Phase
- chyme is released into duodenum duodenum
- presence of chyme causes release of **intestinal gastrin**
- this further stimulates gastric secretions

B. Enterogastric Reflex
- slows stomach emptying to once/~20 seconds
- signaled by **stretch receptors** induodenum
- speed of reflex varies by
  - types of foods
    - eg. fats - slow; proteins – fast
  - fluidity
    - solids – slower; liquids – quicker
  - age
    - infant – fast; adult – slower

C. Presence of fat (fats float → last to leave stomach) in duodenum stimulates release of **GIP** (gastric inhibitory peptide)
→ shuts down gastric secretions

4. Bile

when chyme enters duodenum
→ secretes cholecystokinin
→ stimulates peristalsis of gall bladder

5. Pancreatic Juices

when chyme enters duodenum it causes the release of:

cholecystokinin

→ stimulates pancreas to release enzymes

secretin

→ stimulates pancreas to release bicarbonates

6. Duodenal Enzymes

may be another hormone that stimulates release of duodenal enzymes

don't know now

<u>Absorption</u>

~9-10 liters (2.5 gallons) of food, liquids and GI secretions enter tract/day

~500 – 1000 ml reaches the large intestine

150 ml is expelled as feces

~half of that is bacteria from intestines

→ 75 ml wastes

absorption occurs throughout digestive tract but most (90%) occurs in small intestine; 10% in large intestine and stomach

Stomach

some water
alcohol
a few drugs

Small Intestine

absorb ~90% of materials
absorbs virtually all foodstuffs
absorbs 80% of electrolytes
absorbs most water

Jejunum

all food stuffs
most water
most electrolytes

Ileum

reclaims some additional bile salts

Small intestine is greatly modified for absorption

→ epithelial cells are joined by tight junctions
substances cant move between cells
materials must pass through cells to get to interstitial spaces
=transepithelial transport

→ surface area is greatly increased for more efficient absorption of nutrients:

1" diameter x 10' long
→ if smooth tube **= 0.33 m^2 (3 sq ft)**

but: interior is folded
→ increases area ~3 x's

also: fingerlike projections = villi
~1mm tall
contain capillary beds
contain lacteals
→ increases area another 10x's

also: each epithelial cell of villus has microvilli
up to 1700/cell
=brush border
→ increases area another 20x's

→→→ 200m^2 (1800 sq ft)

Large Intestine
excess water and some additional nutrients

absorption can be an active or passive process:

1. most nutrients are absorbed by active transport
   eg. glucose
   amino acids
   some minerals
2. some lipids are absorbed by diffusion to lacteals
   eg. fats
   fat soluble vitamins
3. water is absorbed by osmosis
4. large molecules are absorbed by pinocytosis
   eg. a few large fats and proteins

passed to lacteals with other fats

Absorption of Specific Nutrients

especially in jejunum

1. **Carbohydrates**
   mono → facilitated diffusion → capillaries

2. **Proteins**
   amino acids → active transport → capillaries
   each requires a specific carrier
   eg. genetic diseases

   whole proteins → endocytosis → capillaries
   rarely absorbed,
   but more common in newborns
   results in food allergies
   may also be how IgA are absorbed from mothers milk

3. **Lipids**

micelles → diffusion → chylomicrons → lacteals

bile salts are essential for absorption as well as digestion
micelles = collections of fatty elements clustered together with bile salts
polar on outside
nonpolar core
micelles are much smaller than emulsion droplets and easily diffuse between microvilli to come in contact with cell surface
fats, cholesterol, fat soluble vitamins then leave the micelles and move through the cell membrane by diffusion into epithelial cells of villi
fat absorption is completed in ileum

in absence of bile, (eg gall stones), most fat passes to large intestine

once inside epithelial cells:
triglycerides are coated with proteins to produce **chylomicrons**
golgi bodies process and secrete them

a few enter capillary beds (too large)
most enter **lacteals** in villi

once in blood:
hydrolyzed back into free fatty acids that can be used by cells for energy production or converted to fat in adipose tissue

4. Nucleic Acids

nucleotides → active transport → blood

5. Vitamins

water soluble → diffusion → blood
except B12, very large, charged molecule
binds to intrinsic factor produced by stomach
taken in by endocytosis

fat soluble → micelles → etc

6. Electrolytes

most are actively absorbed throughout the length of intestine

Fe and Ca^{++} mainly in duodenum
for most nutrients the amount reaching the intestine is the amount absorbed
But absorption of Fe and Ca is closely tied to body's need:

Fe

is actively transported into mucosal cells
binds to protein **ferritin**
stored until needed or lost as cells sloughed off
women have 4x's more transport proteins than men
in blood Fe binds to protein = **transferrin**, for transport

Ca

regulated by Vitamin D
acts as a cofactor to facilitate Ca absorption
eg. <Bld Ca → >PTH:
→ >Ca release from bone
→ >reabsorption of Ca by kidney
→ renal activation of Vit D to increase

Na^+ is coupled with active absorption of glucose
and Amino acids
K^+ moves in by simple diffusion
most anions passively diffuse along a gradient
but Cl^- is actively transported

7. Water

9 L of water enters small intestine daily
95% is absorbed by small intestine (osmosis)
coupled to solute uptake
rest is absorbed by large intestine
of ~ 500 ml of chyme entering large intestine
~150 ml of feces is produced

Liver

is the largest gland in body

lies immediately under the diaphragm

consist of 2 lobes

Functions of Liver:

1. store carbohydrates, iron, vitamin A, B12 & D
2. metabolize fats, carbos and proteins
3. detoxify blood from digestive system
4. secrete bile to aid in digestion (~1pt /day)

Food, Nutrition, Metabolism

the food that we eat must do 2 things:

1. serve as building blocks, ie. nutrients
   used to maintain and build tissues

2. release energy when metabolized in cells
   breaking bonds releases energy
   we break down large organic molecules to release their energy and make ATP

food → **matter** (building blocks)
food → **energy** (metabolism, ATP)

1. Building Blocks

nutrients → the most basic atoms or molecules that we need to survive

essential vs nonessential nutrients

the body can make some nutrients itself given proper elements

some nutrients the body cannot make
→ must be in food

45 –50 different nutrients are essential nutrients
→ can't make them ourselves
eg. elements, vitamins, some AA's

elements:

macronutrients		**micronutrients**
C	18.5%	Cr, Co

H	9.5%	Cu, F
O	65%	Mo, Se
N	3.2%	Si, Sn (tin)
P	1.0%	Zn, V
Ca	1.5%	

molecules:
- O_2 (oxygen gas)
- vitamins
- 8 amino acids
- 2 fatty acids

2. energy

we break down organ foods (sugars, lipids, etc) to extract energy

chemical bond energy: break bonds
→ release energy

most cells prefer glucose but can also use lipids, proteins, etc

some cells can only use glucose

glucose + O_2 → CO_2 + H_2O + ATP

most foods are a combination of essential and nonessential nutrients that we use as building blocks and as energy

as a general rule the foods we eat contain the essential nutrients and energy sources in roughly similar amounts as they are found in the body

→ we are what we eat!

but if our diets aren't carefully selected:
- → can get too little or too much of a particular nutrient
  - eg. deficiencies may cause diseases
  - eg. excesses may be toxic
- → can bet too much or too little energy
  - need ~ 2000 Cal/day
- → may contain various additives that could be beneficial, neutral or toxic to body

Carbohydrates

Kinds in food:

mainly from plants (fruits, vegetables, and grains)

simple sugars: mono & disaccharides (honey, fruits, lactose is from milk)

complex carbohydrates = polysaccharides: starches and fiber from plants; glycogen from meats

"starch"

- virtually all starchy foods come from plants
- plant cells store glucose as starch
- long branched or unbranched chains
- packed tightly in wheat and rice grains and tubers
- also high in legumes (peas, beans)
- almost all "starchy foods" are from plants
- provide much of the food energy for people worldwide:
  - rice → Asia
  - wheat → Canada, US, Europe
  - corn → Central and South America
  - millet, rye, oats, barley

glycogen

- =animal starch
- long heavily branched polymer
- animal cells store a small amount of sugar as glycogen
- meats only contain a limited amount since its broken down quickly after slaughter
- not found in plant cells
- important in our bodies
  - each of our cells stores some sugar in form of glycogen
  - ~1lb/person
  - ~1/3rd in liver cells
    - liver glycogen plays critical role in glucose homeostasis
    - can quickly release glucose into blood when levels drop
  - ~2/3rd's in muscle tissue
    - muscles can respond to energy demands quickly by converting it to glucose for energy production

"fiber"

- structural part of plant
- not same thing as starch → undigestible
- eg. cellulose – cannot digest but essential for digestion

= roughage, fiber ["natural fiber" = sawdust]
cellulose, hemicellulose, pectins, lignins, cutins, tannin, gums
different kind of linkages between subunits
→ body lacks enzymes to split them apart
fibers important nutritionally:
affect time to absorb other nutrients from GI tract
improves flow of materials through intestine
used as fiber in breads etc = "sawdust"
some may be fermented by gut bacteria to produce additional nutrients

soluble fibers:	*fruits, oats, barley, legumes*
	slow stomach emptying
	delay glucose absorption
	lower cholesterol levels
insoluble fibers:	*veggies, wheat, cereal*
	accelerates chyme thru intestine
	?delays? glucose absorption

pectins
= jellies and jams

lignins
→ resist decomposition

<u>Uses in body</u>

energy
all carbohydrates are polymers of monosaccharides
are main energy source of all cells

ribose and deoxyribose to synthesize DNA and RNA

fiber enhances digestion
complex carbohydrates, the body cannot digest
but required for digestion

excess sugars converted to: glycogen & fats
glycogen
each cell, esp liver and muscle can store some
excess glucose as glycogen
~ 1lb/person
1/3rd in liver
2/3rd s in muscle tissue
provides quick energy in muscle cells
in liver helps maintain glucose blood levels

fats
all excess is converted to fats (adipose tissue)

