Pathophysiology All Material PHS 3400

Lecture 1 - Respiratory Dysfunction

Clinical Manifestations of Pulmonary Alterations

1. "Pnea" - meaning respiration or breathing

   - Dyspnea: sensation of difficult or uncomfortable breathing; sensation of shortness of breath, laboured, preoccupied with breathing

     SIGNS: flaring of nostrils, use of accessory muscles of respiration & retraction; variety of possible reasons

     - initially on exertion, then at rest

   - Orthopnea: difficulty breathing (shortness of breath) when lying down – usually result of increased fluid in lung that is helped by being upright – e.g. left ventricular heart failure, pulmonary edema for any other reason
   - Apnea: temporary cessation of breathing (e.g. sleep apnea)
   - Bradypnea: slower rate of breathing < 12 breaths/min; e.g overuse of narcotics, brain disorders, hypothyroidism
   - Tachypnea: higher rate of breathing > 20 breaths/min (shallow breaths) – causes include lung disease, anxiety, obesity, pulmonary embolism

2. Some abnormal breathing patterns/sounds: eupnea is rhythmic (8-16 breaths/min; tidal volume = 400-800 ml); short expiratory pause; sigh breaths (10-12/hr)

   - Kussmaul respiration: slow, deep breaths – e.g. advanced ketoacidosis
   - C**heyne-Stokes respirations** (any condition that slows blood flow to brain stem; heart failure or brainstem disease)
   - Examples of abnormal breath sounds: wheezing (asthma), crackles (pneumonia, pulmonary fibrosis), stridor (airway obstruction)

3. Hypoventilation: results in hypercapnia - blood pH falls and becomes alkaline ($PCO_2 > 44$ mmHg) & decreases blood pH
4. Hyperventilation: not to be confused with hyperpnea or with tachypnea; results in hypocapnia ($PCO_2 < 36$mmHg) cause increase in blood pH and acidosis
5. Cough: protective; clears lower airways; triggered by irritation of mucosa; occasional coughing normal; persistent cough indicative of a disorder or disease

   - acute, nonproductive (nothing coming up) cough often suggests bronchitis or viral pneumonia
   - persistent dry cough often suggests a tumor, congestion or hypersensitive airways
   - productive cough with purulent sputum usually suggests an infection
   - hemoptysis (blood is bright red, alkaline pH) – damage to bronchi, cancer,

6. Cyanosis: bluish discolouration of skin & mucous membranes due to excess of reduced hemoglobin
   - 2 ex of inadequate oxygenation of tissues that don't show cyanosis : 1. anemia not enough red blood cells and whatever hemoglobin is saturated but don't have enough for whole body. 2. CO poisoning - 200x affinity for oxygen binding sites so coloration is the same but really CO is bound
   - Central cyanosis (mucous membranes) vs peripheral cyanosis (nail beds)
7. Pain: inflammation/infection of pleurae or major airways or muscle/rib pain associated with chest wall
8. Clubbing: selective bulbous enlargement of distal segment of a digit; usually painless
   - diseases that interfere with oxygenation (lung cancer, cystic fibrosis, pulmonary fibrosis, lung abscess, congenital heart disease)
9. Abnormal sputum: changes in amount, consistency can give info about progression of disease, effectiveness of therapy; also identification of microorganisms

Introduction

- major function: supply body with O2 and dispose of CO2
- respiration consists of 4 distinct processes

  i. Pulmonary ventilation: air in and out of lungs- act of breathing -resp system

  ii. External respiration: exchange of gases between lungs & tissues - resp system

  iii. Transport of gases: blood to transport gases between lungs & tissues - responsibility of CVD system

  iv. Internal respiratory: exchange of gases between capillaries and tissues -CVS system
- Tree-like branching to get down to alveoli where gas exchange occurs but problems can occur anywhere.
- Type 1 cells — MC and make up wall of alveoli
- Type 2 — responsible for making surfactant
- Dust cells — macrophages, go around inner surface of alveoli trying to keep as clean as possible; we clear/swallow > 2 million dust cells per hour

<u>Respiratory Distress Syndrome of Newborn (RDS)</u>

- surfactant deficiency & deficiency in alveolar surface area for gas exchange. Characteristic in preemie babies
- surfactant production occurs late in gestation (development of fetus); appreciable levels don’t each surface of alveoli until 28-38 weeks gestation (variable)
- surfactant — amphiphilic - allows to insert into water when we breath out we don't let all air our so its easier to breath in again (like blowing up balloon); without surfactant more likely for alveoli collapse to occur (all air out) and harder to breath in again
- premature infants have small, underdeveloped alveoli with little surfactant
- Surface tension: at gas/liquid boundary, liquid molecules more strongly attracted to each other than to the gas -> tension ar liquid surface & resists any force to increase SA.

- Note: water has high surface tension; water only in alveoli would cause collapse

What influences the surface tension of alveolar fluid?

- Surfactant: detergent-like lipoprotein produced by alveolar type II cells - interferes with cohesiveness of water molecules meaning less energy required to overcome surface tension

*IRDS: premature infants; too little surfactant; alveoli collapse & must be re-inflated with every breath — positive pressure respirators and surfactant spray used.

- Attraction w water molecules with surfactant disallows the collapse of alveoli therefore less energy is required to overcome surface tension when breathing in next. Surfactant disrupts the surface tension.
- Surfactant must be replenished constantly (1/2 life lecithin = 14 h - type two cells constantly making new surfactant - breathing normally is stimulus for surfactant production. With rib injury one must be careful because could become deficient in surfactant since not breathing as deep as usual due to pain. This leads to insufficient gas exchange so type 2 cells to getting enough stimulus to produce normal amounts of surfactant.
    - Therefore: normal ventilation most important stimulus (O2 used in synthesis)
    - hypoventilation can lead to atelectasis - alveolar collapse!
    - a deep sigh or breath can be sufficient to induce new surfactant synthesis
    - surfactant also waterproofs lungs - keeps fluids from moving into alveoli from capillaries; therefore prevents tie against problems with fluid accumulation in lungs
    - IRDS most well-known result of insufficient surfactant production, but ARDS (A= acute or adult also exists)

Adult Respiratory Distress Syndrome (ARDS)

- Some Underlying Causes of ARDS:
    1. Reduced perfusion - decreased blood flow through lungs (eg. cardiogenic schock, trauma, major burns)
    2. Increased capillary permeability - more fluid to come across and fill alveoli (pneumonia, sepsis, drug reaction)
    3. Direct tissue/capillary insult - unclean things getting in too much oxygen (eg: aspiration GI contents, near drowning, oxygen toxicity)

       Oxygen toxicity: no nitrogen (which is main component of air) present to stay behind & keep alveoli expanded. Oxygen is toxic to surfactant-producing cells. High level of production of free radicals

       -Lung facts strongly (almost excessively) to these insults
- Injured Lung goes through 3 phases:
    1. Exudative: damage to alveolar epithelium & vascular endothelium -> leakage of water protein, inflammatory cells & RBCs into interstitial & alveolar lumen (hyaline membrane disease); damaged type 1 cells replaced by proteins, fibrin & cellular debris and surfactant production by type 2 cells replaced by proteins, fibrin & cellular debris and surfactant production by type 2 cells is compromised; fluid accumulation can be heard as crackles and measurements of arterial blood gases will provide clues. Damage can be

due to lake water, acidic GI contest, not enough BF and this causes fluid accumulation with protein, inflammatory cells from immune system therefore RBCs in interstitial fluid.

2. Proliferative: Some replacement of type 1 and 2 cells .

   -hyaline membrane - junk that is precipitating out and making significant phys. barrier between air and blood therefore gas exchange is compromised.

3. Fibrotic: Often excessive collagen deposition as fun attempt to self-repair causing a decrease in elasticity and contractility in future.

Note: repeated damage causes alveoli to become more fibrous which causes gradual change in structure of lungs and is harmful to gas exchange.

- Symptoms of ARDS
  a. Dyspnea - difficulty in breathing
  b. Severe hypoxemia - severely reduced levels of O2
  c. Decreased lung compliance - lungs having trouble allowing good volume exchange
  d. Diffuse bilateral pulmonary infiltrates (anything more dens ethane air: blood, tissue fluid, pus, protein, etc.)
- Management
  - maintain lung ventilation while giving it time to heal and minimizing the work it has to do
  - positive pressure ventilation to prevent alveolar collapse - but gently so as not to cause more damage — often cared for ICU
  - steroid use (anti-inflammatory) is controversial (not suggested early in disease, but maybe in later phases) and antibiotics only if required due to presence of microorganisms; can also drain fluid from lungs (steroids controversial because allow immune system to be functional as possible)
  - recovery usually begins in around 2 weeks, but overall mortality still ~32-45%
  - higher mortality rates associated with patients who are elderly, are immunosuppressed or have chronic liver disease
  - of those who do recover, most regain about 75% of lung function

<u>Anatomy Reminder: Pleural coverings of the lungs</u>

- thin, double-layered serosa; parietal and visceral (pulmonary) layers
- pleural fluid allows lungs to slide during breathing
- surface tension of pleural fluid also keeps 2 pleurae together
  - Pleurisy — little to no pleural fluid and this causes dry membranes thing to slide over each other making it painful to breath
  - Although the diagram doesn't make this clear, the pleurae also provide separate cavities for each of the lungs and heart - from a disease perspective why is this advantageous? -
- Reminder: Pressure Relationships in Thoracic Cavity
  - atmospheric pressure = 760 mm Hg (sea level)

- respiratory pressures are described relative to atmospheric pressure

1. Intrapulmonary pressure (=pressure within alveoli of lungs) -> rises & falls with breathing but eventually equalized with atmospheric (and always aims to be same as atmospheric)
2. Intrapleural pressure (=pressure within pleural cavity) -> ~4 mm Hg less than atmospheric (760-4 = 736) therefore always little bit negative to atmospheric pressure, this hep the lungs to be flush against rib cage and diaphragm so that they follow your breathing

Note: any condition that equalized intrapleural pressure with intrapulmonary pressure causes immediate lung collapse!!

Pneumothorax: air in intrapleural space - e.g. from a chest wound

<u>Pleaural Effusion</u>

- Accumulation of fluid in the pleural space from blood or lymphatic vessels associated with pleural membranes. It was pushed out from blood stream or lymphatic vessels.
  - Can be transductive (fluid is watery; due to disorders that increase BP or decrease capillary oncotic pressure) or exudative (fluid contains protein; due to inflammation, infection, malignancy)
  - Most common presenting symptom is dyspnea - hard to breath
  - Inability to ventilate lung(s) because they have harder time following what is being done with rib cage and diaphragm so may impair ventilation and lead to hypercapnia
  - Small effusions may resolve with treatment of cause; large effusions may require chest tube to drain fluid

Physical Factors Influencing Pulmonary Ventilation

1. Respiratory passageway resistance:
   - resistance determined by diameters of conducting tubes
   - resistance usually insignificant in health individuals because:

     a) airway diameters at beginning are large

     b) gas flow stops at terminal bronchioles
   - PNS closes it; SNS - opens it during fight or opens it during fight or flight to maximized airflow
   - NUERAL INFLUENCES;

     a) PNS: (eg: inhaled irritants, histamine) -> strong construction of bronchioles (also occurs during acute asthma attack) trying to protect the body

     b) SNS: dilates bronchioles -> decreased resistance

     - sources of airway resistance in disease: accumulation of ucus, infectious material, tumors
   - Causes of increased resistance in airways:
     - obstruction of airway (mucus)
     - thickening of airway walls (smooth muscles0

- loss of elasticity
- bronchoconstriction - tightening of surrounding smooth muscle

2. Lung compliance: ease with which lungs can be distended and extent to which they exhibit good recoil
   - Depends on:

     a) elasticity of lung tissue

     b) elasticity of thoracic cage note: relaxing muscles will force ai out naturally in most cases
   - Compliance is diminished by any factor that:

     a) reduces natural resilience of lungs (eg: fibrosis - less elasticity; formation of excess fibrous connective tissue in an organ or tissue in a reparative or reactive process)

     b) blocks bronchi or smaller resp. pathways

     c) increases surface tension of alveolar fluid - therefore lack of surfactant allows alveoli to collapse and harder to inflate because lack of surfactant = higher surface tension

     d) impairs flexibility of thoracic cage (ossification of costal cartilages
   - Elasticity of lungs important fro both inspiration & expiration

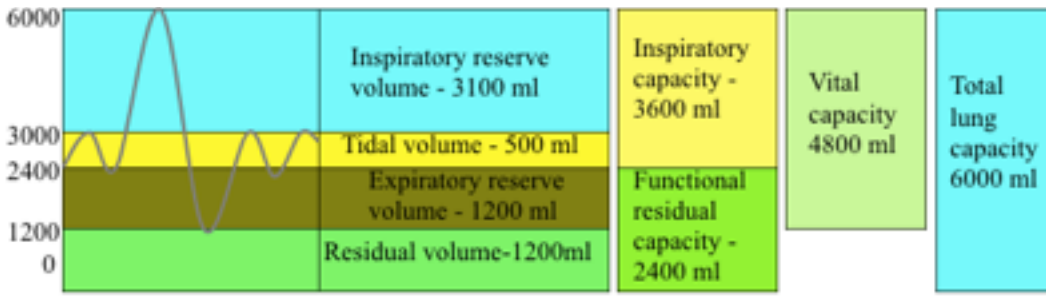
Pulmonary Function Tests

- Can distinguish between:
  - Obstructive pulmonary disease — something in way; e.g. bronchitis, asthma; increased TLC, FRC RV due to hyperinflation of lungs
  - Restrictive diseases — less healthy lung tissue for breathing in and out; ie. TB and polio; decreased VC, TLC, FRC, RV because lung expansion is limited
- Some useful tests:

  A. Minute/total ventilation: total air in or out in 1 min (usu. ~6L/min if healthy)

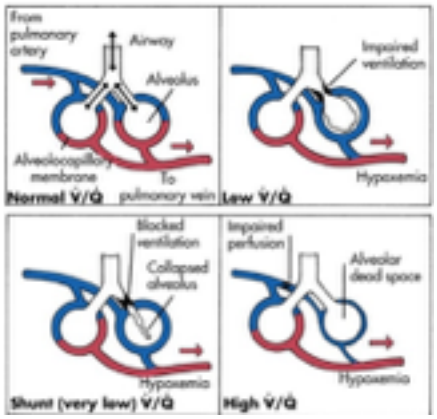
  B. Forced vital capacity: deep breath in and then exhale forcibly (low in restrictive disease)

  C. Forced expiratory volume: eg. FEV = 80% if healthy (low in obstructive disease)



Dead Space:

- air in passageways that doesn't participate in gas exchange (~150 ml = wt. in lb) - only n conducting zone doesn't participate in gas exchange (doesn't go into alveoli - in trachea nasal cavity and bronchi)
- 500 ml tidal volume = 150 ml dead space + 350 ml alveolar ventilation
- Note: if some alveoli no longer functional: total dead space = 150 ml + alveolar dead spaces - like in someone with emphysema



Ventilation-Perfusion Coupling = coupling between amount of gas reaching alveoli and blood flow in pulmonary capillaries