Requirements

no essential carbohydrates

the amount in diet is not critical for essential nutrition

recommend 45 – 65% SN03 of diet is carbohydrates;
120-175 g/day

minimum 100g/d to prevent shift to proteins and fat catabolism

a diet high in complex carbohydrates helps control body weight
crowds out fat
reduces hunger
reduces "empty calorie" intake

enough fiber to promote digestion

recommended sugar intake ≤ 10% total energy intake

US consumption

carbohydrates comprise 51-33%SN03 of food we eat

about half of our sugar intake is natural and half consists of refined sugar (sucrose)

200-300 g/day
much refined sugar
(45 lbs/yr); >46% caloric intake

Imbalances

Deficiencies:
if not enough carbo's the body shifts to fats and proteins for energy
but some cells cannot effectively do this and may become energy starved

tissue wasting,
metabolic acidosis (from excessive fat breakdown)

Excesses:

cells convert some to glycogen (animal starch)
esp liver and muscle cells
→ allows a quicker response to energy demands
→ glycogen in liver plays critical role in maintaining blood sugar levels between meals

sugar:
US → 45 lbs/yr
"empty calories" → contribute to energy needs but no nutrients
therefore, need to consume even more calories to get proper nutrients
eg. soda: 200 cal → ~0 nutrients
3 slides bread: 200 Cal → includes 9g proteins and some B vitamins
even being careful in food selection it takes at least 1500 calories to get all needed nutrients
the less active a person is the more critical this becomes
→ sugar isn't bad, but nutrients must come 1st
dental caries (refined sugar)
obesity
not only getting more calories
but most foods with added sugar are also high in fats
heart disease
(in carbohydrate sensitive people)
?hyperactivity in children, criminal behavior
no confirming data; just anecdotes

starch & fiber:
(generally, high carbohydrate diets benefit by reducing fat intake and obesity,
reduce risk of heart disease,
reduce risk of cancer,
reduced risk of diabetes,
better GI tract health),

but excessive fiber intake in malnourished,
elderly & children can reduce mineral absorption

Lipids

a diverse group of compounds including:
triglycerides
phospholipids
sterols (including cholesterol)
eicosinoids, prostaglandins

most are polymers of fatty acids

Kinds in foods

95% of dietary fats & oils are triglycerides

responsible for much of the flavor, tenderness, aroma of food

plants high in lipids
- → nuts,
- → vegetable oils } mainly polyunsaturated fats)

animal products high in lipids
- → meats, esp organ foods
- → dairy products } most saturated fats
- → eggs

animal products are only dietary source of cholesterol

fats carry with them fat soluble vitamins (A,D,E & K)

polyunsaturated fats mostly in plant oils (grains, seeds, nuts, leafy vegetables)

cholesterol: animal foods only, not plants
esp. egg yolks, organ meats such as liver, whole milk, butter, cheese

Uses in Body

triglycerides:
- alternate fuel (concentrated stored energy)
- shock protection pads
- insulation from cold
- insulation around neurons and nerves

phospholipids:
- cell membranes
- emulsifiers to keep fats suspended in blood and fluids

sterols:
- hormones (adrenal cortex, gonads)
- bile salts
- cell membranes (0.9 of all body cholesterol)

Requirements

2 essential fatty acids: linoleic and linolenic acids

(high in fish, grains, seeds, nutsw, leafy veggies)
→ needed for
normal brain development
maintain cell membrane
make hormones
immune response

fat soluble vitamins are usually dissolved in fats ad oils we eat

80-100g/d; 25 - 35%SN03 of calories should be from fats
unsaturated better than saturated fats
≥3% required Fatty Acids (1-1.5 g/day)
<250 mg/d cholesterol

US Consumption

32 - 34%SN03 of calories in our diets are from fats

only get 10% of required amount of linoleic acid

Imbalances

(of all nutrients fats are most often linked to chronic diseases)

Deficiencies:

mainly due to inadequate amounts of essential
fatty acids;
mainly seen in infants and young children fed
nonfat milk and low-fat diets

retarded growth
reproductive failure
skin lesions
kidney and liver disorders
neurological and visual problems

Excesses:
of all nutrients, excess fat is most often linked to
chronic diseases:
obesity
>50% of those in US are overweightSN03
obesity costs ~$117 Billion/yr in USSN03
cardiovascular disease
(esp. high cholesterol
& high LDL)

some cancers (total fat intake)

Nutritional BS

1. Lecithin supplements
   - a phospholipid
   - not essential
   - body digests it like other fats
   - taken at "dosages" recommended; 7g/d
     - → can alone add 6.5 lbs/yr excess fats
   - large doses may cause GI tract distress

2. All cholesterol is bad for you
   - its made and used by liver
   - liver makes much more cholesterol than we get in diet
     - 50,000 trillion (50 quadrillion) molecules/second or 800-1500mg/d
   - need cholesterol for cell membranes
   - synthesis of steroid hormones
   - to make bile salts

   cholesterol in blood:
   - LDL's = bad guys
     - linked to increased risk of heart attack
   - HDL's = good guys
     - represent cholesterol being returned to liver for breakdown
     - high levels → decreased heart attack risk

optimal ranges	
total cholesterol	<200mg/dl
LDL	<130
HDL	>35
Triglycerides	<200

food cholesterol does not raise blood cholesterol as much as saturated fat in diet does

→ sat fats are main cause of >LDL & <HDL

Proteins

Kinds in food:

animal proteins: meats, fish, poultry, cheese, milk, eggs

plant proteins: nuts, cereals & grains, legumes

Uses in Body

amino acids to synthesize the 50,000 or so proteins in our cells
enzymes hormones regulators
transport antibodies actin/myosin
fiber(collagen) buffers complement
active transport hemoglobin clotting salt/water balance
energy alternative (last resort, muscle wasting)

Requirements

~half of 20 amino acids are essential, must be gotten in diet
10 essential in children
8 essential in adults

(body cant make proteins if any one of the Amino Acids are in short supply)

complete protein (generally animal protein)
= all essential amino acids
(meats, fish, cheese, milk, eggs)

incomplete protein (most plant protein)
= missing 1 or more essential amino acids
(nuts, cereals, legumes)
a few plant foods have complete proteins but even then most are "lower quality" → essential AA's not present in adequate amounts
(eg. soybeans have complete proteins)
vegetarians must plan meals well to get complete complement of essential AA's:
eg. blackbeans and rice
eg. peanut butter on wheat bread
eg. tofu & veggies on rice

need to maintain nitrogen balance:
within each cell, proteins are constantly being made and broken down
body can't store excess amino acids, it converts them to lipids
free amino acids may be
used immediately
released into blood
used for energy

+ Nitrogen Blance (synthesis > decomposition)	- Nitrogen Balance (synthesis < decomposition)
increased GH, Sex Hormones children pregnant women repair of injury recovery from illness	increased glucocorticoids physiological or emotional stress poor dietary intake starvation

when glucose and FA's are not available cells use AA's for energh
and to make glucose
over time, wasting of lean body tissue
carbo's and fats "spare" proteins

recommend 10 - 35%SN03 of calories from proteins

(0.8g/kgwt/day ≈ 1 - 8oz serving of meat/d)

US Consumption

15%SN03 of calories from proteins
1.5 - 2 lbs per day, also mostly also high in fats

Imbalances

Deficiencies:
can have devastating effects, esp on children
eg. Protein-Energy Malnutrition
Marasmus & Kwashiorkor
affect >500 mil children worldwide;
includes most of 40,000 children who die PER DAY
impaired brain and learning development
GI tract fails
anemia
edema
due to deficits of plasma proteins
during pregnancy – miscarriage or premature birth

Excesses:
may be risk factor in heart disease
some cancers (colon, breast, pancreas, prostate, kidney)
adult bone loss and calcium loss increases with

excessive animal (not plant) proteins in diet
obesity (protein rich foods are usually fat rich foods)

Nutritional BS

1. Protein and amino acid supplements:
   all reasons touted for their use are unfounded
   a. athletes take them to build muscle
   b. dieter to spare protein while losing weight
   c. women to strengthen fingernails
   d. individual AA's to
      cure herpes (lysine)
      sleep better (tryptophan)
      to lose weight
      to relieve pain and depression (tryptophan)

   normal healthy people NEVER need protein supplements
   they are expensive
   they are less completely digested
   when used as "replacement" they are dangerous
   eg. liquid protein diets
   → caused death in many users
   single AA's do not occur naturally in foods ad offer no benefit to the body
   the body was not designed to handle the large amounts of individual AA's in supplements
   → can create such a demand for a carrier that it prevents the absorption of other AA's
   some can be toxic at high levels

Vitamins

vitamins are organic molecules:
1. other than proteins, carbohydrates, lipids and nucleic acids
2. used in very small amounts
3. most cannot be made by body
4. don't form polymers
5. cannot be broken down for energy

categorized as:
water soluble and fat soluble vitamins
→ affects: what foods they are found in
if and where they are stored in body
toxicity

how they are eliminated

Water Soluble

dissolve easily in water, not fat
sensitive to heat and light
→generally don't store well
→lost in cooking
absorbed directly into blood and travel freely throughout the body
generally not stored well in body
→eliminated daily by kidneys
→fewer toxicities
→ needed in frequent, small doses
B's, C

B Vitamins

(B1, B2, Niacin, Biotin, Pantothenic Acid, B6, Folic Acid, B12)
not used directly as fuel
but help body *use* fuel
act as coenzymesw in many energy reactions
eg. NAD, NADP
others help in new cell formation
deficiencies cause major shutdown in body systems
toxicities are uncommon but do occur in
"pill takers"
toxicities when obtained from food alone are unknown

Vitamin C

coenzyme
collagen formation
antioxidant

Fat Soluble vitamins

dissolve easily in fat, not water
generally more heat and light stable
→not destroyed by cooking or storage
first enter lymphatic system
generally require protein transport molecules to travel in blood
blood concentrtions are maintained because body retrieves them from storage as needed
stored in liver and fat cells and accumulate; not readily excreted
→don't need every day
→easier to have toxicity: can reach toxic levels

if consumed in excess
→ needed in less frequent doses

play major roles in growth and maintenance
their presence affects health and functions of
eyes
skin
GI tract
lungs
bones and teeth
nervous system
blood

tend to appear in different foods than water soluble vitamins

A, D, E, K

Vitamin A

promotes
vision
growth
bone remodeling
immune system

animal foods, liver, fish, butter, eggs
fast foods often lack vitamin A
Vit A for acne → no effect (altered form = accutane is)
retin A for wrinkles, long term effects unknown

Vitamin D

not essential
body can synthesize it with UV
UV and liver ad kidney convert precursor to active form
liver and kidney disease can cause symptoms of deficinecy
acts like hormone
increases Calcium absorption and raises blood calcium levels

egg yolks, liver, fish, butter, fortified milk
sunscreen >spf 8 prevents activation
whites just need 15 minutes of sun on hands, face and arms
darks need up to 3 hours of exposure

Vitamin E

antioxidant: protects lipids and cell membrane

vegetable oils, fruits

does NOT:

- improve physical performance
- enhance sexual performance
- slow aging
- prevent gray hair
- prevent wrinkles
- slow parkinsons

Vitamin K

blood clotting

synthesized by bacteria in GI tract

liver, leafy green veggies, cabbage

Minerals

inorganic elements

cannot be changed or broken down

→ no special care to preserve during storage or prep

→ but may leach into water and be lost during cooking

4% of body weight

some minerals are easily absorbed into blood and transported

others need carriers to be absorbed and transported

body requires relatively large amounts of 7 minerals:

- **Calcium** [2.5lbs/132lbs]
- **Phosphorus** [1.3 lbs/132 lbs]
- **Sulphur** [1/3rd lb/132 lbs]

} 75% = calcium and phoshorus

- **Sodium**
- **Potassium**
- **Cloride**
- **Magnesium**

} [1/2 lb/132 lbs]

Calcium :

bones and teeth

membrane transport

nerve transmissions

muscle contractions

heart rhythm

blood clotting
enzyme cofactor

Phosphorus :
bones and teeth
ATP
creatin phosphate
DNA & RNA
phospholipids
active transport

Sulphur
most proteins

K, Cl, Na
osmotic balance
nerve impulses
muscle contractions

Magnesium
coenzymes

trace amounts of 12 others:

F, I, Fe,
F → strengthens bones
I → thyroid hormones
Fe → hemoglobin

Co, Cr, Cu, Mn, Se, Zn
cofactors for enzymes

in general, the body absorbs nutrients bet from foods in which they are diluted a dispersed

taken in pure concentrated form they are more likely to interfere with absorption other nutrients:
eg. >Zn → hinders Cu and Ca absorption
>Fe → hinders Zn absorption
>Ca → hinders Mg and Fe absorption
>Mg → hinders Ca and Fe absorption

eg. even fortified foods can cause problems
> ß carotene → interferes with Vit E metabolism
> Vit E → interferes with Vit K activity

several professional nutritional societies have indicated
that people should ordinarily SHOULD NOT use
supplements

when one does need nutrients
- 1st try to get them from foods
- 2nd multivitamin, mineral supplements
  - betw 50-150% RDA for each nutrients are best
    (these are ranges normally found in foods and are therefore within tolerances)
- 3rd treat any supplement like medicine

Vitamin & Mineral Supplements BS

~40% of US population takes supplements regularly
~$4 Billion/year spent

~20% take multivitamins

others take large doses of single nutrients

especially:
- Vit C
- Iron
- Calcium

Most are self prescribed; only a few are physician recommended

why:
- dietary insurance -just in case not getting
  - adequate amounts
- to protect against certain diseases

vitamins are best taken as supplements:
- after complete nutritional assessment
- in such cases mineral supplements may be as
  - important as vitamin supplements
    - → people whose diet lacks certain vitamins
      probably lack several minerals as well

Arguments Against taking supplement:

1. Toxicity

Often goes unrecognized, esp if chronic

Eg. A woman took 1000 RE vitamin A/day for > 10 years (75-750 RE is safe range)
Was diagnosed with liver disease
Condition cleared up when she discontinued supplements

toxic overdoses in children are fairly common
poison control center gets >30,000 calls/yr on children
<6yrs old swallowing large doses of supplements
fruit flavored, shaped like cartoon characters

Iron containing supplements are esp toxic and fatal

some believe supplements should have warning labels

2. Often accompanied by life threatening misinformation

some ill people believe high doses of a vitamin or mineral can be therapeutic

false claims are exceedingly common
eg. member of Consumer Health Education Council called 41 Houston area health food stores
asked to speak to person who provided nutritional advice
caller said that they had brother sick with AIDS
All 41 offered proiducts they said could "strengthen the immune system
30 said they sold products that would cure AIDS

similar inquiries found people who said they could treat:
headaches dizziness fatigue
kidney stones glaucoma sudden wt loss
stress cancer

none recommended callers obtain medical advice

people with health problems are more likely to take supplements than others
yet, today's health problems un US ar more likely to be due to overnutrition and poor lifestyle choi8ces than to nutritional deficiencies

many falsely believe that
the food supply contains inadequate nutrients
that supplements provide energy
supplements can enhance athletic performance
supplements can build lean body mass without work or

faster than work alone

3. **On individual basis we have Unknown Needs**
   no one knows how to formulate the ideal supplement:
      what nutrients should be included
      how much of each for each person

   surveys have shown no relationship between the supplements
      people take and the nutrients they actually need

4. **May give a false sense of security**
   may lull people into eating irresponsibly
   produce self diagnosis when symptoms of a disease come on

Good Reasons to take Supplements:

1. **To Correct Overt Deficiencies**
   eg. scurvy, pellagra, rare but still occur
   may require therapeutic doses 2-10x's RDA's

2. **Improve Nutritional Status**
   subclinical deficiencies are more difficult to see and
      are probably much more common
         eg. habitual dieters, vegetarians, elderly
   few people get RDA for all nutrients every day
   but most receive average needs for all nutrients

3. **Reduced Disease Risk**
   may help,
   eg. may be susceptible to osteoporosis
         esp if lactose intolerant or allergic to
         milk

4. **To Support Increased Nutritional Needs**
   eg. in certain stages of life cycle
      eg women of childbearing age → folate
      eg pregnant or breast feeding women
         → Fe, Ca^{++}, folate
      eg. newborns → Vit K

Metabolism

Digestion breaks down complex organic molecules into their component parts:
glucose, glycerol, fatty acids, amino acids,
nucleotides

metabolism focuses on what happens to these substances in the body cells

metabolism = sum of all chemical reactions that occur in the body
anabolism = synthesis; requires energy
catabolism = decomposition; releases energy

energy transfer
couples anabolism to catabolism: ADP $\rightleftharpoons$ ATP

often an energy releasing step is **coupled** with a energy requiring step

Metabolic Pathways

Metabolism in most cells is a collection of groups of enzymes forming a metabolic pathway

many of the reactions occurring in cells occur in a sequential, stepwise fashion = **metabolic pathways**

→**intermediate products**
→branching
→end product inhibition
→genetic errors

Most chemical reactions and entire metabolic pathways that occur in cells are **reversible:**
same enzyme may catalyze reaction in either direction
reaction rate and direction depends partly on the concentrations of substrates and products
=Law of Mass Action

$$\text{eg. } H_2CO_3 \xrightarrow[\text{carbonic anhydrase}]{} H_2O + CO_2$$

{rate & direction of reaction depends on substrate concentrations}

Major Catabolic Pathways
(energy producing)

Carbohydrates

carbohydrates are broken down into simple sugars (=monosaccharides) by digestion and absorbed into the body

most cells use glucose as their main energy source

complete breakdown involves 3 metabolic pathways:

1. Glycolysis
2. Krebs Cycle
3. Electron Transport Chain

1. Glycolysis

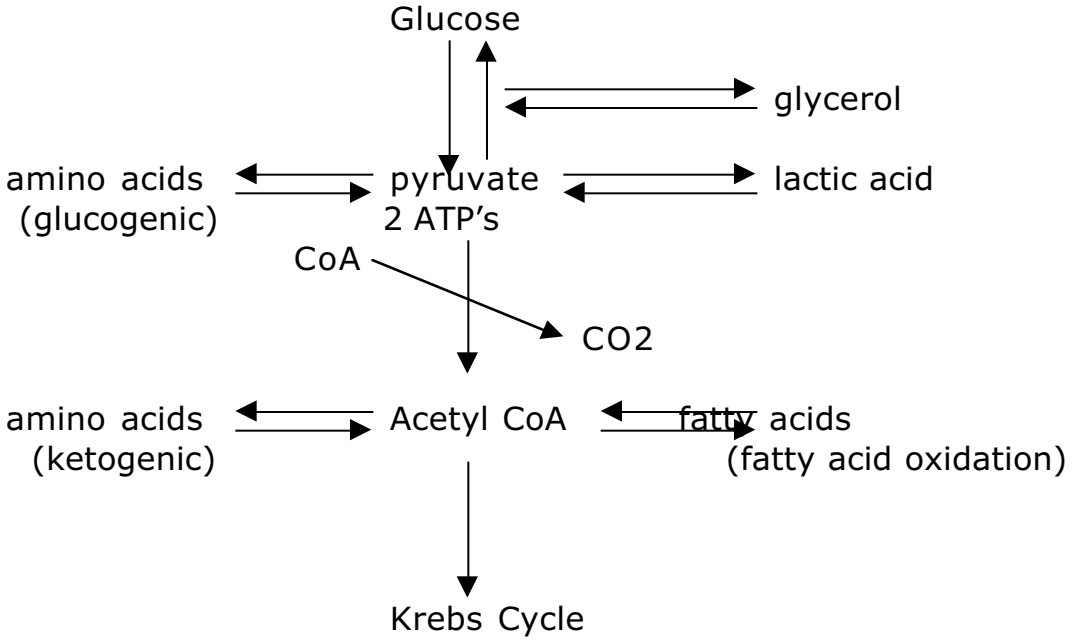
glucose is broken down into 2 pyruvic acids