- pulmonary circulation sending for blood to alveoli to unload CO2 and pickup O2. So when there is blockage there's no point in sending blood there
- Q for perfusion because next letter in alphabet
- hypoexmia - low oxygen levels in blood
- perfusion - passage of fluid through circulation system
- V = ventilation / Q = perfusion
- When standing, blood flow is not equal to all parts of the lung. What would happen to this distribution in someone on bed rest? - dorsal effects; gravity makes it easier to go to dorsal side of body but harder for ventral aspects to get blood
  - minimal perfusion - blood cut off from alveolus ; intermittent perfusion - due to impaired ventilation ; continuous perfusion - normal ventilation
    - Low V/Q (underventilated): V/Q mismatch
    - Normal V/Q:
    - High V/Q (underperfused): V/Q mismatch

Impairments to Oxygen Transport = Hypoxia

- If fair-skinned, skin/mucosae become bluish when Hb saturation < 75% (cyanotic - not enough oxygen)

a) Anemic hypoxia: too few RBCs or RBCs w inadequate/abnormal Hb

b) Ischemic hypoxia: blood circulation impaired or blocked (congestive heart failure, embolism, thrombosis) either localized or general

c) Histotoxic hypoxia: eg. metabolic poisons such as cyanide - enough O2 devliered, but cells cannot use it

d) Hypoxemic (hypoxic) hypoxia: reduced arterial PO2; eg. pulmonary diseases impairing ventilation, breathing low O2 air, CO poisoning (200x higher affinity for Hb blocks it and O2

can't bind); signs of CO poisoning include confusion & throbbing headache, fair skin is cherry red

Remember: the respiratory system can influence blood pH through effects on CO2 - if breathing more rapidly and deep unload CO2 and if breathing more shallowly retain CO2

- blood CO2 levels drive respiration!
- slow shallow breathing — CO2 accumulates in blood & blood pH drops.
- rapid, deep breathing (in absence of exercise): CO2 fluted out of blood & blood pH rises

$$CO_2 + H_2O \leftrightarrow HCO_3^- + H^+$$

- ^ This works both ways:

1. If blood pH changes: drop or rise will affect respiration rate

2. If respiration rate changes: due to disease will cause changes in blood pH as well - breathe more then drop in pH, breathe more then drop in pH (more acidic because less CO2 in blood) , breathe less then raise pH (more basic because more CO2 in blood)

Some Consequences:

1. Anxiety attacks: hyperventilate involuntarily causing hypocapnia (reduced CO2 in blood) leading to cerebral blood vessels constriction -> cerebral ischemia causing dizziness and fairness
2. Low PCO2: causes respiration to be inhibited (hypoventilation->slow shallow breathing which can have periods of apnea until increased PCO2 stimulates respiration.

- Diving: hyperventilating before is dangerous because CO2 levels are low so it doesn't feel like you need to breath but you are running out of Oxygen you will black out without knowing.

Sleep Apnea

- One or more pauses in breathing or very shallow breaths while sleeping
- Pauses can be seconds to minutes
- Accumulation of CO2 and drop in O2 stimulate resumption of breathing, often with a loud snort or choking sound
- Usually obstructive sleep apnea (relaxation of muscles that support soft tissues of throat and tongue blocks airway passageway)
- Other possibility is central sleep apnea (defect in resp. centre in brain- temporary reduction in blood flow or absence in signal to tell you to breathe)

Obstructive.Restrictive Change in Pulmonary Function

A. Acute Obstructive Airway Disease

- 2 main types: acute bronchitis & asthma
- Acute = no accumulation of damage after attack
- in both cases, obstruction is intermittent & reversible

A1. Acute Bronchitis

- e.g. influenza viruses, adenoviruses, rhinoviruses, Mycoplasma pneumoniae
- Increased mucus secretion, bronchial swelling, dysfunction of cilia causing increased resistance to expiratory airflow & nonproductive cough
- Productive cough - purulent mucus; of existing/concurrent bacterial infection; wheezing
- Once infection agent gone, swelling decreases & airways return to normal

A2. Asthma

- episodic, acute airway obstruction resulting from stimuli that would not elicit such a response in healthy individuals
- ~5% of industrialized population affected by asthma
- Common features: hyper-responsiveness & inflammatory response in airways; lungs usually relatively normal between acute attacks
- "The current view is that asthma is basically an inflammatory disease with airway hyper-responsiveness as a secondary feature"

i) Extrinsic (allergic asthma) MC: better understood than intrinsic, often children or teens with family history of allergies, hives, rashes, eczema

  - attacks triggered by exposure to allergens (mites pollen, animal dander, cold, even viral respiratory infections); often goes into remission in early adulthood but can reappear later
  - diagnostic approach can include skin tests for allergies
  - can be seasonal and can be helped by allergy shots

- Pathophysiology of extrinsic asthma:
  - IgE - mast cell interaction (triggered by allergen) leads to release of histamine, prostaglandins, leukotrienes causing OBSTRUCTION:
    - constriction of bronchial smooth muscle (bronchospasm) - wheezing sounds
    - increased secretion by goblet cells
    - Mucosal swelling (thickening of wall by nflammatory response of increased capillary permeability
  - 2 phases -> lead to narrowing of airway:
    1. early acute phase that peaks wishing 15-30 min (mainly bronchospasm)
    2. late phase (peaks in 2-6h) due to airway edema & increased mucus production (requires initial predisposition to bronchospasm)
  - Often allergy is not sole factor: can be triggered by exercise, infection, emotions
  - Once one precipitating factor present (even low levels), responsiveness to 2nd factor increases!

ii) Intrinsic (non-allergic) asthma (less common, diagnosis at >20):

  - Usually affects adults, more common in women

- Can have a negative personal history for allergy, eczema, rashes, hives (not IgE-mediated - not an allergic response)
- Caused by anything other than allergens: e.g. - can be triggered by exercise, anxiety, stress, cold air, dry air, smoke, viruses, hyperventilation, aspirin
- Will not be seasonal; will not be held by allergy shots; usually develops later in life

• Clinical Manifestations of Asthma: signs & symptoms closely linked to status of airways

1. Bronchospasm leads to obstruction of airways, air then being left behind and becomes trapped air in lungs
2. Trapped air in alveoli flattens diaphragm (not as effective in inspiration); lower chest cannot expand properly because intercostal muscles pulled horizontally. people start to get anxious as they can feel what is happening
3. Wheezing: initially wheezing during expiration; then both inspiration & expiration
4. Pulmonary function tests reveal decreased peak expiratory flow rate and forced expiration volume
5. Blood gases show decreased PCO2 & respiratory alkalosis early, but hypercapnia & hypoxemia will develop due to exhaustion (fatigue a key problem - extra work to breath)
6. mucus is thick & very obstructive
7. Difficult to breathe -> anxiety -> increased difficult to breathe -> increased anxiety

Treatments: bronchodilators & corticosteroids

TAV: due to collapse of small and mid-sized airways during expiration; Asthma is leading case of hospital admission and school absence among children

B. Chronic Obstructive Pulmonary Disease

• 4th leading cause of death; also liability & hours lost from work like asthma in that:

i) expiratory airflow is obstructed

ii) exacerbations & remissions common

but lungs do not return to normal between exacerbations & pulmonary damage accumulates!

B1. Bronchiectasis — permanent dilation & distortion of bronchi & bronchioles: result of breakdown of airway smooth muscle & CT due to chronic infection & inflammation due to repeated infections.

• incidence declining due to earlier & more effective treatment of chronic bronchitis, asthma, cystic fibrosis & childhood immunization

• recurring infection & inflammation -> permanent dilation of bronchi & bronchioles causing targets for infection

• Symptoms: chronic productive cough; dyspnea, fever, weakness & weight loss all possible

• Prevention, Treatment: risk reduction measures for chronic bronchitis, asthma, immunization; antibiotics

B2. Cystic Fibrosis — hereditary disorder: over secretion of viscous (thick) mucus -> clogs respiratory pathways & predisposes child to eventually fatal respiratory infection

- At risk continually for lung infections; also affects secretory surfaces of GI & genitourinary systems, sweat glands
- CAUSE: faulty gene coding for cystic fibrosis transmembrane conductance regulator (CFTR) protein (chloride channel; chromosome #7)
- Symptoms:
    - secretion of tenacious mucus in airways -> combinations of atelectasis, pneumonia, bronchitis, emphysema, etc - material infection common
    - pancreatic insufficiency -> abnormal stools, malnutrition, abdominal pain; often have to take digestive enzymes to help with digestion due to insufficiency on pancrea
    - chronic cough, persistent lung infections
    - sterility in males (blockage of vas deferens); reduced fertility in females due to thick cervical mucus
- Pathophysiological Basis:
    - dysfunctional CFTR means reduced chloride secretion and it usually has an inhibitory effect on sodium reabsorption but since impaired sodium comes into mucus making more thick
    - CFTR usually has an inhibitory effect on sodium reabsorption (ENaC -specific type of sodium channel in lungs)
- Diagnosis: must meet 3 of 4 criteria:
    1. increased sodium and chloride in sweat
    2. deficient pancreatic enzymes in GI secretions
    3. chronic pulmonary infections
    4. family history
- Treatments:
    - chest physiotherapy, fluids & electrolytes, inhalation of mucolytic agents (to liquify agents)
    - amiloride = Na+ channel blocker -> Na+ reabsorption/viscosity of secretions
    - testing uridine triphosphate - stimulates chloride secretion by non-CFTR pathway; gene therapy to bring normal CFTR genes to lungs
- Prognosis: survival increased from ~3 yrs (early 1960s) to close to 40 years; usually death due to recurrent infections leading to antibiotic resistance & extensive bronchiectasis

<u>B3. Chronic Bronchitis:</u>

- continued bronchial inflammation & progressive increase in productive cough/dyspnea not attributable to specific causes
- usually due to chronic irritation of bronchi by cigarette smoke, atmospheric pollutants, infections - result is thickening/rigidity of mucosa due to vasodilation, congestion, edema
- 90% chronic bronchitis patients are current/former smokers; 15% of smokers will develop this disease

- infiltration with lymphocytes, macrophages, polymorphonuclear leukocytes
- **excessive secretion of mucus** -> obstructed airways, ⇓ lung ventilation
- frequent infections because bacteria thrive in stagnant mucus
- hypercapnia - more CO2 because harder to breath and have gas exchange

B4. Pulmonary Emphysema:

- most common chronic pulmonary disease; usually a late manifestation of repeated inflammatory episodes of chronic bronchitis
- it is due to destruction of tissue and therefore loss of elasticity of lungs
- pink puffers - early stages of emphysema as still sending blood there to the alveoli that are still healthy
- (2% of cases - genetic AAT deficiency can predispose to earlier onset)
- permanent **enlargement** of alveoli + **deterioration** of alveolar walls
- Signs: pursed lips expiration to slow down rate of breathing to try to keep airway open and not allow it to collapse leaving trapped air and causing alveoli to burst; if still smoking especially will continue to lose healthy lung tissue; lungs become less and less efficient in gas exchange as alveoli continue to die and collapse
- Pathophysiology:
  - injuries accumulate over time (inflammation, proteolytic enzymes, toxins)
  - elastin/fiber network of alveoli lost - alveoli enlarge, many walls destroyed
  - formation of unusually large alveolar air spaces - greatly reduces diffusion SA
  - alveolar destruction also undermines support structure for airways, making them more vulnerable to **expiratory collapse**
  - once begun, destruction progresses slowly & inconsistently
  - main destructive effect is loss of **elastic recoil** of lungs - lungs remain more distended & air trapped inside of lungs —> **barrel chest** of emphysema
- Clinical Manifestations:
  - no symptoms until disease progresses; arterial O_2 & CO_2 remain normal until late in disease - because of redirection of BF

- initially just dyspnea (trouble breathing) upon exertion —> then even at rest

i) accessory muscles enlisted to help - 15-20% body energy (vs 5%)

(1) prolonged FEV_1 (*pursed lip exhalation)*

(2) ⇓ vital capacity despite increased total overall lung capacity

ii) air trapped in alveoli - > expanded “barrel” chest - air left behind

- hypoxia stimulates EPO release (to try to increase O2 levels get to levels faster) -> increased RBC synthesis (even though have sufficient levels already) -> polycythemia, increased blood viscosity and reduced O_2 delivery to tissues
    - hypercapnia (- not as much gas exchange occurring and less airways open, harder to breath; dyspnea)
    - can eventually lead to ***respiratory failure***
- Treatment/Prevention:
    - disease rare in nonsmokers; AAT deficiency treated with enzyme replacement
    - oxygen therapy, pulmonary rehab (exercise), surgical reduction of lung volume; single or bilateral lung transplants
    - mechanical ventilation used reluctantly (risk of pneumothorax or diaphragm reconditioning

C. Restrictive and/or Infectious Diseases of Respiratory Tract

C1. Tuberculosis: infectious (*Mycobacterium tuberculosis);* spread by air-borne bacteria

- estimated that 1/3 population infected; most don't develop active TB because primary infection walled off in fibrous/calcified ***tubercles or granulomas***
- but bacteria still survive; can break out when immunity low →→ fever, night sweats, weight loss, racking cough + blood
- up to early 1900s - 1/3 of deaths (20- to 45-year-olds); antibiotics in 1940s reduced threat; since 1985 alarming increase (20%) in TB (HIV infection, but also malnutrition + close living, alcoholism, age, diabetes)
- TB bacterium grows very slowly; 12-month drug therapy needed; **drug-resistant strains develop in those who stop taking antibiotics**
- antibiotics for an extended period of time to get rid of completely; when exposed to bacterium not aware often, then walled off in area of lungs then when immune system compromised it will break out and be successful and really cause problems.