2 ATP's are made in the process

if free oxygen is available pyruvic acid is converted to **Acetyl CoA**

if no free oxygen is available it is converted to **lactic acid** (toxic waste product)

fatty acids and amino acids can also be broken down into Acetyl CoA:



Fats

most (95%) are triglycerides;
→digested to glycerol and fatty acids

glycerol is converted to pyruvate

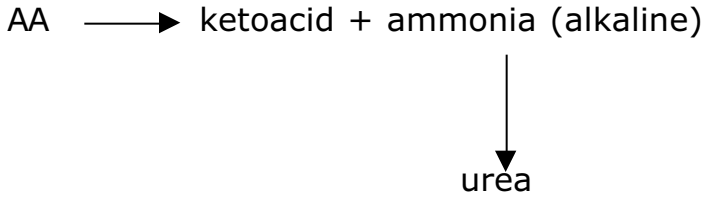
fatty acids are taken apart 2 Carbons at a time to make Acetyl CoA

cells can make glucose form pyruvate and other 3-C compounds, but NOT from 2-C fatty acid fragments

therefore, for the most part, fat cannot provide energy for RBC's or the brain and nervous system
→ only glycerol from fats can be converted
(~5% of wt of triglyceride)

Amino Acids

if consumed in excess of need to make new proteins they are 1st deaminated:



liver takes the ammonia to make urea

most are glucogenic
→can provide glucose to body

some are ketogenic
→ can be used to make body fat, not glucose

some enter Krebs Cycle directly
→ or can be used to make glucose

Therefore, proteins, not fats are a fairly good source of glucose when carbohydrates are not available

only some AA's are essential; others can be made given a source of Nitrogen:
=**Transamination**

transfer amino group from one AA to a keto acid

mainly occurs in the liver
liver makes ammonia → kidney excretes urea
high bld ammonia → liver disease
high bld urea → kidney disease

need water to excrete urea (osmosis):
with high protein diet excess water is lost as more urea is excreted
→ apparent weight loss with high protein fad diets

2. Krebs Cycle & Electron Transport

if energy is needed, Acetyl CoA will enter the Krebs Cycle and ETS

In Krebs cycle H's, CO_2 and ATP are made

ETS involves a series of proteins that serve as electron carriers

electrons are removed from hydrogen atoms

energy is removed from electrons

last step requires O_2 to form water

process cannot occur without adequate O_2

The Body's Energy Budget

energy is measured in unites called kcals = Calories

the more H's a molecule contains the more ATP (energy) can be generated

of the various energy pathways:
fat provides the most energy for its weight
note all the H's → more oxidation can occur

eg: glucose has 12 H's → 38ATP's
a 16-C FA has 32 H's → 129ATP's

we take in energy continuously
we use energy periodically

optimal body conditions when **energy input = energy output**

any excess energy intake is stored as fat

average person takes in ~1 Million Calories and expends 99% of them
→ maintains energy stability

1 lb of body fat stores 3500 Calories

454g: 87% fat 395g x 9 Cal/g = 3555 kcal

would seem if you burn an extra 3500 Cal you would lose 1 lb; and if you eat an extra 3500 Cal you would gain 1 lb

not always so:

1. when a person overeats much of the excess energy is stored; some is spent to maintain a heavier body
2. People seem to gain more body fat when they eat extra fat calories than when they eat extra carbohydrate calories
3. They seem to lose body fat most efficiently when they limit fat calories

For overweight people a reasonable rate of wt loss is
1/2 – 1 lb/week
→ can be achieved with Cal intake of ~ 10 Cal/lb of body wt.

Quicker Weight Loss:

1. may lose lean tissue
2. may not get 100% of nutrients
3. may result in binge eating/crash diet cycle
4. quick weight changes are not just fat
   normal, long-term wt gained or lost = 75% fat, 25% lean
   starvation: ~ 1/2 and 1/2 fat to lean

eg. **fasting** after a meal:

1. when we eat, excess C, P, F converted to glycogen and fat

2. later (hrs to ~1 day) glycogen and fat are used for energy

3. continued fast (or starvation)
   proteins and fats are used for energy

low bld glucose → liver begins to make glucose
from lactic acid and amino acids

normally, brain and nerve cells consume
~2.3 of daily glucose needs
(400-600 Cal; 20% of all energy used in body/day)

therefore, body protein in muscles and liver always breakdown to some extent during fasting

the amino acids that can't be used to make glucose are used as energy source by other cells

this breakdown of body protein is an expensive way to get glucose

in 1st few days of a fast:
→ body protein provides ~90% of glucose
→ glycerols provides ~10%

if protein loss were to continue at this rate
→ death would occur in ~3 weeks regardless of the quantity of fat someone had stored

but; as fast continues, fat breakdown also increases (almost doubles)

brain cells adapt:
→ uses AcetylCoA units made from fatty acids to make **ketone bodies**

brain can use these ketone bodies for energy

after ~10 days ketone bodies are meeting much of the brain's energy needs

but some areas still rely exclusively on glucose
→ body protein is still needed

ketone bodies ~ ketoacids
→ body goes into acidosis; bld pH declines
→ ketone bodies spill into urine =ketosis
→ ketosis suppresses appetite

this has served as justification for ketosis producing diets

but

1. *any* kind of food restriction leads to reduced appetite
   → a well balanced, low cal diet induces loss of appetite without harmful side effects

2. ketosis reduces metabolism to conserve tissue
   → loss of fat is greatly reduced (less than what would be lost on low cal diet)

Low Carbohydrate Diets

similar to fasting
glycogen reserves are spent
protein is metabolized to make glucose
eventually get onset of ketosis

hype:
brings dramatic wt loss in 1st few days

but:
much of this loss is glycogen and protein and large amounts of water and minerals

eg. 7 lb loss in 2 days:
1 or 2 lbs of fat
5-6 lbs of protein, water, minerals

after diet, weight quickly rebounds

Protein Sparing Diets

ingesting only protein
but this protein is used to supply glucose
carries serious health risks:
ketosis
vitamin and mineral deficiencies
fluid loss
poor long term record of success
→ people generally regain weight
now sold only to doctors or hospitals and must carry a "Protein Diet Warning"

Measuring Energy Input (Food Calories)

Bomb Calorimeter
→ burn food and see how much heat it gives off

but: body is less efficient than the calorimeter in converting food to energy. Can be corrected

also varies by proportion of Carbos, Fats, Protein in the food

Food intake:
controlled by many factors that affect hypothalamus

most eat at 4 hr intervals; stomach is designed this way

empty stomach delivers "hungry" message to brain
→ people who restrict their E intake → hunger diminishes with time

people can adapt to excessive amounts as well

Measuring Energy Output

the body converts E in food to ATP at ~50% efficiency

the rest is lost as heat

when ATP is used again to do work (movement, heartbeat, nerve impulses, active transport, etc) again ~50% is lost

→ overall efficiency of converting food to work ~25%

the other 75% is lost as heat

the work itself also generates heat

therefore, the total amount of heat the body produces reflects the amount of energy it is burning

measured by **direct calorimetry**
= heat production

or by **indirect calorimetry**
= amt of O_2 consumed or CO_2 expelled
use a respirometer
→ every time 1 L of O_2 is consumed,

4.83 Calories of heat har produced

There is a tremendous variation in daily caloric requirements

1300 - 5000 Cal/day

average male = 2900
average female = 2100

affected by:

1. age
   2 yr old burns 2x's Calories/lb as an adult

2. Weight
   the more a person weighs, the more total energy is required but probably less energy/lb
   → normal wt adult may be 1.5x's more BMR/lb than obese person
3. exercise
   strenuous exercise can increase metabolism up to 40 x's for a short period

4. stress
   severe stress can increase metabolism over 160 x's over short time

5. metabolic hormones
   eg pituitary, thyroid, GH
   eg. GH can raise BMR 15-20% during growth stage

6. body temperature
   1º C → 10% increase in MR
   high fever may double the metabolic rate

7. pregnancy
   20% increase last trimester
   60% increase during lactation

   → difficult to define a "normal" metabolic rate

Components of Energy Expenditure:

1. Basal Metabolism (60-65%)
2. Physical Activity (25-30%)
3. Thermic Effects of food (10%)
4. Adaptive Thermogenesis (?)

1. Basal Metabolic Rate

easier to define a "**Basal Metabolic Rate**" =
- is the metabolic rate
  - at rest
  - after a 12 hour fast
  - after > 1 hour after exercise

is NOT a minimum

at least 2/3rds of energy spent each day
- maintain body temperature
- nerve impulses
- heart beat (100,000x's/day)
- posture
- kidney filtration
- etc

2/3 – 3/4 of body energy is used for maintenance
- = Basal Metabolism

only 1/4 – 1/3 is used in voluntary muscle activity

BMR represents our major energy expenditure
- ~1 Cal/kg/hr
  - eg. 150 lb person = 55 Cal/kg/hr = 1320/day

BMR is highest in people with more lean body mass

BMR is also greater in tall people → >surface area

BMR declines with age ~5%/decade

2. Physical Activity

most variable component of energy expenditure

a heavy person uses more energy/minute than thinner person

3. Thermic Effect of Food

the body uses energy to process food
- eg. GI tract muscles
- eg. secretory cells

eg. active transport

is proportional to energy intake

usually ~10% of food intake is used to digest and absorb that food

eg. 2000 Cal → 200 Cal used to digest and absorb

4. Adaptive Thermogenesis

some energy is spent when body must adapt to changed conditions
eg. cold
overeating
starvation
trauma
stress

→ need to build hormones and enzymes necessary
to cope

extremely variable

not usually included in calculations

Regulation of Body Temperature

regulation of body temperature is vitally imortant
→ enzymes work in narrow temperature range

even slight shifts can disrupt metabolic balance and produce disorders

normal temperature of body core = 98.6º F (37º C)

homeostasis requires that
heat energy output = heat input

skin plays a key role in this process

all chemical reactions produce heat as a byproduct
→ more activity → more heat is produced

muscle cells are the major heat producers

<u>Heat Homeostasis</u>

Excessive Heat (Body Temp Too High)

nerve impulses from skin and body and warmed blood send message to thermostat in hypothalamus

causes dilation of blood vessels in skin

also deeper blood vessels constrict
→ blood is diverted to body surface

heat is lost by:

1. **Radiation (IR energy)**
   most heat is lost this way
2. **evaporation**
   nerves stimulate sweat glands in skin to release fluid
   as fluid evaporates it absorbs heat
   eg. sponge bath for fever patients
3. **conduction**
   contact transfer
   eg. chair seat, clothes, etc
4. **convection**
   heated air moves away from body
   cooler air moves in

Inadequate Heat (Body Temp Too Low)

brain triggers different response to reduce heat loss
→ skin blood vessels constrict
→ sweat glands become inactive

if the body is still losing too much heat may stimulate muscles to contract slightly
→ increases cell respiration → releases more heat

also may get shivering
→ rhythmic contractions to increase metabolism of muscle cells to produce more heat

Body Weight, Body Composition & Health

weight gains and losses tell little about how the body's composition may have changed
→ but this is how most judge their "fittness"

for most: "overweight" = "overfat"

healthy body weight is defined by 3 criteria:

1. a weight within a suggested range
2. a fat distribution pattern associated with a low risk of illness
3. no medical conditions that would suggest a need for weight loss

Healthy Weight Standards

often do not account for age or gender

based on insurance data which underrepresents minorities and elderly

Body Mass Index

many prefer BMI to Weight tables

= kgwt/(ht in m)^2 or wt (lbx705)/(ht in inches)^2
normal: males 20-25
females 19-24

overweight if BMI = 25-30
obesity if BMI = >30

if >30 → greater risk of premature death
if >35 → 2x's as likely to die prematurely
if >40 → greater CV disease

US average BMI = 26.3

studies show a "J" shaped relationship between body weight and mortality
→ people who are underweight or extremely overwieght carry high risks of early death

Health Risks of Underweight

1st to die during famine

more at risk when tests require fasting

in greater danger when fighting a wasting disease like cancer
→ many people with cancer die not form cancer but from malnutrition

underweight women more likely to be infertile

pregnancy may result in unhealthy infant

Health Risks of Overweight

obesity hs been declared a "disease" because so many health risks are associated with it:

diabetes	cardiovascular disease
hypertension	sleep apnea
osteoarthritis	abdominal hernias
some cancers	varicose veins
gout	gall bladder disease
liver malfunction	arthritis
flat feet	respiratory problems

complications in surgery and pregnancy
greater rate of accidents

obesity related illnesses cost $39 Billion/yr (1986)

Some Examples:

1. **Cardiovascular Disease**
   - strong relationship
   - central obesity is as important risk factor as high blood cholesterol, hypertension and smoking
2. **Diabetes**
   - Adult Onset (Noninsulin dependent) diebetes is 3x's more likely to develop in obese than nonobese person
   - Central body fat cells appear to be larger and more insulin resistant than lower body fat cells
3. **Cancer**
   - risk of cancer increases with body fat
   - not sure why – may be correlated with greater levels of some hormones
     - eg. estrogen in women

Total Body Fat

variable

can be estimated in several ways:

1. **skinfold measurements**
2. **waist/hip ratios**
3. **Hydrodensitometry**

1. skinfold measurements

~ 1/2 the fat in body lies directly beneath the skin

the thickness of this subcutaneous fat is directly reated to total body fat

fat fold measurements correlate directly with the risk of heart disease

they asses risk better than BMI

2. waist/hip ratios

is also a good indicator of fat distribution

waist circumference/hip circumference = WtoH Ratio

but may not be appropriate for women, older people or some ethnic groups

may also not be useful in assessing **changes** in body fat

3. Hydrodensitometry

take two weights: one on land, other in water

gives a measure of the body's volume

can calculate the body density

from this can estimate % Body Fat

<u>Fat Values</u>

eg normal wt male: 10-25% body fat
normal wt female: 18-32% body fat

athletes gererally lower
eg. males: 5-10%
females: 15-20%

some need more fat than others
eg. Alaskan fishermen
eg. starting pregnancy

research has shown that health problems develop when fat exceeds:

22% in men <40 yrs old
25% in men >40 yrs old
32% in women <40 yrs old
35% in women >40 yrs old

if not enough body fat:

1. reduced hormone synthesis
2. infertility
3. depression
4. abnormal hunger regulation
5. unable to keep warm

→ fashion models are generally unhealthy

Fat Distribution

may be more important than % fat alone

2 major kinds of fat distribution patterns:

1. lower body fat
2. upper body fat

1. lower body fat

fat around hips and thighs

is most common in women in reproductive years

is not associated with any health risks
(except children!)

2. upper body fat

(=central obesity, = intra abdominal fat)

stored around abdomen

presents a greater risk than fat elsewhere in body

increases risk of premature death due to:
heart disease
stroke
diabetes
hypertension

some cancers

abdominal fat is common in men and in women
after menopause

also, people with central obesity smoke more and drink more than average
→ smoking *may* directly affect fat distribution

more exercise → less central obesity

upper body fat seems to go straight to liver
→ LDL's

Urinary System

Urine production and eliminations are one of the most important mechanisms of body homeostasis
→ composition of blood is determined more by kidney function than by diet

all body systems are directly or indirectly affected by kidney function

kidney function is closely tied to circulatory system

typically referred to as "excretory system"

excretory wastes = metabolic wastes
→ chemicals & toxins produced by cells during metabolism

but we have several organs that serve an **excretory function** other than kidneys:

1. **kidneys**
2. **skin**
   sweat glands rid body of water, minerals, some nitrogenous wastes (ammonia)
3. **lungs**
   rid body of CO_2 from energy metabolism of cells
4. **intestine**
   in addition to getting rid of undigested food residue
   feces also contains some metabolic wastes as well

bile pigments
salts
calcium
some toxins

Functions of Urinary System:

1. removal of metabolic wastes
2. elimination of toxins
3. elimination of excess nutrients
4. elimination of excess hormones
5. regulation of fluid volume
6. regulation of electrolytes
7. regulation of acid base balance
8. regulation of blood volume and pressure
9. erythropoiesis
10. calcium absorption

Histology of Kidney

nephron is basic functional unit of the urinary system
can find various parts of the nephron and its blood supply in the cortex and medulla of kidney

Nephric Tubule

the nephric tubule is organized into several discrete structures

Bowman's Capsule
cup shaped mouth of nephron
usually in cortex

Proximal Convoluted Tubule
attached to Bowman's Capsule
highly coiled (convoluted)
inner surface contains microvilli

Loop of Henle
large loop consisting of:
descending limb &
ascending limb
extends down into medulla

Distal Convoluted Tubule
appears similar to PCT

Collecting Tubule

many DCT's drain into one collecting tubule
bundles of collecting tubules = **pyramids**

Pyramids drain into **Calyces** (sing. = **calyx**)

Calyces coaslesce to form **pelvis**

Blood Supply

kidneys are highly vascularized

every minute, 1200 ml/min of blood flows through kidneys
→=1/5th of cardiac output
45 gallons/day
all blood ~60x's/day

Renal Artery
brings blood to kidney
branches into smaller and smaller arterioles

Afferent Arteriole
bring blood to individual nephrons

Glomerulus
dense capillary bed
formed by afferent arteriole
inside Bowman's capsule
Bowman's Capsule + Glomerulus = Renal Corpuscle

Efferent Arteriole
blood leaves glomerulus via efferent arteriole
[→ artery→capillary bed→ artery]

Peritubular Capillaries
efferent arteriole divides into another capillary bed
surrounds the rest of the nephric tubule
(PCT-LH-DCT-CT)

Urinary Physiology

urine formation in nephrons occurs by:
1. **filtration**
2. **reabsorption**

3. secretion

1. Filtration

occurs in renal corpuscle:

Glomerulus → Bowmans Capsule

water, salts, small molecules and wastes are filtered out of blood

capillaries of glomerulus:

fenestrated capillaries

→ act like sieve

have **higher filtration pressure** than other capillaries of body

afferent arteriole is larger than efferent arteriole

→ increases pressure in glomerulus

presssure ~45mmHg

(vs 35 mmHg in most capillaries)

not all water leaks out, some is retained since proteins and solutes that remain in blood attract water by osmosis

(water follows salt)

if blood pressure is reduced

→ urine formation slows down

kidneys can maintain a fairly constant filtration rate by:

1. renal autoregulation

   kidney adjusts its own resistance to blood flow despite changes in systemic blood pressure by constricting and dilating local arterioles

   = autoregulation

2. renin-angiotensin system

   mainly controls systemic blood pressure in emergencies but will also increase pressure in glomerular capillaries

   renin is secreted by cells in walls of DCT (juxtaglomerular cells) in response to:

   decreased BP: below 80 mmHg

   eg. hemorrhage, dehydration

   direct sympathetic stimulation

renin activates angiotensin (plasma protein)
angiotensin causes vasoconstriction of arterioles throughout the body
→ raises blood pressure

3. local chemicals
some chemicals secreted by kidney have local effect on blood vessels

eg. prostaglandins (tissue hormones)
→ some vasodilators
→some vasoconstrictors
eg. NO → vasodilator
eg. kallikrein (renal enzyme)
→ vasodilator
eg. adenosine
eg. endothelin