- Pathophysiology
    - bacteria settle in lungs & trigger local inflammatory response - within 4-6 wks cell-mediated immune response contains bacteria within a tubercle (dormant)
    - active disease develops if tubercle breaks - destructive inflammation; spread by lymphatics; can enter blood & infect other sites
- Clinical Manifestations of TB:
    - initial infection: can by symptom-free or mild bronchopneumonia
    - skin tests convert to positive; sputum culture confirms presence of bacterium; tubercles may be seen on chest radiograph
    - **active TB:** signs of chronic inflammation (anorexia, weight loss, fatigue, low-grade fever, night sweats); if **advanced necrosis**: chest pain, cough, necrotic areas/pleural effusions on radiograph
- Prevention & Treatment:

- education & screening (also TB skin testing)
- antibiotics (**isoniazid** + **rfampin** in combination for 1-3 yrs); other antibiotics also used due to development of resistant strains of bacteria

- Prognosis & Outcome:
  - favourable in developed countries
  - still kills 2.5 million/yr in developing countries
  - concerns: AIDS, emerging resistant strains

C2. Bacterial Pneumonia - pneumonia is defined as inflammation of the respiratory unit tissues (alveoli, alveolar ducts, respiratory bronchioles)

- either *community-acquired* or *hospital-acquired;* **life-threatening for aged, chronically ill, immunosuppressed**
- infection occurs due to:

  i) decreased bactericidal ability of alveolar macrophages

  ii) extreme virulence of bacteria

  iii) increased susceptibility of host to infection

^ in individuals who are immunologically compromised

- also, *aspiration pneumonia*
- most commonly due to *streptococcus pneumoniae*
- acute inflammatory response ⇒ excess water & plasma proteins to lower lung lobes
- RBCs, fibrin & polymorphonuclear leukocytes infiltrate alveoli
- build-up of fluid & hemorrhagic exudate in alveolar spaces Ø medium for proliferation & spread of bacteria

- Clinical Manifestations:
  - fever, tachypnea, cough, pleuritic chest pain
  - production of rusty-coloured sputum
  - **tracheal intubation single most consistent factor in hospital-acquired pneumonia; also excessive antibiotic treatments ➔ "super infections" with gram-negative bacilli

- Preventions & Treatment:

  √ immunization of high risk patients

  √ post-op care: turning, deep-breathing exercises, early ambulation - get them walking asap to avoid fluid accumulation

  √ antibiotic therapy - hydration & rest important - if bacteria

  √ treat respiratory failure with drugs, oxygen, possibly mechanical ventilation

C3. Viral Pneumonia

- often mild & self-limiting in adults; can progress rapidly & be fatal in children
- common viruses are: *influenza, adenovirus, chickenpox virus* (high risk patients should be immunized against influenza)
- major concern is damage to terminal/respiratory bronchioles ØØ susceptible to 2^0 bacterial invasion that then spreads to alveoli

Croup

- MC upper respiratory obstruction in children underneath where larynx is located (6 months - 5 years)
- Usu viral in origin; peak incidence between October and March (most common cause:parainfluenza virus)
- Subglottic inflammation and edema narrow airway
  - Begins w sore throat and mild fever
  - Signature barking cough, hoarse voice and inspiratory stridor indicating blockage
  - Inspiratory accessory muscles needed to maintain lung ventilation
  - Usually mild and will resolve in 5-7 days
  - Some cases severe and extent of airway obstruction requires urgent intervention
- Treatment
  - If mild, can be treated at home and steam inhalation has long been used to help move out mucus and lubricate the throat, although scientific proof of effectiveness remains to be demonstrated
  - Pharmacologic interventions include:
    - Oral, IV or nebulized corticosteroids to reduce inflammation
    - Nebulized epinephrine in cases of severe respiratory distress (effects are short-lived; should be used only as a stop-gap until corticosteroids start to take affect)

In the News

SARS (Severe Acute Respiratory Syndrome)

- viral (SARS-associated coronavirus [**SARS-CoV**])
- usually begins with fever > 38^0; chills and aches also possible
- diarrhea in 10-20% of cases
- dry, nonproductive cough possible after 2-7 days
- progression to hypoxia with possible requirement for mechanical ventilation
- most patients develop pneumonia
- thought to be spread by respiratory droplets; is virus also airborne spread? - possibly with cough?
- incubation is 2-7 days, possibly longer (10-14 days in some cases)
- treatment as for community-acquired atypical pneumonia

Enterovirus D68

- enteroviruses = group of viruses that cause symptoms that range from mild and cold-like to more severe illness that includes fever & rashes to neurologic problems (including muscle weakness, flaccid paralysis)

- Regarding Enterovirus D68
  - first identified in 1962
  - children & teenagers most at risk; children with asthma often respond with more severe symptoms
  - outbreaks usually in late summer/fall; spread via respiratory secretions
  - outbreak in mid-west US and parts of Canada especially significant in summer/fall 2014; hard to track because many don't seek medical help

Legionnaire's Disease

- bronchopneumonia caused by gram-negative rod: *Legionella pneumophilia*
- First recognized in 1976 (American Legion convention in Philadelphia)
- Bacteria persists in warm, standing water

- Symptoms: malaise, weakness, lethargy, fever (can be very high), dry cough →→ progresses to pneumonia, diarrhea, hyponatremia, confusion
- Treatment: antibiotics (without delay)

Lecture 2 — Cardiovascular Pathophysiology

CH. 15 ALTERATIONS IN BLOOD FLOW

Altered Blood Flow

- Decreased BF to tissues by arteries: any dec. in supply of oxygen — hypoxia and can happen from many causes:
  - Anemia: dec. Hb from eg. blood loss, low iron
  - Impaired lung function, eg. asthma
  - Arterial obstruction — ischemia
- Decreased BF from tissues by veins
  - Leads to venous engorgemtn called edema causing decreased removal of CO2 and wastes
- Dec. flow of lymph — accessory system of thin vessels
  - Allows excess fluid/plasma to diffuse b/t capillaries, interstitial spaces, and lymphatic vessels
  - Also plays key role in imm1ne system
  - Blockage -> lymphedema

Thrombus: Stationary blood clot in artery, vein or on wall of heart

- Pathologically formed: not normal/physiologic homeostatic mechanism; made up of aggregated platelets, clotting factors and fibrin
- Causes:

    - Atherosclerosis - principle causes of thrombus in body
    - after MI - causes damage to heart
    - Damage to/replacement of heart valve
    - Drugs, eg. oral contraceptives
    - Dec. venous BF, eg immobilization can cause in legs and very dangerous, can cause localized edema or dislodge and travel to vessel smaller than them and get stuck and cut off blood supply to that part which could be cerebral or to a lung leading to be deadly
    - IV catheters (inflammation -> thrombophlebitis)
    - Disseminated intravascular coagulation very rare but dangerous (see below)
    - Clots can form due in heart due to abnormal heart rhythm
- Risk factors:
    - Dehydration; Trauma
    - Heart failure; Surgery
    - Shock; Smoking
    - Aging; Sedentary lifestyle
- Clinical manifestations:
    - Arterial: intermittent claudication (activity leads to pain
    - Venous: none/edema/life-threatening pulmonary embolus
- Interventions:
    - Address risk factors
    - Prevent - anticoagulant drugs (eg. heparin)
    - “Clot buster” (eg. tissue plasminogen activator - tPA)
    - Surgical removal

Embolus

- Part of thrombus free, travels in blood stream until it lodges in distal artery
    - Results in completely blockage (occlusion of artery)
    - Thrombi from left side of heart -> brain: results in ischemic stroke
    - Venous thrombi -> lungs: pulmonary embolism (PE)
    - Clinical manifestations:

      -Stroke: cognitive/motor/sensory (location dependent)

      - PE: none/shortness of breath/ inc. resp rate/ pain/death
    - Prevention: anticoagulant drugs (eg. heparin, warfarin)
    - Rx (treatment): none/filters/tPA (ischemica stroke - tricky - blood supply to brain is stopped or hemorrhagic stroke where blood vessel ruptures and floods out into the brain. Careful because ischemic stroke can turn into heammorhagic stroke / surgery
    - Other causes: Fat(trauma/surgery), tutors (metastases), bacterial clumps, air (5-100ml), amniotic fluid-labour & delivery

Reduced Vascular Blood Flow

- Vasospasm — sudden constriction of artery -> flow obstruction
    - Coronary: variant/prinzmetal angina — caused by a spasm in the coronary arteries which can be induced by cold weather and stress
    - Cerebral:

    - Hemorrhagic -> ischemic stroke
    - Migraine due to vasodilation after vasospasm
- Inflammation:
    - Vasculitis (artery) / phlebitis (vein) - coronary artery blockage always starts with inflammation
    - Causes: eg. infection, adverse drug reaction, autoimmune
    - Can be focus for thrombus formation
- Mechanical Compression — from trauma, casts/tight dressings, bleeding, edema

Blood/Lymphatic Vessels: Structural Alterations

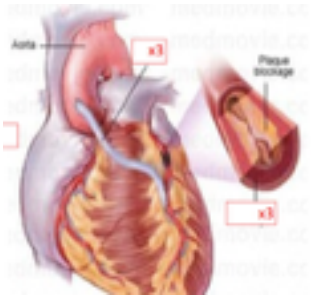
- Valvular Incompetence
- Arteriosclerosis / atherosclerosis
- Aneurysms
- Arteriovenous fistula: artery and vein abnormally connected
    - eg. brain arteriovenous malformation (AVM) these are congenital and are often silent/ undetected until there is a bleed or ischemic stroke; sometimes preceded by headaches; when they bleed they become immediately obvious; can be focus of dementia because of AVM
    - Dementia - can't just say they have Alzheimer's disease; gotta rule out all other some of which are treatable causes. AVMs can be removed

Alteration in Arterial Flow

<u>Arteriosclerosis/ Atherosclerosis:</u>

- Note that "arteriosclerosis" is hardening/thickening of artery walls from any cause, whereas "atherosclersis" is a specific type/process (but terms often used interchangeably)
- Response to trauma/irritation to inner arterial wall -> platelet aggregation following inflammation
- Medial smooth muscle proliferates
- LDL cholesterol and fats leak into vessel wall
- Fibrous collagen cap covers plaque
- Lesions slowly grow to decrease vessel diameter/ blood flow. Plaque is not a clot, it is growing capped area loaded with LDL and fats, as it gets bigger more BF is compromised. When it bursts this is when clot forms because bleeding into artery happens and clot will lock entire diameter of BV.
- Leading cause of death in first world counties
    - Coronary artery disease -> lead to MI
    - thrombi: brain (stroke), extremities, etc.
- Modifiable risk factors:
    - Obesity, physical inactivity
    - Lipids: high triglycerides/LDL cholesterol and low HDL
    - Active/passive cig smoke
    - Hypertension (also an outcome); Diabetes
    - Stress, depression — less likely to try to modify risk/seek treatment
- Non-modifiable risk factors:
    - Aging and gender: M at greater risk than female until menopause

- Family history
- Ethinicty: African-American/Hispanic higher and Asian lower risk



- Diagnosis
  - Patient history and physical assessment (H&P)
  - Exercise stress test, ultrasound, angiography
- Treatment
  - Weight loss/ diet/ exercise/drugs (hugely important)
  - Laser/balloon angioplasty, coronary artery bypass graft (CABG) can be done without stopping the heart now

Thromboangitis Obliterans (Beurger Disease)

- Inflammation small/medium extremity arties/veins
- Rarer cause of alteration of arterial BF. Pathogenesis is hereditary but has strong link to smoking
- Amputation may be necessary

Reynaud Syndrome

- extreme vasoconstriction-> cessation of flow to fingers/toes/earlobes/nose
- initiated by cold or emotional distress
- can affect local nerve function leading to extreme pain or numbness

Acute Arterial Occlusion

- Medical emergency -> gangrene/sepsis/amputation
- Multiple possible causes/Rx
- S&S: 6 P's! Pallor, parenthesis, paralysis, pain, polar (cold), pulses

Aneurysms

- Local weakness/dilation of artery wall
- Causes: congenital (born w it), not hard to diagnose; aneurysms can be silent for decades
- Diagnose: MRI/CT/angiography/transesophageal echocardiography
- Discovered when they rupture - medical emergency; can cause intracranial pressure increase/stroke
- Dissecting aortic aneurysm: blood into wall tear; severe pain; medical emergency when the rupture because lose a ton of blood and you will go into shock
- Rx: medical/surgical

Reduced Venous Vascular Flow: Incompetent Vein Valves

Incompetent Vein Valves

- Deep: 1) Chronic venous insufficiency
  - S&S: warm/tough skin, edema, pain, stasis ulcers (open unhealed wound)
  - Pooling of blood -> inflammation
  - Rx: as with varicose veins
- Deep: 2) Deep venous thrombosis
  - S&S: none, edema, inflammation, pain, +/- dilated superficial veins
  - Rx: aggressively because pulmonary embolus can form - use anticoagulants right away with IV/input then chronic anticoagulants

Reduced Lymphatic Flow: Lymphedema

- Inflammatory response: pitting edema -> hypertrophy of subcutaneous fat tissue, fibrosis
- Primary — congenital OR from worm infection (90 million worldwide)
- Laterogenic cause: surgical lymph node removal or lymphatic vessel destruction during radiation therapy
- Usu. in extremities, also head/neck/trunk/genitalia
- Early diagnosis/Rx or chronic: thick/rough skin (brawny edema), large deformed limb
- Diagnosis: R/O other causes localized edema. U/S. CT, MRI, lymphosinctigram
- Rx: No cure. External compression, skin care, massage, exercise. Surgery limited: SQ tissue resection, lymphatic -venous anastomosis. New: liposuction

CH. 16 ALTERATIONS IN BLOOD PRESSURE

Determinants of Systemic BP

- BP must be sufficient to move blood through body to satisfy need for O2 and nutrients
    - Tissue/organ damage if BP to low OR too high
    - BP = Cardiac Output (CO) X Systemic Vascular Resistance
        - CO = Stroke volume (SV) X HR
        - Stroke volume = volume of blood leading the heart after each contraction. It is determined by:
            - V of blood in heart before systole — preload
            - Contractility of myocardium
        - SVR = arterial radius and compliance — after load
            - Constrict/relax (dilate) arterial smooth muscle
            - Increase in SVR, decrease BF from heart

Components of BP Measurement

- From highest during systole - ventricular contraction to lowest during diastole - ventricular relaxation
- Average systolic pressure 110 mm Hg in adults
- Average diastolic pressure 70 mmHg in adults
    - Pulse pressure: difference between averages (~40mmHg)
- Risks to health begin with BP elevations > 120/80
- Standards for children (3.5%) incidence!!) based on height, age, & gender

Blood Pressure Measurement

- Using sphygmomanometer/ stethoscope; automated oscillometric; wireless wrist monitor (“less accurate”)
    - Many sources of error:
        - Readings vary over time
        - Time between readings
        - Cuff size
        - White coat HTN (home monitoring)
        - Exercise/food/smoking
        - Visual/auditory accuracy of clinician/device

- Auscultatory gap: low systolic to high diastolic readings

Mechanisms of BP Regulation

- Complex: neural + humoral - in body fluids/blood (e.g. hormones, level of sodium in blood) + renal
  - Must remain stable
  - Yet ever-changing internal/external environment
  - Rapid short/long term control
    - Autonomic NS - SNS and PNS
    - Baroreceptor Reflex - where blood pressure monitors near heart between heart and brain and when BP/BF up to brain starts to stop the baroreceptor reflex kicks in and increase CO output
  - Long term control:
    - RAAS: Renin-angiotensin-aldosterone system - bodies way of over week to months adjusting BP

<u>Short-term Regulation (seconds)</u>

- ANS

  -Sympathetic (NT epinephrine and norepinephrine)

  -Heart Beta1 receptors -> heart rate increase

  -Artery alpha1 receptor interaction -> vasoconstriction

  - Brain alpha 2 receptors -> E/NE decrease (-ve feecback)

  -Parasympathetic (NT acetylcholine)

  -Heart ACh receptors -> heart rate decrease (opposite effect)
- Baroreceptor Reflex (ie. rapid, uncontrolled?)