Sympathetic stimuli can override the above:

renal autoregulation can be overridden by emergency or stress

sympathetic fibers trigger strong constriction of afferent arterioles

shunts more blood to heart, brain, muscles

filtrate is essentially the same composition as plasma without formed elements or proteins

solutes (filtrate) enter Bowmans capsule

2. <u>Tubular Reabsorption</u>

urine is not the same composition as this filtrate
needed nutrients are conserved
wastes and toxins are eliminated
blood levels of fluids, salts, acidity etc are actively reglulated

reabsorption is more selective

occurs all along nephric tubule

overall, ~99% of glomerular filtrate gets reabsorbed

only ~1% of original filtrate actually leaves the body as urine**Composition of Plasma, Filtrate & Urine** (solids in grams/24hrs; water in liters/24 hrs)					
			Reabsorbed		
	Plasma	**Filtrate**	**Amount**	**%**	**Urine**
Proteins	8,000	15	15	100.0%	0
Glucose	180	180	180	100.0%	0
Salts	1,498	1,498	1,486	99.1%	12
Water	180,000	180,000	178,500	99.2%	1,500
Urea	53	53	28	52.8%	25
Uric Acid	8.5	8.5	7.7	90.0%	0.8
Creatinine	1.4	1.4	0	0.0%	1.4

different substances are reabsorbed back into blood from different parts of tubule:

Proximal Convoluted Tubule

~80% of materials to be reabsorbed are reabsorbed in PCT

cells lining PCT have

microvilli

more motochondria

all small proteins, glucose, amino acids are reabsorbed

most water, most salts are reqbsorbed

some wastes

Loop of Henle

additional Cl^+ and Na^+ ions are reabsorbed by active transport

countercurrent mechanism:

high salt conc is maintained in medulla around loop

ascending limb is impermeable to water

creates high conc of salts

Distal Convoluted Tubule & Collecting Tubule

high salt conc around nephric tubule causes water reabsorption in DCT and CT

both salt and water reabsorption is partially controlled by hormones:

Na^+ & K^+ by aldosterone

H2O by ADH & aldosterone (indirectly)

Aldosterone:

secretion controlled by K^+ & Na^+ ion concentrations in tissue fluids

also affect reabsorption of water

tied to renin secretion

diuretics tend to increase Na^+ reabsorption and increase K^+ loss

AntiDiuretic Hormone:

No ADH → tubules are practically impermeable to water →release hypotonic urine

with ADH → tubules are permeable to water

osmosis causes water reabsorption →release hypertonic urine

3. <u>Tubular Secretion</u>

cells of DCT and CT can secrete some substances

esp K^+ and H^+

also NH4 and

some drugs (eg. penecillin)

can be active or passive processes

usually urine is slightly acidic

→ normal diet produces more acid than alkaline waste products

<u>Renal Clearance Rate</u>

the concentration of wastes in blood leaving kidneys (renal vein) is usually lower than their conc in blood entering kidneys (renal artery)

→ blood is cleared of wastes

can estimate filtration rate of kidneys

need chemical that is filtered but not reabsorbed

eg. creatinine (but some is secreted too)

eg. inulin

measure how much of a known amount appears in urine then

Glomerular Filtration Rate = Renal Clearance Rate

Average Renal Clearance Rate
for most substances is ~20%
→~20% of materials in renal blood are
filtered and not reabsorbed/transit

requires many passes thru kidneys to completely rid blood of something

Reabsorption & Secretion of Specific Nutrients

1. Glucose

easily filtered
requires energy to reabsorb
minimum amount of glucose in plasma to cause
glucose to appear in urine
= renal plasma threshold
= 180-200 mg/100 ml

glycosuria/hyperglycemia
→ plasma glucose >200 mg/100ml

2. Amino Acids

all require carriers for active transport
presence in urine may be due to:
excess amounts in blood
missing or defective carriers

Inherited Diseases Associated with Presence of Specific Amino Acids in Urine

Amino Acid	Disease	Cause of Disease	Effects of Defect
cystine	Cystinuria	defective cystine carriers	kidney stones
tryptophane	Hartnup disease	defective tryptophane carriers	cells deficient in NAD and NADP
methionine	Homocystinuria	enzyme defect causes buildup of this intermediate product	speech defects, mental retardation
phenylalanine	Phenylketonuria	enzyme defect causes buildup of this intermediate product	severe mental retardation

3. Sodium

90% of filtered sodium is reabsorbed in PCT
additional 10% may be absorbed in LH due
to effects of Aldosterone:
without aldosterone
→8% of rest is reabsorbed

→2% is lost in urine (~30g/d)

with aldosterone

→ all 10% is reabsorbed

→ urine has 0 sodium in it

4. <u>Potassium</u>

90% of filtered potassium is reabsorbed in PCT

high blood $[K^+]$:

may occur in metabolic acidosis

can cause cardiac arrhythmias

low blood $[K^+]$:

can cause arrhythmias, muscle cramps

additional 10% may be absorbed in LH due to effects of Aldosterone:

without aldosterone

→ all 10% is reabsorbed

with aldosterone

→stimulates secretionof K^+ into DCT

up to 50x's more than was originally filtered

diuretics cause

greater reabsorption of sodium and

increased loss of potassium

→ may require KCl supplements

5. <u>Hydrogen Ions (H^+)</u>

linked to potassium secretion

6. <u>Bicarbonate Ions ($HCO3^-$)</u>

usually all is reabsorbed

Urine Analysis

the kidneys perform their homeostatic functions of controlling the composition of internal fluids of body

the by product of these activities is Urine

urine contains a high concentration of solutes

in a healthy person, its volume, pH and solute concentration vary with the needs of body

during certain pathologies, the characteristics of urine may change dramatically

an analysis of urine volume, physical and chemical properties can provide valuable information on the internal conditions of the body

Physical Characteristics

1. Volume

normal = 1000 – 1800ml/day (2-3.5 pints)
influenced by:
- blood pressure
- blood volume
- temperature
- diuretics
- mental state
- general health

2. Specific Gravity

weight compared to water
- water = 1.000

measures solute concentration
average range: 1.008 - 1.030

3. Color

normal = yellow-amber (from hemoglobin breakdown)
influenced by:
- ratio of solutes
  - → >solute conc. = darker yellow to brownish
  - → <solute conc. = less color to colorless
- diet (eg. beets)
- blood in urine

4. Transparency

turbid indicates mucus, bacteria or cells

5. Odor

normal = musty
diabetics → sweet odor

6. pH

normal urine is slightly acidic: 5.0 - 7.8
influenced by:
- diet
  - eg. high protein → acidic
    vegetables → alkaline

metabolic disorders:
eg. lungs, kidneys, digestive system, etc

7. Cells and Castings

normally find epithelial cells and some bacterial cells and varous cells casts

Bacteria

< 100-1000/ml = contamination by normal flora

>100,000/ml = indicates active colonization of urinary system

RBC's & WBC's

presence is almost always pathological

inflammation of urinary organs

pus from infections

Chemical Characteristics

1. Water

normally is 95% of total urine volume

remaining 5% consists of solutes

2. Normal Solutes

mostly wastes or excess amounts of nutrients, hormones, etc

organic – mainly 'nitrogenous' compounds:

urea (95% of N wastes)
from deamination of amino acids

creatinine
from breakdown of energy transferring molecule especially in muscle cells

uric acid
from breakdown of nucleic acids

inorganic –

chlorides and salts

ammonia – N containing cmpd, not much produced, very toxic

phosphates

sulfates

3. Abnormal Solutes

normal constituents of plasma

usually do not appear in urine:

too large to be filtered out

all is reabsorbed

a. albumin (protein)

normally too large to filter out
presence indicates increased permeability of glomerular membrane due to:
injury
high blood pressure
irritation
toxins

b. glucose
normally, all is filtered and all reabsorbed
body reabsorbs as much as is needed
when it appears in urine indicates high blood sugar concentrationsj
→ symptom of diabetes mellitis

c. ketones
produced when excessive quantities of fats are being catabolized
high quantities may be caused by:
diabetes
starvation
dieting
→too little carbohydrates in diet

Other Functions of Kidneys

in addition to their primary role in removing metabolic wastes and excess nutrients and hormones from the body, kidneys also:

5. Control rate of erythropoiesis

kidneys produce hormone = **erythropoietin** that regulates erythropoiesis:

hypoxic → secretes more erythropoietin
excessive O2 inhibits hormone production

testosterone enhances kidney production of erythropoietin
estrogen and progesterone have no effect

6. Affects the absorption of Calcium from intestine

activates Vitamin D circulating in blood

7. Help to regulate blood pressure & volume

[more later]

renin-angiotensin mechanism

lower BP:
→ kidneys release enzyme = renin
→ renin triggers production of angiotensin II
→ angiotensin causes:
vasoconstriction → raises BP
release of ADH → conserves water to raise BP

helps maintain high filtration pressure in Renal corpuscles

blood pressure is directly affected by the volume of fluids retained or removed from body:

greater volume → increases BP
eg. excessive salts promote water retention
lower volume → decreases BP
eg. dehydration
eg. internal bleeding

Kidneys can directly affect blood volume by altering salt and water reabsorption under influence of Aldosterone and ADH

eg. Aldosterone promotes salt retention and therefore water retention by kidneys
eg. ADH promotes water retention by kidneys

8. Regulate pH of body fluids

[more later]

able to actively secrete excess hydrogen ions

Fluid & Electrolyte Balance

body is ~2/3^{rds} water (males=63%; women=52%)

this water occupies three "compartments":

intracellular → 63% (or 40% of body wt) facilitates chemical reactions, solvent		25L
extracellular → 37% (or 20% of body wt) provides internal environment for cells and transport, protection, etc		[15L]
transcellular (CSF, eye, synovial joints, bursae)		
interstitial lymph	30%	12L
plasma (=intravascular)	7%	3L
	Total:	40L*