  -eg. If BP drops:

  -Arterioles constrict -> peripheral resistance increase

  -Veins constrict -> venous return/preload increase

  -Heart rate increase

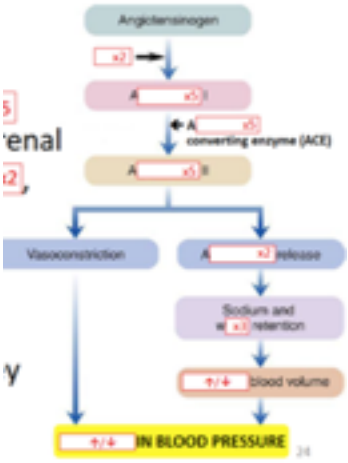
<u>Long-term Regulation (weeks-months)</u>

- Renin-Angiotensin-Aldosterone System (RAAS)

  -BP drops: kidneys produce renin

  -Renin causes formation of vasoconstrictor angiotensin -> causes vasoconstriction

  -Angiotensin also acts on adrenal glands releasing aldosterone which acts on kidney to reabsorbs water and sodium to increase blood pressure



- Also: Antidiuretic hormone from brain acts on kidney to reabsorbs water and increase BP.
- Long term mechanism; remember aldosterone acts on kidney and the production is stimulated by angiotensin on the adrenal glands

Hypertension

- Current/projected prevalence of HTN is stunningly bad
    - 30% of adults in U.S. and 25% in the world projected to be 29% in 2025. 1.26 billion individuals
    - Results in part from lifestyle choices: obesity & sedentary lifestyles increase; alcohol/cig consumption; diet deficient in fruits/veggies
    - HTN increases morbidity and mortality from:
        - Heart disease (CAD, angina, MI, heart failure)
        - Kidney disease
        - Retinal damage
        - Peripheral vascular disease
            - Stroke (hemorrhagic - blood vessel bursts and bleeds into brain)
    - By 2020 MC risk factor of worldwide annual death rate
- Primary (essential) Hypertension
    - 90-95% of known cases - rare in children less than 10 yo
    - Idiopathic - no cause why it's happening & no identified etiology. However

Non-Modifiable Risk Factors	Modifiable Risk Factors
• Increasing age • Family history	• Obesity; Sedentary lifestyle • Metabolic syndrome: elevated circulating insulin & lipid levels, HTN, obesity • Dietary factors: inc. fat & sodium, inadequate potassium and Ca++ • Tobacco use • Lab data: elevated blood glucose, cholesterol, triglycerides, LDLs; decreased HDLs
	During pregnancy: smoking/poor diet/ inadequate Ca++, poverty, Breast feeding protective

- Treatment of Primary HTN
    - Target: 140/90 (130/80 with diabetes/kidney disease)
    - First: lifestyle modifications (weight loss, exercise, diet)
    - Not at target BP: single drug/multi drug combinations - drugs taken life-long - only 1/4 full BP control
- Secondary HTN
    - Specific cause: Text in boxes 16-2, 16-3) must be treated
    - Adults <10%/ children are common
    - 5-12% pregnancies: preeclampsia/eclampsia (if seizures)
        - Multiple fetus/mother consequences

        - Drug treatment used cautiously
    - Need for thorough medical evaluation:
        - History/physical exam, medication history, ECG, full set standard blood tests,…
- Hypertensive Urgency/Emergency
    - 1% will experience sudden increases in systolic and/or diastolic BP (DBP > 120 mmHg) Greater than 25% of ER visits
    - S&S: severe chest pain/headache/anxiety, confusion, blurred vision, N&V, shortness of breath, seizures
    - Seen both in previously undiagnosed or chronic HTN
    - If also end-organ damage, Urgency turns into EMERGENCY — ischemic/hemorrhagic stroke, encephalopathy, MI, HF, pulmonary edema, aortic dissection, retinopathy
    - R/O causes of rapid-onset reactive HTN
        - Anxiety/pain/ alcohol withdrawl/ full bladder/ abrupt discontinuation of antihypertensive meds
    - Treatment: Rapid controlled BP reduction:
        - Hypertensive urgency: over 1-2 days, Oral meds
        - Hypertensive emergency: over 1-2 hours, IV meds needed

Orthostatic (Postural) Hypotension

- On standing, 500-1000 ml of blood pools in leg veins - (Cardiac output: 5-6 L/min)
    - BP falls: Baroreceptors spring into action sending signal to vasomotor centre in brainstem.
    - Causes Sympathetic NS to activate
    - Speeds up HR and cause arteries to constrict
    - Blood pressure normalizes
    - If this mechanism fails … Blood pressure - and possibly individual - will get up and fall and therefore could cause serious injury
- Decrease in DBP > 20 mmHg / Increase HR 20-30 bpm within 3 min
    - Widespread (6-30% elderly) but often unrecognized
    - Dizziness/blurred vision/confusion -> syncope (fainting) /falls
    - Long-term: cardiovascular/stroke/cognitive impairment
    - Many causes:
        - CNS/ANS problems (eg. MS, Parkinson’s disease)
        - Dysrhythmia: drug side effect - always get complete drug history on a patient; Bed rest
        - Fluid intake decrease; Blood/fluid loss increase; Coughing

- Stress/pain/unpleasant events; Heat exposure

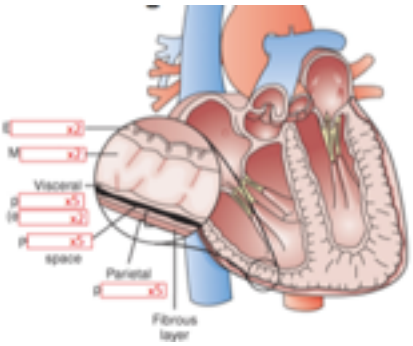
- Management:
  - Slow position change; if heat exposure then treat that; if any evidence of heavy metals in diet check in blood test and correct; canes/walkers
  - Binders (for legs and abdomen)
  - Sit/squat/bend (lower head), tighten leg/buttock muscles
  - Require Thorough evaluation

CH. 17 CARDIAC FUNCTION

Cardiac Anatomy

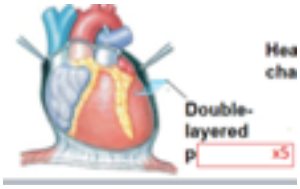
Layers of the Heart

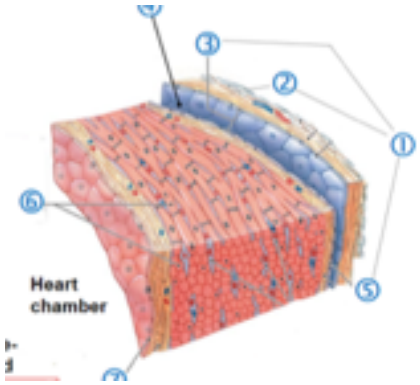
- Epicardium: Covers outer surface. Inner part of 2-layered pericardium. Fluids can fill it and this is called Peripheral** check Effusion
- Myocardium: Muscle - provides contractile force
- EndocardiumL Lines 4 chambers and valves - prevents clotting and RBC damage as it provides smooth and frictionless blood flow



Coverings of the Heart (Exterior to Interior)

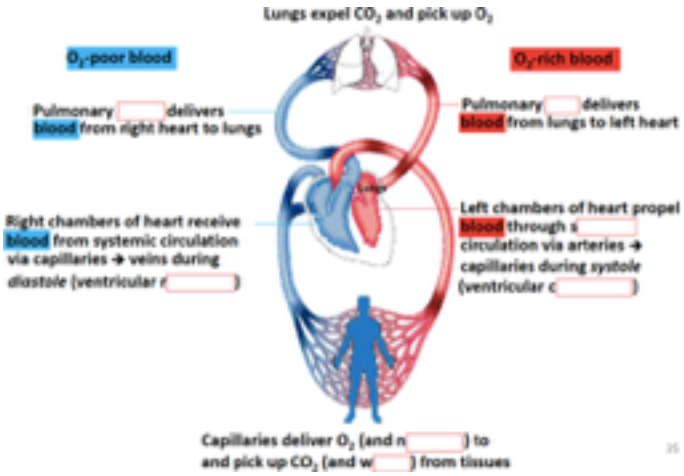
- Pericardium (1) double layered sac:
  - Fibrous pericardium(2) -dense CT: protect/ anchor/ prevent overfilling
  - Serous pericardial (3), parietal layer
  - Pericardial space (4) — has scours fluid for frictionless glide as heart beats
  - Serous pericardium (5) , l visceral layer (epicardium)
  - Myocardium (6)
  - Endocardium (7)





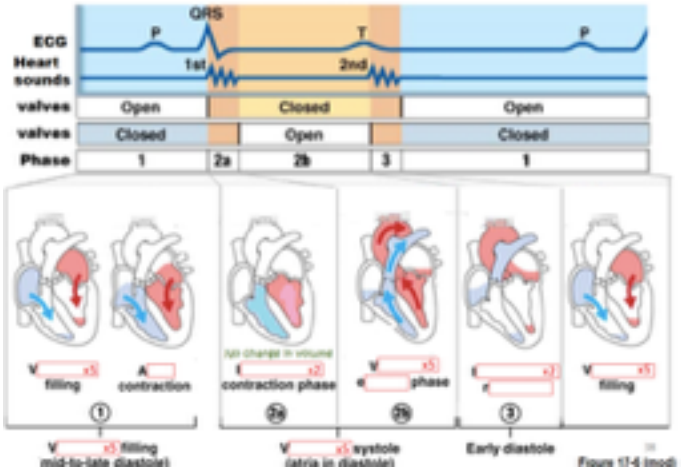
Circulatory System

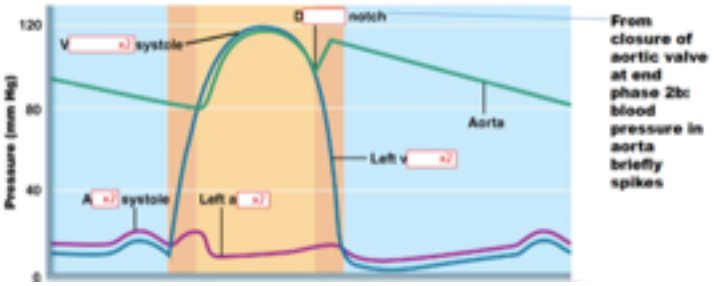
1. pulmonary artery
2. pulmonary vein
3. through systemic
4. ventricular contraction
5. and nutrients
6. and wastes
7. ventricular relaxation



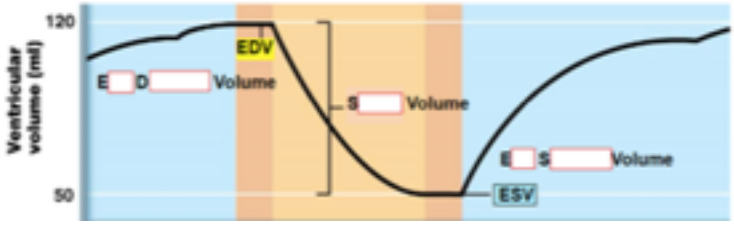
Cardiac Cycle

- The pathway of blood flow through the heart





- Dicrotic notch - closure of aortic valve at end of phase 2b. BP briefly spikes
- End diastolic volume - refers to ventricle volume of ventricles when fully realized and end of diastole



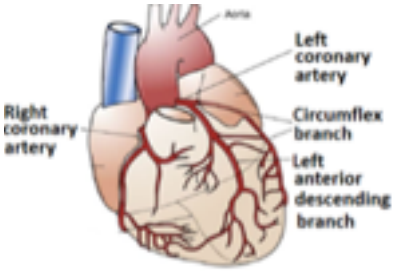
- Stroke volume - what is squeezed out of heart
- End systolic volume - when ventricles contract, what does the volume shrink down to

Geriatric Considerations

- Changes in the Aging Heart:
  - Resting heart rate in elderly unchanged but with stress/exercise: can't respond as quickly with elevated rate
  - Maximal HR elevation is recused and once HR is elevated, takes much longer to return to resting level
  - Stroke volume/cardiac output decreases with age
  - O2 consumption in myocardium reduced

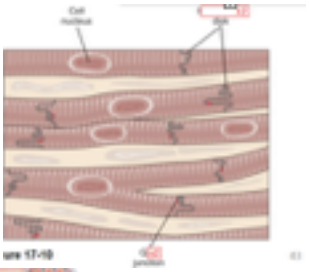
- Less efficient function when stressed
- Overall decrease in cardiac reserve

Coronary Arteries: Blood -> Heart

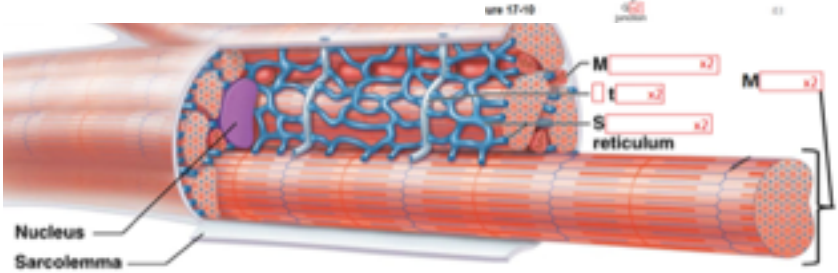


- The heart works very hard and needs second most amount of blood in body (brain is first), arteries provide blood to everywhere in body
- Auto-regulation: artery diameter/BF continuously adjusted to meet myocardial demands
  - Vasodilation with tissue metabolism increase.
    - Driving pressure decreases with vasodilation and increases with vasoconstriction
  - Most coronary BF occurs during diastole: artery resistance markedly increased when heart contracts
  - Disruption of blood flow to heart (ischemia) -> pump failure and damage to cardiac tissue. Causes:
    - Driving pressure decreases (eg. low BP
    - Artery diameter decreases (wall hypertrophy/thrombi/ASHD)
    - Perfusion time decreases (tachycardia/dysrhythmias) — perfusion: amount of blood flow through the arteries of heart
    - Metabolic demands increase due to fever/sepsis/anemia

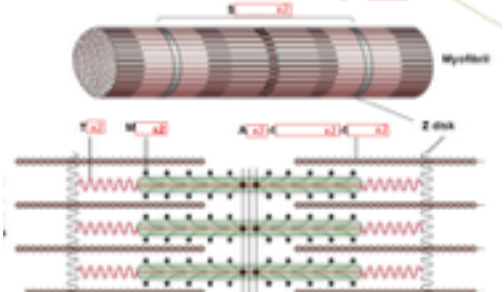
Cardiac Myocytes



- Working (pumping) cells — not pacemakers
- Packed with c_____ filaments
- Can't proliferate (mitosis), but can increase in size make more contractile proteins (hypertrophy - typically not good sign, sign of failing heart)
  - But - new myocytes can be formed from stem cells
  - Have high turnover rate: 11-15X over lifetime



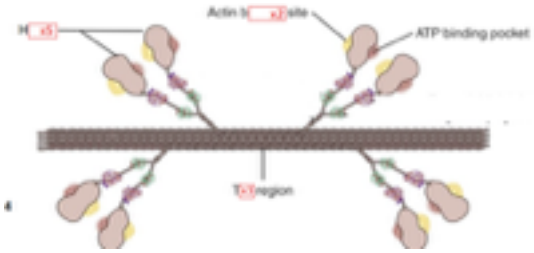
- Joined end-to-end by interpolated disks
- Contain gap junctions to allow rapid passage of electrical impulses
- Cells coordinated/work together ("functional syncytium")
- Sarcolemma form T-tubules that penetrate cell, cry extracellular fluid/ions (especially Ca) inside cells
- Ions -> cellular excitation/contraction
- Sarcolemma also turns into sarcoplasmic reticulum (SR) — extensive labyrinth store intracellular Ca
- Many mitochondria (that make ATP), extensive capillary networks
- Made up of many myofibrils -actual rodlike contractile elements



Structure or Contractile Apparatus

- Myofibrils composed of myofilaments & myosin (thick filaments) and actin (thin filaments)
  -Thin filaments also contain tropomyosin & troponin
- Filaments arranged in sarcomeres- lie between Z disks. Thing filaments are attached to Z discs and thick filaments held by titan - also attached to Z disk

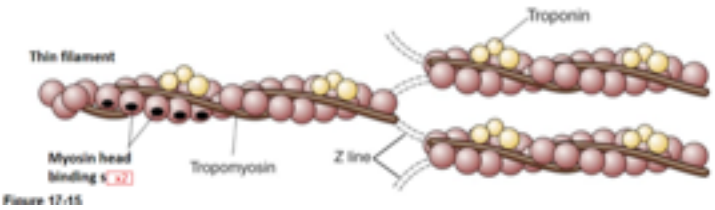
Contractile Filaments:



Myosin

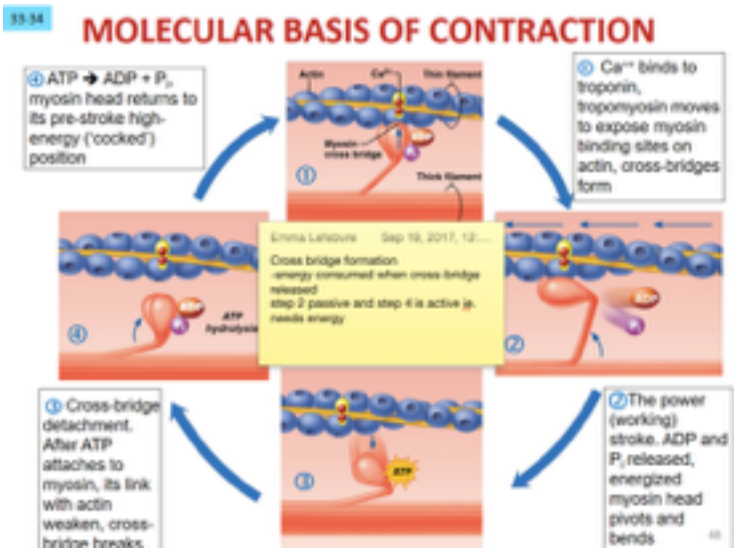
- Myosin has a tail and two globular heads
- Thick filaments: have many myosin molecules, tail regions bundled together and heads protruding at intervals
- Head regions are flexible, can bend & pull on actin filaments to cause actin to slide - note their actin binding sites
- Heads have enzymatic properties: can cleave ATP (energy for muscle contractions)

Actin



- Thin actin filaments: polymers of globular actin proteins like two string beads twisted to form a couple helix — each bead has a site that can bind with two myosin heads
- Tropomyosin's: bind to string of 6-7 actin beads — inhibit myosin-biding sites when muscle relaxed
- Troponin — controls position of tropomyosin and regulates availability of binding sites by moving the tropomyosin

Molecular Basis of Contraction



- Sliding Filament/Cross-bridge Theory
  - Myosin heads grip binding sites on actin beads
  - This forms cross-bridge
  - Flexible myosin heads move and tug on actin filaments
  - Thus, myosin heads bend back-and-forth, binding and pulling on actin filaments in a step-like fashion
  - Each step moves actin filaments minutely therefore many sequential cross-bridges required to shorten entire sarcomere
  - Making & subsequent breaking of each actin-myosin cross-bridge requires one molecule of ATP
  - Therefore tremendous quantities of ATP are hydrolyzed with each cardiac contraction
- Role of Ca++ in Muscle Contraction

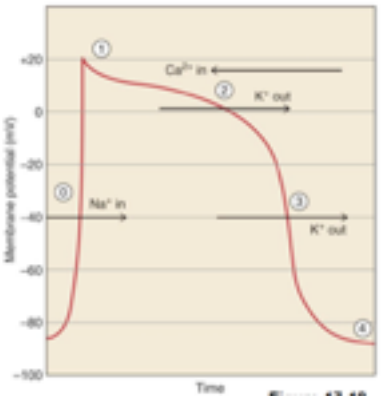
- Muscle contraction needs adequate Ca++ in cytoplasm
- At rest, tropomyosin prevents myosin heads from binding to actin by inhibiting actin-binding sites
- Tropomyosin position controlled by troponin
- When Ca++ is absent: troponin induces tropomyosin to inhibit actin-binding sites
- Ca++ binds to troponin: tropomyosin exposes binding sites and cross-brdiegs can form
- Concentration of Ca++ determines how many actin sites exposed and for how long; hence determining # of cross-bridges and strength of muscle contraction
- Release of Ca++ into cytoplasm regulated by numerous NTs and hormones that affect contractility

Energy of Muscle Relaxation

- Muscle relaxation is not a passive phenomena - it requires sufficient energy to pump Ca++ from cytoplasm and to keep tropomyosin binding sites blocked by troponin
  - As [Ca] decreases, Ca diffuses away from troponin and tropomyosin covers actin-binding sites. New cross-bridges can't form. Thick/thin filaments slide back to resting positions
- Rigor mortis — muscle stiffening after death; without ATP, so cross-bridges can't detach and muscles are unable to further relax

Cardiac Electrophysiology

- Cardiac Action Potential (AP):
  - Depolarization of cardiac cells beyond threshold point opens membrane ion channels and the 5-phased AP shown results:



1. Phase 0: Na+ channels open; rapid influx on Na+. Cell depolarizes sharply. Note that RMP is -85/-90 mV.
2. Phase 1: Small depolarizations as Na+ channels close. Transient efflux of K+ through K+ channels
3. Phase 2: Plateau phase: little change in membrane potential. Influx of Ca++, continued efflux of K+
4. Phase 3: rapid return to RMP; Ca++ channels close, K+ ions leave more rapidly. Na+ channels of cell are reason for:

-Absolute refractory in phases 1, 2, early 3 — nothing can happen with Na+ channels and if they don't open the cell is unresponsive to stimulation because can't create an AP

-Relative refractory during late phase 3 — larger than normal depolarizing stimulus required because membrane potential dips below RMP because K+ channels don't close as soon as RMP is reached so it is a little more negative till they all close and membrane potential passes to RMP

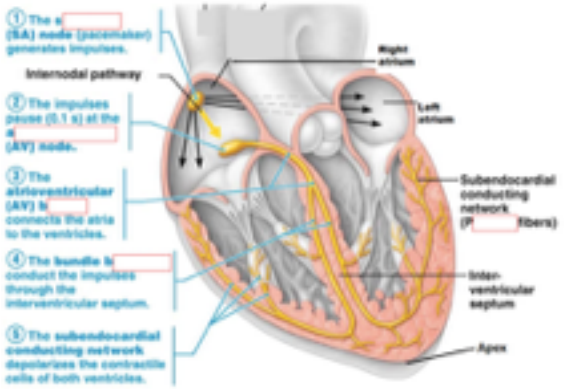
5. Phase 4: Time between APs, RMP in contractile myocardial cells flat - no spontaneous depolarization. Pacemaker cells have sloping phase 4 and automatically depolarize

** Na+, -K+, & Ca++ pumps work continuously through all phases to establish internal and external concentration levels and thus requires energy

Cardiac Conduction System

- Spread of electrical action potentials across heart via its conduction system causing myocardial contraction

- Specialized non contractile pacemaker cells generate APs spontaneously (rhythmicity/automaticity)
    - Normally, sinoatrial node (SA) in right atrium “paces” heart at 60-100 APs/min and 60-80 bpm -> If it fails than other pacemaker cells face heart at slower rate
    - Impulses travel via atrioventricular node (AV) to:
    - AV bundle (of His) to:
    - Right and Left bundle branches to:
    - Purkinje fibers -> ventricular myocardium
    - With APs/depolarizations, atria contracts then ventricles

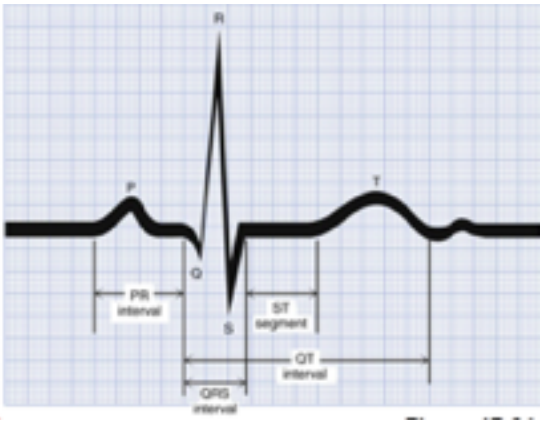


ANS Regulates Heart Rate/Rhythm

- Sympathetic Stimulation:
    - HR inc. — chronotropic effect
    - Speed of conduction inc.
    - Contraction force increase (inotropic effect)
    - Mediated by norepinephrine
- PS Stimulation
    - HR/speed of conduction decrease
    - PS innervation via vagus nerve
    - Mediated by acetylcholine
    - Controls resting heat — sympathetic control: HR 60 -> 100bpm
    - Vasovagal response — increased vagal tone by eg. breath-hold strain during defecation, press carotid artery -> dec. HR leading to dizziness and syncope

Electrocardiography

- As APs spread through myocardium, electrical current transmitted to body surface & can be detected by electrodes placed on skin
- Electrocardiogram (ECG) recording of electrical currents (activity of conducting system)
- Indicator of conduction system, impulse initiation conduction rates/pathway irregularities
- Major deflections: P wave — atrial depolarization
    - PR interval — atrial, AV node and purkinje depolarization
    - Q wave — septal depolarization
    - R wave — apical depolarization
    - S wave — lateral wall depolarization
    - T wave —ventricular repolarization (relaxation?)



Cardiac Output Determinants

- CO = HR X SV
- Determinants of HR:
    - Controlled by ANS — normally PNS
    - Sympathetic NS triggered by decrease BP/O2 or inc wastes (CO2)
    - Also higher CNS (fear, stress, etc) and many drugs
- Determinants of SV:
    - Preload — coulee of blood in the heart
        - Determined by amount of venous return (end-diastolic-volume EDV)
        - Frank-Starling law: inc. EDV = inc. contractility
    - After load — impedance to ejection
        - Primarily determined by aortic BP
    - Heart muscle contractility
        - Positive inotropes increase contractility and negative inotropes decrease contractility
        - Many drugs have such properties

Endocrine Function of the Heart

- In addition to its pumping function, heart also has an endocrine function: secretion of natriuretic peptides
- Atrial natriuretic peptide (ANP) synthesized by myocytes in atria and released in response to atrial stretch — increased atrial stretch occurs when blood volume excessive
- Ventricles produce a related peptide (B-type natriuretic peptide, BNP) when chronically over-distended — elevated BNP marker for congestive heart failure
- ANP/BNP cause enhanced excretion of Na and water by kidney
- Natriuretic peptide effects antagonistic to renin-angiotensin-aldosterstone system (RAAS)

Tests of Cardiac Function

<u>Electrocardiogram</u>

- 10 skin electrodes (6 on chest, 4 on limbs) give standard 12-leadECG (pt supine and generally not naked)
- Each lead provides different “view” — and corresponding tracing of current through heart, Normal ECG below
- Discover HR, rhythm, gives multiple data
- Standard ECG recording less than 30 sec readily obtained
- 24-48 hour: ambulatory ECG (holter monitor)
- Sequential ECGS record changes over time
- ECGs used to monitor heart during exercise (treadmill stress test)
    - Impaired coronary circulation - ST segment elevation and abnormal T waves

<u>Magnetic Resonance Imaging/ Computer Tomography</u>

- Can diagnose eg. myocardial thickening, pericardial sac disease, valves, congenital malformations, acute and chronic MIs, coronary plaque burden, assess vulnerable plaque morphology in a arterial walls

<u>Echocardiography</u>

- Ultrasound images of cardiac structure and motion

- Useful for diagnosing heart enlargement, valvular disorders, fluid collections in pericardial space, cardiac tumours, abnormalities in left ventricular motion, estimations of ejection fraction, assessments of ventricular systolic and diastolic function

Nuclear Cardiography

- Radioactive tracers (eg. thalium-201, technetium-99): image blood flow/detec areas with impaired perfusion
- Gated pool SPECT (single-photon emission computed tomography
- Positron emission tomography scans: cardiac perfusion and metabolism using eg. carbon-11 glucose

Cardiac Catheterization / Coronary Angiography

- Catheter inserted (via femoral artery/vein) directly into coronary arteries or pulmonary arteries/veins
- Allows visualization and management of coronary artery obstructions
- Can also visualize/assess heart chambers and valves, measure cardiac output/ejection fraction, insert probe for obtaining intracoronary ultrasounds
- Frequently used to evaluate coronary bypass graft patency (still open?)
- Commonly followed by interventions to treat detected abnormalities: direct thrombolytic agents to the site of coronary thrombosis / laser therapy / coronary balloon angioplasty / stent placement

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Lecture 3 — Cardiovascular Part 2

CH. 18 ALTERATIONS IN CARDIAC FUNCTION

Coronary Heart Disease

- Overview:
    - Incidence rapidly increasing during 20th century, peaked late 1960s
    - The decrees with improved treatment/prevention
    - Still leading cause of death globally: 17.5 million people died in 2012 (31% of all deaths)
    - Will cover:
        - Coronary Artery Disease (Atherosclerotic Coronary Vascular Disease, ASCVD)
        - Diseases of the Layers of the Heart (Cardiac Valve and other endocardial Disease, Diseases of the myocardium, Diseases of the pericardium
        - Congenital Heart Disease

ASCVD Risk Assessment

- 2013 ACC/AHA* Guidelines
    - Gives mode of intervention (diet, exercise, drugs)
    - +ve risk factors: increasing age, African-American race, HTN, diabetes, cig smoking, low HDL
    - -ve risk factors (beneficial): high HDL
    - 10 year ASCVD Risk: Framingham Risk Prediction Score

* Optimal risk factors: total cholesterol 4.4 mmol/L, SBP 110mm, not taking HTN meds, not diabetic/smoking

Atherosclerosis Mechanisms

- Probably due to abnormal lipid metabolism

- Lipids (cholesterol/triglycerides) move in blood within lipoprotein spheres
- Surface apoproteins (Apo) direct binding to peripheral tissues (eg. blood vessels/liver)
- CHD varies with type of lipoprotein
    - Low density & very-low-density lipoproteins (LDL and VLDL) increase risk by transporting cholesterol from liver to peripheral tissues where it forms atheromatous plaques
    - High density lipoproteins (HDL) decreases risk — transport cholesterol from peripheral tissues back to liver removing plaque
- Lipid-Lowering drugs mainstay of Rx/prevntion
- LDL/triglyeride-level Rx targets set

Plaque Formation

1. Chronic endothelium “injury”: HTN, hyperlidemia, smoking, elevated homocysteine levels, hero dynamic factors, toxins, viruses, immune reactions
2. Endothelium dysfunction, increased permeability, inflammation
3. Activated monocytes invade arterial wall and smooth muscle proliferators
4. Macrophages engulf lipid to become foam cells
5. Lipid core forms in arterial wall and a fibrous cap (plaque or atheroma) evolves

Pathophysiology of Ischemia

- Plaques generally increase in size over many years
- Significant flow reduction when plaque occupies >/= 75% of arterial lumen
- Places may be located anywhere within the three major coronary arteries/secondary beaches
- Alternative (“collateral”) pathways develop: preserve flow despite almost total occlusion of a coronary artery