*based on 70kg(154lb) person

Total amount of water & water in each compartment remain relatively constant

water content and movement is tied to electrolytes and solute concentrations and movement

eg. if solutes leave a compartment by diffusion;
water also leaves by osmosis
→ water follows salt

can't talk about fluid balance without talking about electrolyte balance

balance means: **input = output**

Inputs

1. digestive tract: food and drink
2. metabolism: each cell produces water in catabolism of glucose

Outputs

1. urine (kidneys)
2. lungs: water vapor expired with air
3. sweat (skin)
4. feces (intestines)

output is crucial element in control of fluids and electrolytes

most important output organ is kidney

urine volume is controlled by:
- glomerular filtration rate
- reabsorption by tubules

glomerular filtration rate remains fairly constant
- → not a strong controlling influence on urine volume

major control of urine volume is reabsorption of water

reabsorption can be controlled to make output match input

controlled by two major hormones:

ADH
- decrease in ECF volume stimulates release of ADH
  - ?osmoreceptors in hypothalamus?
- makes distal & collecting tubes permeable to water
  - → increases water reabsorption
  - → decreases urine volume

Aldosterone
- increases tubular reabsorption of sodium and other ions
  - → increases water reabsorption by osmosis
  - → decreases urine volume

additional factors that can affect fluid loss

1. urine volume can also be affected by amount of solutes in urine
   - → the more solutes the more urine

Diabetes mellitis
excess glucose spills over into urine
causes excess water to enter nephric tubule by osmosis
results in excessive water loss & dehydration

2. hyperventilation
over extended time can lose significant water from lungs
may result in dehydration
3. prolonged vomiting or diarrhea

fluid input can also be regulated to some degree to help maintain fluid balance:

dehydration → salivary secretions decrease → dry mouth → thirst

provides a stimulus for "behavioral modification"

but still requires *voluntary* act

if fluid intake is stopped completely a balance cannot be maintained
→ even if kidneys shut down
still lose water through lungs and skin

Composition of Fluids

these fluid compartments contain critical electrolytes and solutes:

cations: Na^{+}; Ca^{++}; K^{+}; Mg^{++}
anions: Cl^{-}; $CHO3^{-}$; $HPO4^{--}$; Proteins

These electrolytes function:
1. essential nutrients or building blocks
2. serve critical role in regulation of various metabolic pathways
3. affecting membrane potentials of muscle and nerve cells
4. control water movement between compartments by affecting osmotic pressures

Ions in **Extracellular Fluids** differ greatly from those in **Intracellular Fluids**:

	ECF	**ICF**
most abundant cations	Na^{+}	K^{+}; Mg^{+}

most abundant anions	Cl^-; $HCO3^-$	$PO4^{---}$; $Proteins^-$

While the electrolyte content of the **Extracellular Fluid Compartments** (mainly Interstitial Fluids & Plasma) they do differ significantly in the amount of **protein** anions

→ plasma has much more protein than interstitial fluids

proteins generally cannot cross capillary walls or cell walls so they are less common in tissue spaces

the chemical content of these compartments helps to control movement of water between them

<u>Water Movement Between Compartments</u>

2 major factors control the movement of water between compartments:

osmotic pressure (OP)

(electrolytes and solutes)

osmotic pressure develops in compartment with higher concentration of solutes

tends to pull water into compartment

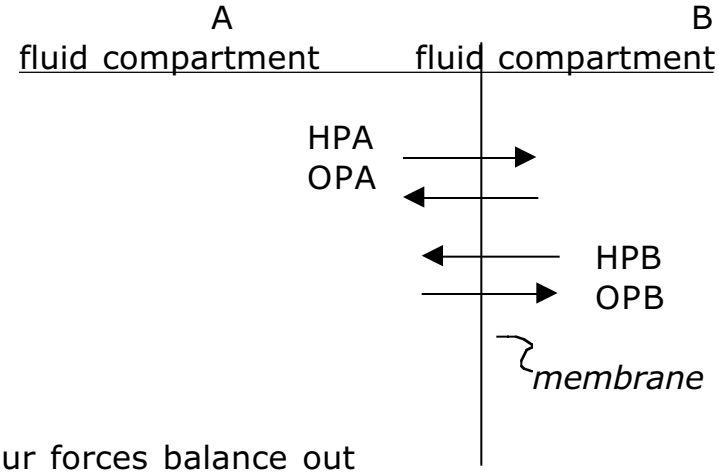
hydrostatic pressure (HP)

(water pressure, blood pressure)

tends to push water out of compartment

the force that moves water between adjacent compartments

= the **effective filtration pressure (EFP)**



If these four forces balance out

→ EFP = 0

there is no net movement of water between compartments

If: HPA + OPB > HPB + OPA

→ fluid leaves A and enters B

If: HPA + OPB < HPB + OPA
→ fluid leaves B and enters A

eg: if B=blood
IF=interstitial fluid
HP and OP measured as mmHg

arterial end of capillary bed:

A	B
(BHP + ISFOP)	(ISFHP + BOP)
(37 + 0)	(1 + 25)
(37) →	(26)

venous end of capillary bed

A	B
(BHP + ISFOP)	(ISFHP + BOP)
(17 + 0)	(1 + 25)
(17) ←	(26)

main factor that controls exchange of fluid between blood and tissue spaces is **hydrostatic pressure**

the mechanism that regulates water movement between capillaries and tissue spaces is essentially the same as that which regulates movement of water from cells to tissue spaces

in this case hydrostatic pressure in both "compartments" is almost 0 therefore major controlling factor is changes in **osmotic pressure**

changes in solutes is controlled by active transport across the cell membrane
esp. sodium/potassium pump

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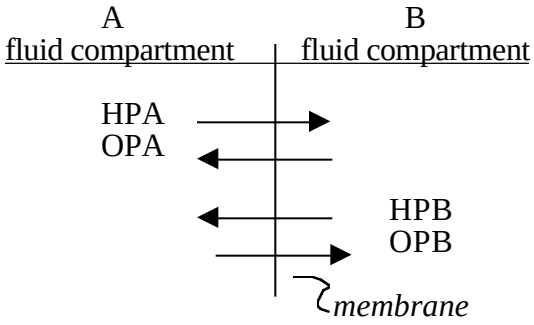

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Water Balance Disorders

eg. dehydration

output > input

caused by:
- excessive sweating
- water deprivation
- chronic diarrhea
- excessive vomiting

Blood loses water → ECF loses water → cells lose water

infants & elderly more likely to suffer dehydration since their kidneys are less able to conserve water

treatment: replace water *and* lost electrolytes

eg. water intoxication

input > output

often happens after dehydration
→ water is taken in too quickly without electrolytes

input → to blood → to tissue spaces → to cells

can cause edema as water collects in ISF

causes cells to swell as it moves from tissue spaces into cells

especially affects cells sensitive to ion concentrations: muscle and nerve cells

can result in:
- heat cramps
- convulsions
- confusion
- coma

eg. edema

=abnormal accumulation of water in ECF

caused by:

- decreases in plasma proteins due to
  - liver disease
  - kidney disease
  - starvation
- obstruction of lymphatic vessels
- increased venous pressure
- increased capillary permeability
  - eg. inflammation
    - sunburn

Acid/Base Balance

some of most critical ions in body fluids are H^+ (hydrogen) and OH^- (hydroxyl) ions

the concentrations of these two ions affect the acidity or alkalinity of body fluids

acidity/alkalinity is measured on pH scale

- 1pH unit = 10 fold change in $[H^+]$
- pH of 7 is neutral
- pH < 7: more H^+, fewer OH^-
- pH > 7: fewer H^+, more OH^-

large organic molecules, especially proteins, are extremely sensitive to changes in pH

→ easily denatured

since proteins serve a wide variety of roles in the body

(enzymes, fibers, carriers, hormones, oxygen transport, immunity, etc)

variations in pH affect almost every aspect of physiology and cell metabolism

even slight changes in pH can be fatal

- blood = 7.35 – 7.45
- ≤7 or ≥7.8 is fatal

various acids and bases continually enter and leave body:

- in foods and drink
- gastric secretions
- bicarbonates from pancreas
- etc

need some mechanism to neutralize them:

body is protected against large changes in pH in two step process:

1. **buffers** – absorb excess hydrogen or hydroxyl ions to prevent drastic changes in pH
2. **elimination** – acids (or bases) are removed from body by:
   - **kidneys** - can secrete H^+ and $HCO3^-$
   - **lungs** – as CO2 is eliminated H^+ are converted to water
   - **skin** – can excrete some acids in sweat

Buffers

a buffer is a substance that prevents marked changes in pH of a solution when acids or bases are added

eg. 1 drop of HCl in pure water
pH = 7 ⟶ 3.5

1 drop of HCl in plasma
pH = 7.41 ⟶ 7.27

→ blood is buffered

buffers act by combining with strong acids or basis and taking them out of solution
→ "absorbs" the H or OH ions

buffers consist of weak acid and its salt

major buffers in body fluids:
- bicarbonate
- phosphate
- hemoglobin
- plasma proteins

all buffers have limited capacity

buffering alone cannot maintain homeostasis indefinitely

at some point the acids and bases must actually be removed from the body

two main removal systems:
1. Respiratory Mechanisms
2. Excretory Mechanisms

Respiratory Mechanisms

respiration plays vital role in removing excess acids

with each expiration, CO_2 and therefore H^+ are removed

$$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} H_2CO_3 \rightarrow H^+ + HCO_3^-$$

pH receptors in arteries can increase or decrease respiratory rate based on buildup of acids in blood

acidosis → stimulates hyperventilation

Excretory Mechanisms

cells of DCT and CT can secrete H^+ & HCO_3^-

if blood pH decreases below normal levels tubules will increase secretion of H^+

more efficient mechanism than respiratory system

usually urine is slightly acidic

→ normal diet produces more acid than alkaline waste products

Acid/Base Imbalances

1. Acidosis

→ accumulation of excess acids

→ excessive loss of bases

a. Respiratory Acidosis

factors that cause buildup of CO_2 in blood

generally due to factors that hinder pulmonary ventilation

symptoms:

- labored breathing
- cyanosis
- depression of CNS → drowsiness, disorientation
- coma → death

can be compensated for by kidneys

b. Metabolic Acidosis

accumulation of non-respiratory acids or
excessive loss of bases
eg. poor kidney function
prolonged diarrhea
severe vomiting → loss of duodenal fluids
diabetes mellitis → ketone bodies are acidic

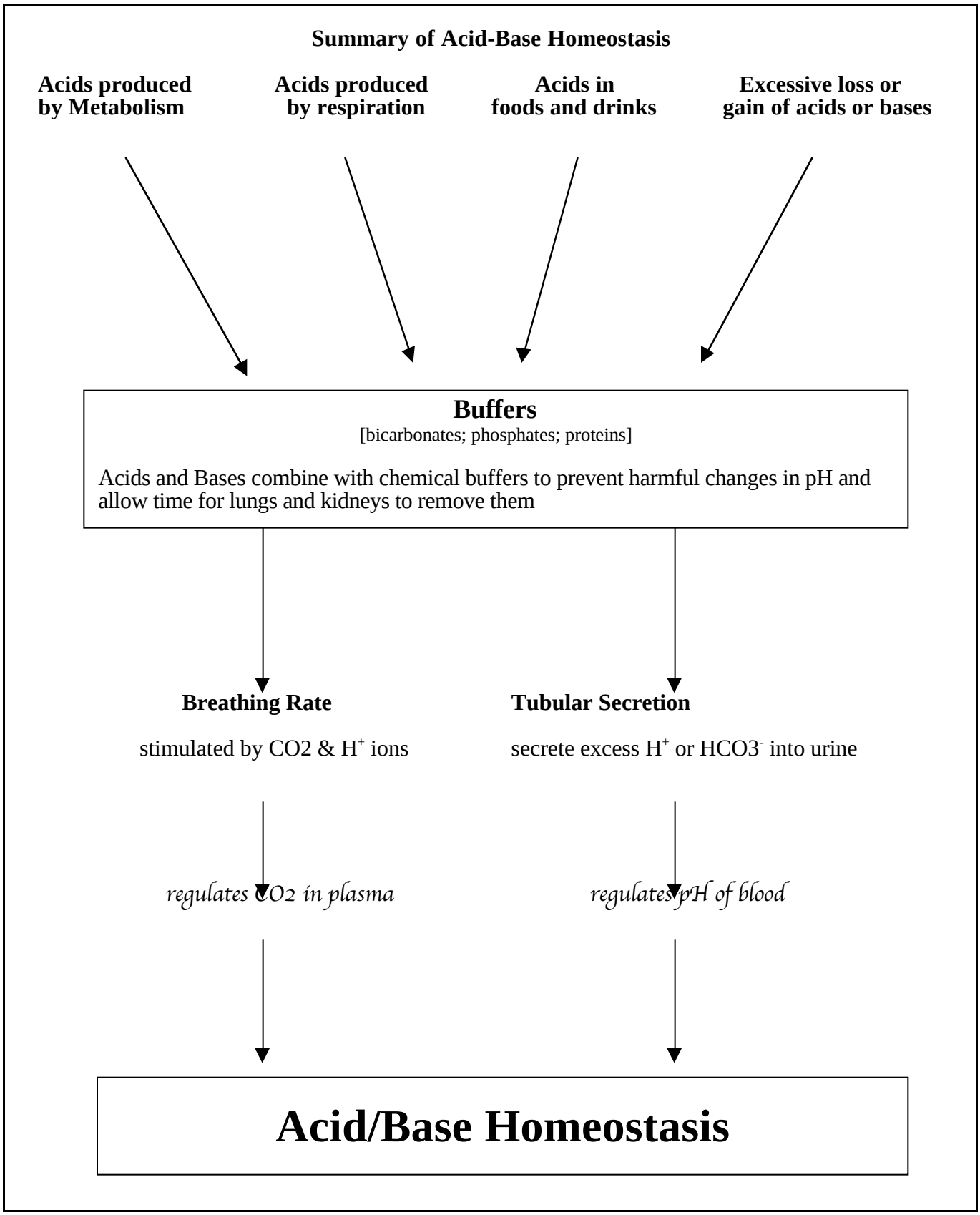
2. Alkalosis

→accumulation of excess bases
→excessive loss of acids

a. Respiratory Alkalosis
caused by **hyperventilation**
anxiety
fever
some poisonings

symptoms:
light headedness
agitation
tingling
dizziness

b. Metabolic Alkalosis
caused by:
gastric drainage (lavage)
prolonged vomiting of stomach contents
too many antacids


Summary of Acid-Base Homeostasis
Acids produced by Metabolism
Acids produced by respiration
Acids in foods and drinks
Excessive loss or gain of acids or bases
Buffers
[bicarbonates; phosphates; proteins]
Acids and Bases combine with chemical buffers to prevent harmful changes in pH and allow time for lungs and kidneys to remove them
Breathing Rate
stimulated by CO2 & H+ ions
Tubular Secretion
secrete excess H+ or HCO3- into urine
regulates CO2 in plasma
regulates pH of blood
Acid/Base Homeostasis

Reproductive System

Function: producing offspring

propagation of the species
→in terms of evolution
– the *only* reason all the other systems exist

only major system that doesn't work continuously
→ only activated at puberty

unlike most other organisms on planet
→ mammals only reproduce sexually

humans are dieocious
→ separate sexed (many animals are monoecious or hermaphrodites)

in 7th week of embryonic development genes are activated that trigger differentiation of gonads

Physiology of Male Reproductive System

male hormone (=androgens) are secreted mainly by interstital cells of testes

additional testosterone is secreted by Adrenal Cortex

at puberty Ant Pituitary secretes FSH & large amounts of LH (ICSH)
FSH & LH cause testes to increase in size and begin sperm production
LH → also triggers testes to produce testosterone

main male hormone is **Testosterone**
There are two male hormones:
testosterone
androstenedione

testosterone functions:
1. development and maintenance of secondary sexual characteristics
   - hair pattern
   - muscular development
   - skeletal changes
   - voice pitch
2. behavioral changes (~sex drive, aggression, courtship

behaviors)
2. stimulates protein synthesis
3. promotes growth of skeletal muscles

Androgens are also produced in women
ovary & adrenal cortex
relatively weak
promotes protein synthesis, growth
not masculinizing

Negative feedback loop maintains constant level of testosterone in blood:
→high testosterone levels inhibit LH

Hypogonadism
is present in 0.13% of males
due to pituitary malfunction
symptoms:
retains juvenile physique
no secondary sex characteristics
voice remains high pitched
some feminizing traits
eg. arrangement of fat deposits characteristic of women
malfunction usually occurs before puberty
but can be caused later by mumps or other inflammation

Hypergonadism
leads to excessive development of genitalia and secondary sex characteristics

Male Menopause
age related, gradual reduction in testosterone and its effects
testosterone production decreases
FSH production increases

spermatogenesis

sperm are produced in seminiferous tubules

develop from **spermatogonia**

<u>Physiology of Female Reproductive System</u>

-maturation of egg
-development of uterine lining
-hormone secretion by ovary

→are **cyclic events**

not continuous as in males

complex combination of several interdependent hormonal cycles

Ant Pituitary begins secreting FSH and LH ~7-8 yrs old

FSH & LH production increases until ~11-13 yrs old
→ triggers menstrual cycle & development of secondary sex characteristics

FSH & LH stimulate follicle cells in ovary to begin secreting estrogen & progesterone

Estrogen function:
1. development and maturation of reproductive tract
2. development and maintenance of secondary sexual characteristics
   - change in fat distribution
   - enlargement of mammary glands
   - inhibits growth of extremities

estrogen concentration in women peaks at puberty → this tends to inhibit GH → growth slows male androgens don't have this inhibitory effect on growth

3. behavioral changes (~sex drive, courtship behaviors)

Progesterone function:
1. has its greatest effect on estrogen primed tissues
2. changes that favor pregnancy and lactation
   - endometrial thickening
   - development of mammary glands

<u>Menstrual Cycle</u>

~28 day cycle

4 phases:

menstrual phase (days 1-6)
- shedding of uterie lining if no fertilization

proliferative (follicular) phase (days 6-12)
- as follicle develops it secretes increasing amounts of estrogen
- endometrium cells proliferate

ovulatory phase (days 12-16)
ovulation→ release of mature egg from ovary
secretory (luteal) phase (days 16-28)
follicle cells left behind after ovulation develop into corpus luteum
corpus luteum secretes increasing amounts of progesterone
continued increase in development of endometrium

This cycle is tied to variations in several hormones

Oogenesis

the eggs develop within follicles under influence of FSH & LH from Ant. Pituitary

egg nest → follicle → antrum develops → Graafian follicle → ovulation → Corpus Luteum → Corpus Albicans

corpus albicans I= scar tissue

as follicle cells develop egg develops within

mature (Graafian) follicule contains egg surrounded by fluid filled antrum

egg undergoes meiosis but stops as secondary oocyte (metaphase II) until fertilization

Mammary Glands

during pregnancy breast development is stimulated by **estrogen** and **progesterone** secreted by placenta

at birth shedding of placenta
→cuts off source of these hormones
→ stimulates Ant. Pit. to secrete prolactin

Prolactin stimulates lactation (devel of milk in glands)
usually takes several days for full milk production

Suckling of infant further stimulates secretion of
prolactin
oxytocin (from Post. Pituitary)
→ promotes ejection of milk into ducts
+feedback: more suckling → more milk released