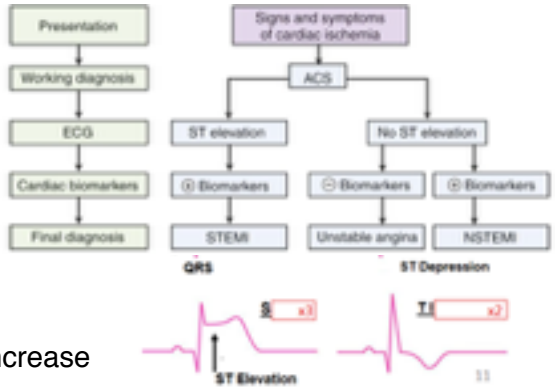
Angina Pectoris

- Intermittent chest pain/myocardial infarction/ cell death
    - Pain “burning/crushing/squeezing/choking”
        - Also back pain/fatigue/weakness
        - Attributed to indigestion/dental pain
        - [Myocardial pain receptors] -> CNS <- [jaw/neck/arm sensory neurons]: referred pain
        - Silent ischemia
    - Stable/classic/typical angina:
        - Increased myocardial O2 demand (exercise/stress): clogged arteries prevent adequate coronary blood flow
        - Predictable/relieved by rest
    - Prinzmental/ variant angina:
        - Unpredictable pain attacks — not exertion/stress
        - May be due to vasospasm

Acute Coronary Syndrome

- Unstable Angina and Myocardial Infarction (MI)
    - Pain may be more severe/last longer than angina
        - May occur in previously symptomatic individuals!
        - MIs may be silent - avoid detection

- Ruptured plaque leading to blood clot (thrombus) and complete coronary artery blockage
  - Unstable angina: partial/temporary blockage
  - MI: permanent/total blockage, myocardial cell death — biomarkers increase in CK-MB, troponin I and T
- EEG ST Segment: elevated STEMI/ not (NSTEMI)
  - STEMI: repercussion Rx (clot busters) - move fast!!!
  - NSTEMI: anti platelet drugs - decrease infant and increase prognosis



- Also inverted T waves
- 12-lead ECGs localize MI: anterior/lateral, etc
- Note: CK-MB biomarkers take hour or so fraction from heart muscle then measure elevations in troponin

Unstable Angina vs MI

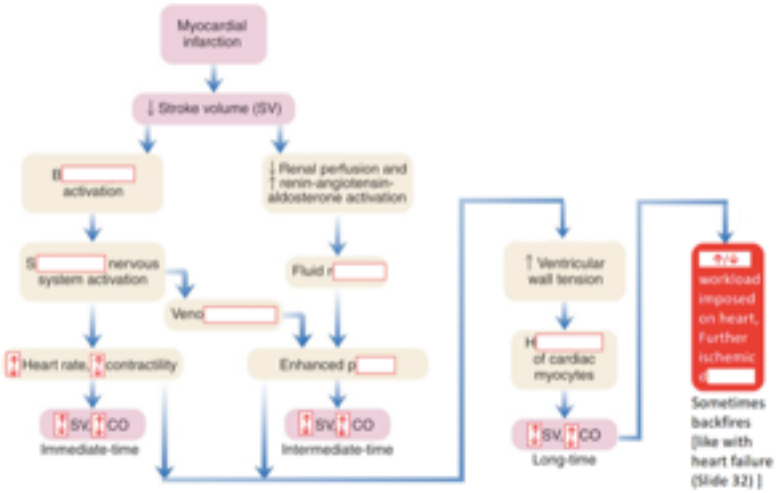
- All have myocardial ischemia/usually angina
- ECG: ST elevation vs no ST elevation
- Cardiac biomarkers then used to make final diagnosis:
  - Most with DT elevation: STEMI
  - Some with no ST elevation but increase markers: NSTEMI
  - No ST elevation/increase markers: unstable angina

Myocardial Infarction

<u>Facts/Figures</u>

- 150,000 deaths/year (US)
  - 1/5 boys <65yo
  - 1/30 girls <45 yo, by 80 yo women catch up
- Cardiac cath/echo, radionuclides also diagnose
- Other S&S: fever, leukocytosis, increase sedimentation rate (ESR), fatigue, restlessness, anxiety, weakness
- Course: compensatory increase HR, contractility, BP, fluid retention. Ultimately backfire leading to heart failure
- Short/long term Rx: drugs (O2/pain/cardiovascular), repercussion (angioplasty/stent/CABG), dec activity
- Variable prognosis: infarct size, health, age
  - Most deaths pre-ER / 10% die input
  - 25% uncomplicated
  - Others: HF/dysrhythmia/shock/pericarditis/thromboemboli

MI: Clinical Course



Sudden Cardiac Arrest/ Death

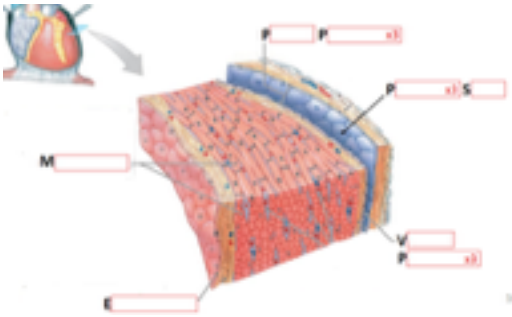
•Unexpected/from cardiac causes < 1hr symptom onset

- Causes: acute MI, lethal dysrhythmia (old MI scarring/diffuse ASHD, electrolyte (Na+/K+/ Ca++) electrolyte imbalance
- Trained CPR/public external defibrillation increase survival
- High recurrence risk

Chronic Ischemic Cardiomyopathy

- Progressive/Insidious ischemic myocardial damage
  - Typically history of angina/MI
  - Atrophic/dead cells throughout myocardium
  - Poor prognosis: ultimately develop heart failure

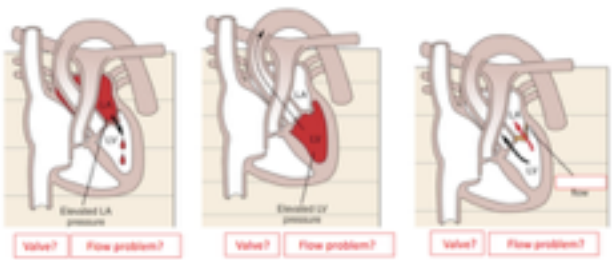
Diseases of the Layers of the Heart



<u>Heart Valve Diseases</u>

Two General Types of Diseases

1. Stenosis — failure of valve to open completely
   - Pressure needed to push blood through valve opening - normally none required
   - Develops slowly over years
   - Compensatory myocardial wall hypertrophy (thickening) results
2. Regurgitation/insufficiency — failure of valve to close completely
   - Back-flow through valves results
   - If sudden (eg. infection, papillary muscle rupture), no compensation possible



- For both: resulting turbulent blood flow causes characteristic heart sounds (murmurs) Give location and type
- Pic: mitral stenosis, aortic stenosis, mitral regurgitation

- Heart murmurs: caused by turbulent blood flow b/o these valvular disorders
    - Normal hearts sounds (lub-dub)
    - S1: valves 1 & 4 closing marking start of systole
    - S2: valves 2 & 3 closing end of systole
    - 1 — tricuspid
    - 2 — pulmonary
    - 3— bicuspid
    - 4 — aortic
    - Mitral regurgitation: leakage of blood back through biscupid (mitral) valve when lt ventricle contracts
    - Mitral stenosis: narrowing oriface of the mitral valve
    - Aortic regurgitation: diastolic flow of blood from aorta back into left ventricle
    - Aortic stenosis: most severe; narrowing of aortic valve
- Mitral valve prolapse: two flaps of mitral valve don't close evenly because they swell up to be like balloons. may be link between this and anxiety
    - Balloons -> L atrium during systole
    - Asymptomatic for 2-3% population, @X more likely to be men
        - Sometimes leads to mitral regurgitation

<u>Other Endocardial Diseases</u>

- Two significant diseases caused by infection:

1. Rheumatic HD:
    - Streptococcal pharyngeal infection (Strep throat) leading to rheumatic fever and auto immune attack on heart valves causing inflammation
    - Rare in West, 15 mill worldwide
2. Infective Endocarditis:
    - Growth of bacteria - laden "vegetations" on valves
    - Embolize causing blood-borne infection
    - 13-50% mortality depending on microorganism

<u>Myocardial Diseases</u>

- Myocarditis:
    - Heart muscle inflammation -> necrosis and degeneration
    - Many causes: infection/allergies/snake bite/ cocaine
    - Clinical course: acute and sudden — either recovery or death in weeks to months
- Cardiomyopathy — general term:
    - Noninflammatory diseases of heart muscle
    - Clinical course: insidious onset (gradual but harmful) over years
    - Classified by cause or functional impairment:
    - Dilated cardiomyopathy - lt ventricle enlarged and weakened - prevents heart from relaxing
    - Hypertrophic cardiomyopathy — heart muscle cell enlargement; blocks blood flow out of ventricle
    - Restrictive cardiomyopathy — stiff heart muscle can't fill as much for contract

Pericardial Diseases

- Pericardium: 2-layered protective coating of heart separated by a fluid-filled space
    - Pericardial effusions — accumulation of noninflammatory fluid
        - If accumulation large: cardiac tamponade: Blood can't readily enter compressed heart.
            - S&S: Beck's triad: decrease in BP, distended neck veins and muffled heart sounds
    - Pericarditis — inflammation leading to chest pain and long term destruction of pericardial sac

Congenital Heart Disease

Heart Embryologic Development

- Fetal life: Blood bypasses lungs
    - No need: O2 from maternal circulation vis placenta
    - Foramen ovale lies between left and right atria to skip ventricles
    - Ductus arteriosus: channel connecting pulmonary artery and aorta - blood flows from pulmonary artery into aorta bypassing collapsed lungs
    - Both these communication generally close after birth

* All congenital heart defects can be repaired surgically if they don't close spontaneously

Left-to-Right Shunts

- Left-to-right shunts:
    - Oxygenated blood L -> R-heart and oxygenated blood is recirculated to lungs recirculated to lungs
    - Infants not cyanotic (acyanotic) but R-heart overworks leading to R ventricular hypertrophy, a R to L shunt can develop
    - Atrial septal defect — foramen ovale doesn't close
    - Ventricular septal defect — ventricular septum doesn't separate ventricles
    - Patent ductus arteriole (PDA) — Ductus arteriosus doesn't close
    - Coarctation of the aorta: can be anywhere (coarctation - narrowing of aorta)

Right-to-Left Shunts

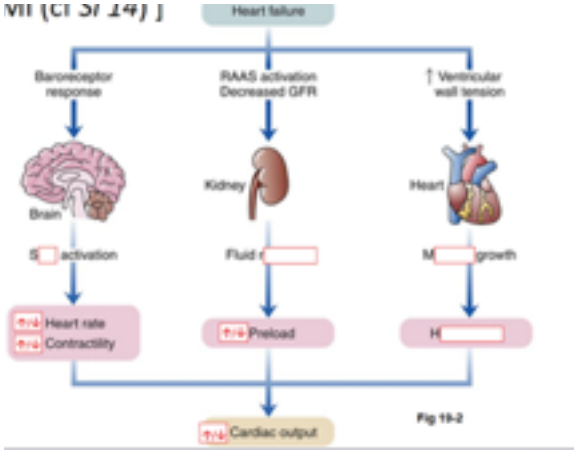
- Right-to-left shunts:
    - Decrease in O2 from R -> L-heart/circulation, bypass lungs
    - More dangerous than L->R shunts: infants cyanotic
        - Tetralogy of Fallot — VSD, "overiding aorta above VSD some of it come out in right ventricle and causes pulmonary stenosis (doesn't open properly and obstructs R ventricular outflow to lungs causing ventricular hypertrophy
        - Transposition of Great Arteries — aorta from R ventricle and pulmonary artery from left ventricle
        - Trunks Ateriosus — aorta and pulmonary artery fuse, single valve, ventricular spiel defect
        - Tricuspid Atresia — blood bypasses R ventricle via an atrial septal defect and perfuses lungs via patent ductus arteriole

CH. 19 HEART FAILURE AND DYSRHYTHMIAS

Compensatory Mechanisms

- Classification:

- Systolic Heart Failure
  - Impaired ability of myocardial fibres to contract
  - Ejection fraction: 15%-40% (normal 60-80%)
  - Decrease inotrophy - loss speed of contraction
- Diastolic Heart Failure
  - Impaired ability of myocardial fibres to relax
  - Left ventricle noncompliant: can't expand because walls have become stiff and can't expand to fill up with blood
- Patients may have isolated systolic/diastolic failure, or both (prognosis worse)



- Short term: helpful helpful [could lead to long term and could be detrimental]
  - Compensated leading to decompensated heart failure and this is similar to MI

Problems with HF Compression

- SNS activation (SNSA)
  - Failure heart has reduced responsiveness to stress
  - Predisposes to cardiac dysrhythmias over time
  - Venous constriction from SNSA initially boosts preload but eventually increases after load/cardiac workload (not good)
- Increased preload
  - Renin-angiotensin-aldosterone (RAAS) activation leading to increased water retention by kidneys leading to increased preload and greater force of contraction by the heart
  - But patients with HF often retain so much fluid that their hearts are functioning ineffectively
- Myocardial Hypertrophy/Remodelling
  - This third mechanism takes much longer (years)
  - Initially, muscle hypertrophy increases pumping force of heart
  - Eventually, remodelled left ventricle to small fibrous and stiff
- Bottom Line:
  - Increased preload/cardiac hypertrophy: heart compensates for years
  - But these result in increase myocardial work therefore more O2 needed & pathologic remodelling occurs
  - Progression/decompensation: primary disease + compensation burdens overwhelm heart

Clinical Manifestations of Heart Failure

- Left-sided ("forward") — insufficient cardiac output:
  - Confusion and fatigue, inc. HR, dec urine and peripheral circulation
  - Also pulmonary congestion: dyspnea (shortness of breath), orthopnea (SOB when lying down), cough, crackles, pulmonary edema (fluid build-up in lungs), hypoexmia (decrease O2 in blood)

- Right-sided (“backward”) failure — systemic venous congestion:
  - Jugular vein distention, hepato/ splenomegaly, abdominal edam (ascites), peripheral edema
  - Frequently L-failure leads to R-failure
- Clinical tests: chest X-ray(CXR)/ echocardiogram/ blood tests (eg. B-type natriuretic peptide -BNP)

TABLE 19-1 (modified) **STAGES OF HEART FAILURE**

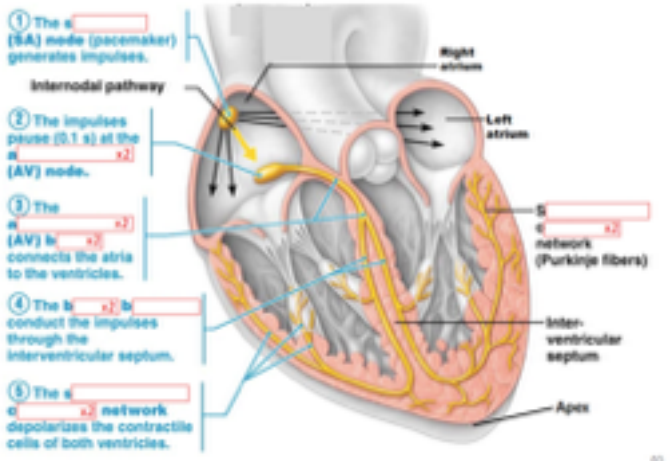
STAGE	DESCRIPTION	CLINICAL CLUES
☐	Patients at high risk of developing HF	Coronary artery disease, hypertension, diabetes, dyslipidemia, family history of cardiomyopathy
☐	Patients who have structural heart disease but have never manifested signs or symptoms of HF	Left ventricular hypertrophy (by ECG or echo), valvular disease, past myocardial infarction
☐	Patients who have current or previous symptoms of HF	Dyspnea, fatigue, exercise intolerance, prior HF hospitalization
☐	Patients with advanced structural heart disease and marked symptoms of HF at rest	End-stage, awaiting transplant, receiving palliative care

Treatment of Heart Failure

- When possible, specific treatment is undertaken to correct underlying cause
- Pharmacotherapy: clinicians get better understanding of underlying molecular mechanisms is needed to improve pharmacologic management
- Pacemakers / implantable LV mechanical assist devices
- Heart transplant

Dysrhythmias

Cardiac Conduction system: Normal Anatomy/Sequence Electrical Stimulation:



Cardiac Dysrhythmias/Arrhythmias

•Cardiac rhythm abnormality affecting impulse generation or conduction

•Causes — hypoxia (not enough O2), electrolyte (K+, Ca++) imbalances, trauma, inflammation, medication, abused drugs

•Clinical significance: indicated pathophysiology, increase cardiac output

•Initiated by three types of depolarizing mechanisms:

•Disturbed automaticity (means SA node fails, AV takes over but if these guys aren’t working properly then have dysthymia): pacemaker cells gone awry

- Triggered activity: heart cells contract twice, although only activated once
- Reentry: a cardiac impulse continues to depolarize in part of heart after main impulse has finished and majority of fibres have depolarized

- Abnormal Sinus Rhythm — can still have dysrhythmias of heart when heart still in sinus rhythm sometimes normal when not enough O2, CO
  - Normal: 60-80 bpm, PR =.12-.2 sec, QRS = .4-.1, regular PP & RR, one QRS per P, no “funny-looking” beats (PVCs)
  - Sinus tachycardia: > 100 bpm, sympathetic activation acting on SA node pacemaker (eg. dec BP/O2/CO, pain/anxiety, etc.

    - Sinus bradycardia: < 60 bpm, from parasympathetic activity (eg. vasovagal/baroreceptor reflexes, drugs, sleep)
- Abnormal Site of Impulse Initiation — failure of SA node to generate impulses
    - Atrial dysrhythmias (eg. atrial fibrillation AF) usually well-tolerated unless ventricular response affected
        - Also AF (quivering atria) leading to blood stagnates leading to clots
    - If frequent PVCs -> decrease in cardiac output: diagnose and manage asap!
    - Ventricular fibrillation: rapid, uncoordinated quivering -> no effective contraction -> death? within minutes
    - Rx: CPR + electrical current to chest — synchronized to ECG (_____) / unsynchronized (_____)
- Conduction Path disturbances — referred to as AV blocks
    - First degree AV block — prolonged PR internal (>.2 sec) no Rx needed
    - Second degree AV block — some non-conducted P-waves: no ___ waves; may progress to 3rd degree AV block
    - Third degree (_____) AV block — no apparent association between atrial and ventricular conduction
    - Bizarre-looking QRS
    - Serious: dec. ventricular rate/cardiac output
- TREATMENT:
    - Rx if serious symptoms produced/expected to progress
        - Worst: severe bradycardia, systole (no impulse imitation - sinus arrest), v tachycardia/fibrillation)
    - Most antidysrhythmic drugs produce dysrhythmias
    - Also use drugs that increase contractility/cardiac output, implanted pacemakers/ defibrillators, radio/surgical ablation of area generating dysrhythmia

CH. 20 SHOCK

Shock

- Life-threatening condition: insufficient delivery of blood/O2 in the microcirculation that can progress to irreversible organ damage, failure and death
- Four cause/types:
    - Cariogenic: Heart disorders -> inadequate cardiac output
    - Obstructive: Circulatory blockade disrupts cardiac output
    - Hypovelomic: loss of blood/extracellular fluids
    - Distributive: Greatly expanded vascular space because of inappropriate vasodilation leading to blood pooling in veins and relative hypovolemia (state of decreased blood volume)

Impaired Tissue Oxygenation

- Consequences:
    - Aerobic -> anaerobic respiration -> lactic acidosis -> acid/base & electrolyte imbalance, heart dysrhythmias
    - Na+/H2O leak into cell -> hydronic swelling (cellular swelling do to the accumulation of water
    - excess Ca++ causing energy production to be further impaired

- Free radicals form: damage membranes, proteins, DNS
- Even when O2 restored, reactive oxygen forms further damaging cell — repercussion injury
- Immune cells (neutrophils) recruited but sources of reactive oxygen and inflammatory cytokines: mediate vascular failure/progressive organ damage
    - Mediators are potential therapeutic targets
- Blood flow auto regulation fails: tissues get either too much/too little blood flow
    - Imbalance leads to oxygen debt in tissues

Compensatory Mechanisms

- Clinical stages: compensated -> progressive -> refractory shock as micrcirulation becomes increasingly impaired
- In an effort to restore adequate tissue perfusion:
    - Baroreceptors -> vasomotor centre -> sympathetic NS -> increase NE/E -> increase cardiac output/vascular resistance -> increase BP
    - Kidney renin-angiotensin-aldosterone system (RAAS) -> vasoconstriction/water retention -> increase blood volume
    - Brain antidiuretic hormone (ADH) also -> water retention
        - However, kidney output falling - often to zero - damages kidney tubules, causing acute renal failure
- Compensatory mechanisms work best with hypovolemic shock — initially — but less effective with cariogenic shock (of vicious cycle in heart failure) and distributive shock (decrease response to sympathetic NS)

Manifestations of Refractory Shock

- Vascular system begins to fail
- Arterioles unresponsive to catecholamines (NE/E)
- Vascular beds: constrict -> dilate
- Falling cardiac output -> severe hypotension
- Tissue damage activates clotting processes
    - Blood flow becomes sluggish
- Inflammatory mediators/vascular occlusion -> organ failure (esp. kidney, liver, lungs)
- Metabolic and respiratory acidosis with hypoexmia

Cariogenic Shock

- Etiology and Pathogenesis
    - Severe dysfunction of L and/or R ventricles leading to inadequate pumping
    - Most common cause: Mi with >40% loss L ventricle
    - Also R ventricular MI, end-stage cardiomyopathy, papillary muscle dysfunction, wall rupture, congenital heart defects
- Treatment difficult: myocardial damage irreversible
    - Increase cardiac output without increasing cardiac demands
        - Intraaortic balloon pump
        - Ventricular assist devices - sometimes temp use could lead to permanent fix

- Heart transplant

Obstructive Shock

- Etiology and pathogenesis — obstruction blocks cardiac output:
  - Pulmonary embolus - from DVTs. Sudden dyspnea. Lung scan to diagnose
  - Cardiac tamponade - fluid in pericardial sac. Trauma, pericarditis/iatrogenic
  - Pneumothorax - air in pleural space. Trauma, spontaneous rupture lung tissue
- Clinical manifestations — R heart failure: jugular vein distention peripheral edema, hepato/ splenomegaly
- Treatment — identify/ remove obstacle. Compensatory mechanisms/interventions generally successful

Hypovolemic Shock

- Etiology and pathogenesis:
  - Decrease blood volume leading to decrease venous return and CO
  - Internal loss: internal hemorrhage, bone fracture, fluid leakage into interstitial? space
  - External blood loss: external hemorrhage, burns, severe vomiting/diarrhea/diuresis (urine)
- Classification:
  - Class I: </= 15% blood loss. Compensation keeps CO/VS stable
  - Class II:15-30% blood loss. Orthostatic hypotension. HR 100-120 / RR~WNL Capillary refill t>2 sec
  - Class III: 30-40% loss. Dec. BP / HR > 120 / RR 20-30 decrease urine output. Patient anxious/confused
  - Class IV: >40% loss (2L). Large decrease in BP, HR >140, RR >30, negligible urine output. Patient lethargic
- Treatment:
  - Control source of blood/fluid loss
  - Replace fluids
  - Restore blood volume
  - Generally, drugs not indicated

Distributive - Analphylactic - Shock

- Etiology and pathogenesis
  - Allergic reaction -> increased vasculature dilation/permeability
  - 1-3% of population, Most mild/no shock
  - Rapid Rx will prevent shock, but 1% fatal (mainly PCN, nuts)
- Clinical Manifestations
  - Onset usu 2-30 min, but can take several hours
  - Anxiety, inc HR/RR, dec. BP, urticaria (hives)/angioedema, pruritus (itch) leading to bronchoconstriction (wheezing & cyanosis) and laryngeal edema (stridor & horseness)
- Treatment
  - Avoid allergen, possibly intubate airway if completely closed off, maintain normal BP
  - Bronchodilators, epinephrine (dec. reaction, increase BP), IV fluids

Distributive -Neurogenic -Shock

- Etiology and pathogenesis
    - Loss of sympathetic stimulation of blood vessels, e.g.
        - Depression of vasomotor centre in medulla
        - Interrupt sympathetic fibers from spinal cord
    - Profound peripheral dilation of arteries/veins
    - Reduced venous return to heart
    - Reduced cardiac output & BP
    - Causes: brain, spinal cord injury
    - Standing worsens and leads to syncope (fainting)
- Treatment
    - Elevate legs/ slow position change/ pressure stockings
    - Vasoconstricting drugs
    - Fluid expansion

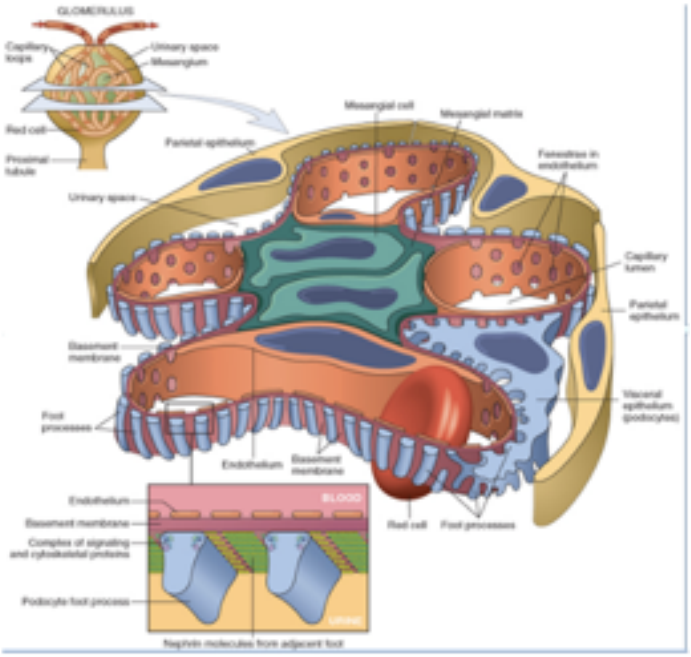
Distributive - Septic - Shock

- Etiology
    - Sepsis: bacteria [bacteremia]/other infectious organisms in blood that spread throughout body
        - Systemic inflammatory réponse syndrome
        - Abnormal vasodilation/hypotension/tissue hypoxia
- Risk Factors
    - Very young/old, chronically ill, malnourished debilitated, immunocompromised (AIDS, CA chemoRx)
    - Invasive lines/catheters/procedures, surgery
- Clinical Manifestations
    - Early: increase CO/HR, warm extremities, yet hypotensive (unique). Fever/chills. decrease consciousness
    - Late: dec cardiac output, cold extremities, profoundly dec BP, unresponsive to pressors (drugs that raise BP), decrease tissue perfusion leading to refractory shock

Complications of Shock

- Acute Respiratory Distress Syndrome (ARDS)
    - Refractory hypoexmia, dec. pulmonary functioning, pulmonary edema, atelectasis (alveolar collapse)
    - 35-65% mortality from multiple organ failure
- Disseminated Intravascular Coagulation (DIC)
    - Immune activated clotting throughout microcirculation -> ischemic tissue damage
    - Risk for serious bleeding: no clotting factors/platelets
        - IV/catheter insertions/suture lines ooze blood, hematuria, hemoptysis, intracranial hemorrhage
- Acute Renal Failure
    - Renal hypoperfusion/afferent artery construction -> acute tubular necrosis (ATN) leading dec. urine output
- Multiple Organ Dysfunction Syndrome (MODS)

Lecture 4 — Renal System



Class Outline

- The filtration system
- Glomerular filtration rate
- Renal pathophysiology
    - Renal disorders:
        - Obstructive
        - Infections
        - Glomerulopathies
        - Acute kidney injury
        - Chronic Kidney disease
        - Treatments?

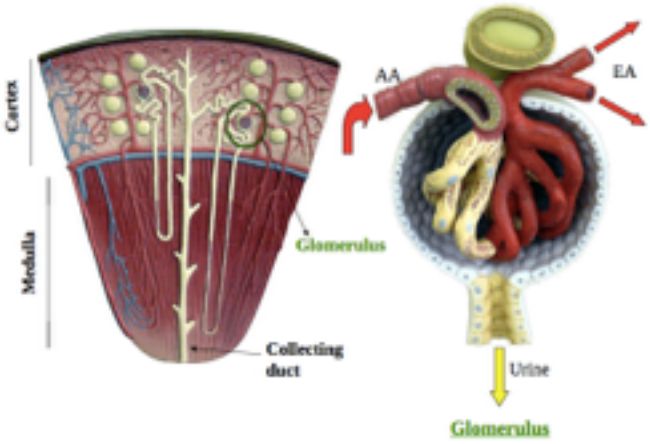
Note: Your kidneys are important.
They filter our waste and extra water from your body, help make red blood cells, and keep your bones strong. If your GFR number is low, your kidneys may not be working as well as they should. This may be a sign of kidney disase.

The Filtration System

1. Renal blood flow=1200ml/minute - blood flowing through kidney per minute.

2. 25% cardiac output goes to kidney:–1-2% goes to medulla–90%goes to cortex cortex

3. 99% - reabsorbed by nephron (180L filtered/24hrs) AND 1% (1-1.8L of urine) excreted



Filters are glomeruli

- Cortex heavily vascularized get lots of blood able to go there to be filtered, where glomeruli are
- Enters afferent arteriole going into bowman's capsule (where filtration occurs) and out the efferent arteriole.
    - Rate of filtration varies between constricting afferent arteriole slow down amount of blood coming in or sped up by opening both afferent and efferent arteriole to speed up path of blood.

Glomerulus — filtration unit of the kidney; Inside of Bowman's capsule

- Green part - mesangial cells pecial type of cell that allows blood to be filtered at a higher rate. Filtration units made up of endothelial cell that lines each of filtration. Contractile in nature and resemble smooth muscle cells

- Orange: glomerular basement membrane made up of proteins that are finger like. They cross stitch together to form mesh which is very porous. Water salt and glucose (small enough) can get through. Larger things like proteins (RBC and WBC) have difficult time getting through.
- Outer aspect of this filter (blue) cells known as podocytes - epithelial cell, atypical from ones in nephrons, these are highly differentiated that have a cell body and have long finger-like projections that come wrap around each of capillaries. Two podocytes wrap around and form interdigitation (interlocked around capillary). And this represents final layer of filtration unit. The bridge is porous and allows water molecules and glucose through but proteins are too big to get through.

Glomerular Filtration Rate

- Rate at which plasma moves through glomerular capillaries
- Units usually ml/min
- Females 85-125 ml.min, Makes 97-140 ml/min for two kidneys
    - Why difference? Because of size, on average male is larger and kidney is larger and will filter at a higher rate
- Children reach adult proportions by 2 years of age

<u>Driving Forces for GFR</u>

- Glomerular capillary hydrostatic pressure = force that is pushing water through hose and nasal is hydrostatic pressure - similar in kidney.
    - Hydrostatic capillary pressure is established by each beat of heart.
- Determinants of GFR (positive rate = forcing blood through filter)

- $GFR = K_f (P_{GC} - (P_T + COP_{GC}))$
- K_f = ultrafiltration coefficient. Includes capillary surface area and fluid permeability
- P_{GC} = glomerular capillary pressure
- P_T = tubular pressure
- COP = colloid osmotic pressure
- UFP= net filtration pressure (ultra) = $(P_{GC} - (P_T + COP_{GC}))$

•There are a number of different places where filtration occurs - adding up all surface area for where filtration can occur, this gives Kf - coefficient of filtration. When Kf drops it affects GFR in negative way

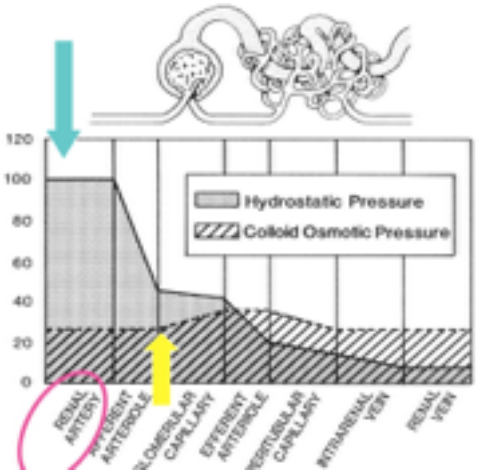
•Glomerular capillary pressure: glomerular blood pressure that provides driving force for water and solutes to be filtered out of the blood plasma. This is the hydrostatic pressure; established by beat up the heart.

•Tubular pressure: negative pressure forcing blood out of filter

- Colloid osmotic pressure — on one side of filtration barrier is protein (albumin) barrier is impermeable of albumin, also have water (on both sides) Force draw water molecules across barrier to try to dilute albumin - trying to get same concentration of both sides. Pressure is exerting in the negative direction trying to dilute proteins on other side of filter that cannot otherwise get through
- UFP = net filtration pressure - gives positive pressure going forward for blood to be filtered. Very bad if net filtration pressure is negative as no blood will be filtered.

*Net filtration forward because hydrostatic is more than tubular & colloid osmotic pressure

- As you go across from one end of filter to other end:
    - Water molecules going into urine but keeping albumin molecules and other large proteins = higher concentration of them.
    - At end of filter lose water molecules to urine and so concentration albumin (proteins) is higher and colloid osmotic pressure near end is going to be higher and hydrostatic pressure will decrease as less water is in blood and not using on walls of epithelium as it has less volume.



How is GFR Measured?

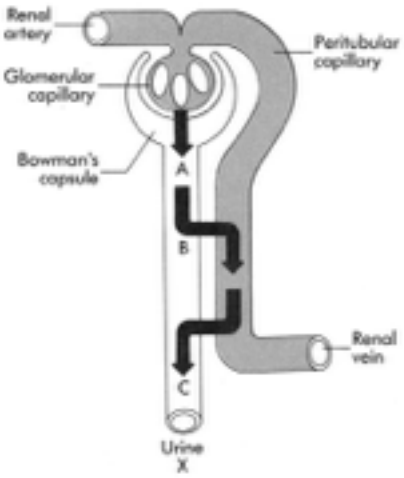
- Reminder: GFR is the volume of fluid filtered from the glomerular capillaries into Bowman's capsules per unit time.
    - Clinically, GFR is measured to determine renal function.
    - Considered most important perimeter to know how kidneys are functioning.
- Imagine: need something to track/trace that's in blood that's going to appear in the urine if kidney is working correctly…

Characteristics of Substances Used to Measure GFR

- Must be freely filtered - get through easily
- Must not be reabsorbed or secreted by nephron
- Must not be synthesized or catabolized by the kidney
- Must not alter GFR

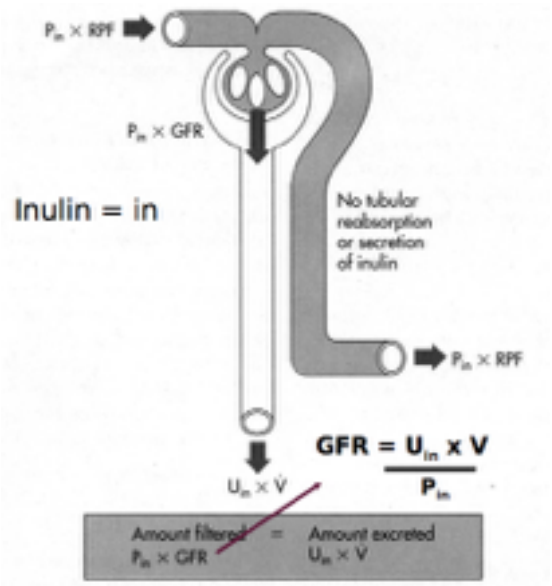
Substances Used to Measure GFR

- Inulin - gold standard molecule, none produced in our bodies (get from plants), meets all other criteria.
- Creatine - clinical standard
    - Excreted mainly by filtration; goes through many times and each time there is less and less in blood so it decreases exponentially.
    - Creatinine is produced by skeletal muscle at a constant rate from creatine-phosphate . It is secreted by muscle and filtered through kidneys like anything else and can use to find out GFR.
    - Cystatin C - used as biomarker for kidney function; protein produced by cells in the body. If kidneys working well , they keep level of Cystatin in blood just right, if there is dysfunction then the levels will be high.
- Some basic ideas and terms:
- A. Filtrate of waste, electrolytes and water filtered through glomerular capillary and travel down collecting duct
- B. Tubular reabsorption — Returns water and solutes needed by body back into ECF and circulatory system.



Amount excreted	=	Amount filtered	−	Amount reabsorbed	+	Amount secreted
X		A		B		C

- C. Secretion of unwanted substances from bloodstream into the filtrate. With B & C completed glomerular filtrate is now urine.
- Ex. Inulin
  - Enters and is freely filtered through glomeruli
  - There is no B or C step ie. no tubular reabsorption or secretion of inulin.
  - Therefore:
    - Amount filtered/(Pin) X GFR = Amount excreted/(Uin X V)
    - GFR = Uin x Volume of urine / amount of inulin in plasma



- Pin = Renal plasma inulin
- Uin = Urine inulin
- V = Volume - urine produced over a period of time (usu 24h)

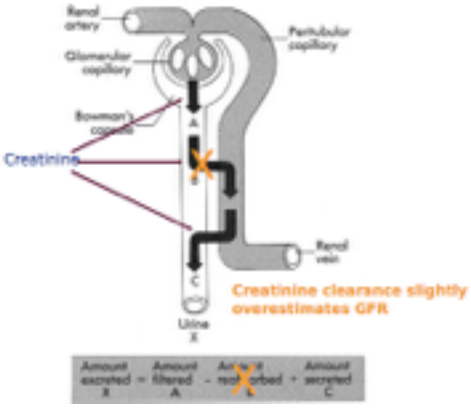
Measuring GFR - Creatinine or Inulin

- C creatinine (Clearence) = GFR
- Requires:
  - 12-24 hr urine collection (timed)
  - Mid-point blood sample
  - [Cr] in urine and plasma

$$GFR = \frac{[Cr]\ urine \times Urine\ flow\ rate}{[Cr]\ plasma}$$

Creatinine Clearance: Slightly overestimates GFR

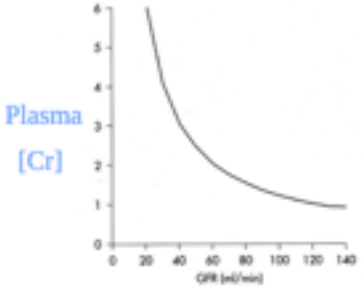
- Won't be as accurate because creatinine is secreted by proximal tubule and dumped into urine.
- So, amount secreted (C) will be higher, and this will overestimate and raise GFR
- Cin = GFR
  - Inulin is excreted at the rate at which it is filtered
- Creatinine > GFR
  - Creatinine is also secreted by proximal tubules



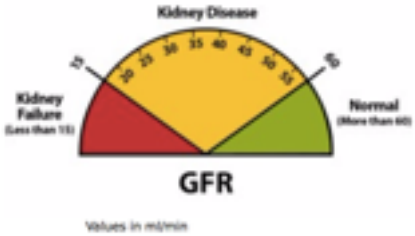
Plasma [Creatinine] reflects GFR in Steady-State Condition

- Creatinine is produced by skeletal muscle at a constant rate
- Creatinine is excreted mainly by filtration Ie. GFR X plasma [Cr]
- Renal excretion = muscle production
- Therefore, plasma [Cr} is constant under normal circumstances
- Range of normal plasma [Cr] is 50-110 umol/L (if more muscle mass then higher end of range)

Plasma [Creatinine] Reflects GFR in <u>Chronic Kidney</u>



Disease (CKD)



- If GFR decreases, then excretion < production, so plasma [Cr] increases
- New steady-state is reached, excretion = production
- Plasma [Cr] is now increased

Plasma [Creatinine] does not accurately reflect GFR in Acute Kidney Injury

- If GFR suddenly decreases eg. to zero, a new steady state will not be reached since excretion will be zero and production continues
- Plasma [Cr] continuously increases
- The increase plasma [Cr] will always underestimate the loss of GFR - lags behind

- See this on the midterm -> Plug into equation. Look out for units! Need to have units the same/ Convert umol into mmol

What equation do we use?

- Don't forget that units of urine and plasma [Cr] must be the same
- The units of urine flow rate will become the units of GFR. For these problems GFR will be in ml/min.
- Serum and plasma concentrations can be considered to be the same
- Conversion factor: 1000 umol = 1 mmol
- GFR = Ucr x V/ Pcr
- Why is there an adjustment for age, black and female?
  - Black — African Americans have higher muscle mass and therefore higher GFR for same level of creatinine.
  - Female — Lower GFR at same level of creatinine, compared to males as males have higher average muscle mass and therefore creatinine generation rate is higher.
  - Age — Younger people have higher GFR than older people at the same level of creatinine. This is due to the higher average muscle mass and therefore creatinine generation rate in younger people

Calculating GFR- Test Your Knowledge

Go to the desert	Plasma[Cr] µmol/L	Urine [Cr] mmol/L	Urine flow ml/min
Sam Extra Water	100	4.7	2.1
Joe-Shade Normal amt	105	10	1.0
Harry No water	110	25	0.42

Problem 2

Plasma[Cr] mmol/L	Urine [Cr] mmol/L	U flow ml/min
0.2	11.7	0.86

What is the GFR in this patient?

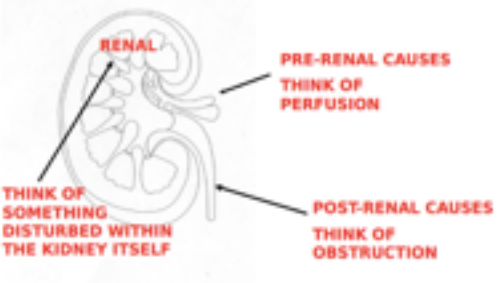
50 ml/min is this normal?

Renal Pathophysiology

Renal Failure - Some Definitions

Acute Kidney Injury (AKI): Sudden decrease in GFR to a level insufficient to maintain homeostasis

- May be caused by factors:
  - Upstream of the kidney i.e. pre-renal failure



- Intrinsic renal failure i.e. primary renal failures
- Downstream of the kidney i.e. post-renal filature

AKI

- Pre-renal failure: usually related to decreased perfusion (GI, losses, burns), Congestive Heart Failure (CHF) or low BP
- Intrinsic renal failure (vascular, glomerular, or tubular):
  - toxins getting in and damaging i.e. mercury or iron
  - construction to blood flow i.e. arterial stenosis
  - renal embolism/thrombosis causing arterial or venous blockage
  - RPGN - rapidly progressive glomeruliephritis, syndrome of the kidney that is characterized by a rapid loss of renal function
    - ANCA, alphaGBM - types of antibodies tricked into thinking it's a foreign body (antigen) and they come and attack the glomerulus
- Post-renal failure: obstruction of urine flow - e.g. prostatic enlargement, urethral obstruction (renal stone lodged in the urethra)

- Bottom line kidney requires blood in order to stay alive, ischemia of kidney (low O2) causing damage. Acute kidney injury has evaded research community to know why it happens but can't predict who will get it.
- <u>In summary</u> - Think perfusion of kidney, intrinsic (in kidney itself), post-renal some sort of obstruction that backs everything up
- When there is blockage post glomeruli the backup pressure will be higher and then the GFR will drop because back up pressure is greater than glomerular pressure.
- GFR is reduced in every nephron and depending on the extent of damage may be reversible in nature
- Depending on the damage, AKI ca lead to chronic Kidney disease
  - RIFLE criteria:
    - Risk - serum creatinine over certain amount of time
    - Injury - doubling of creatinine or urine production
    - Failure - tripling of creatinine or creatinine
    - Loss - persistent AKI or complete loss of kidney function for more than 4 weeks
    - End - stage renal disease; complete loss of kidney function for more than 3 months
- Ex. AKI:
  - Renal artery stenosis — narrowing of arteries that carry blood to one or both of the kidneys. Most often seen in older people with atherosclerosis (hardening of the arteries), renal artery stenosis can worsen over time and often leads to hypertension (high blood pressure) and kidney damage.
    - Juxtaglomerular apparatus, part of nephron - senses and regulates what the GFR and BP is. With stenosis GFR dropped and amount of Na showing up is dropped and this causes Juxta to react to lower chloride and Na will then trigger serious of events by signalling production of renin!

- Renin - enzyme secreted by juxta cells that converts angiotensinogen into angiotensin I and then undergoes further processing to make angiotensin II:
    - active form that does number of things in body. In kidney it is a vasoconstrictor and will constrict blood vessels to increase hydrostatic pressure and GFR; also causing more sodium to be reabsorbed by the tubule. Angiotensin II will usually constrict efferent tubule and try to increase [Na] in juxtaglomerular by slowing blood flow from glomeruli and allowing more time for blood to be filtered.
- Now problem - reabsorbing more sodium but angiotensin II also affects healthy kidney and it's bringing in more salt and now more water and these things go into blood and this expands ECF blood volume and causes increased BP in long run.

Penal Disorders - Post renal

<u>Kidney Stones</u>

- Stones (nephrolithiasis) - made of calcium oxalate/struvite/uric acid etc. which a re crystals that will accumulate
    - Caused by: low fluid intake and high dietary protein/sodium, oxalate, grapefruit juice (acidity)
    - Calcium oxalate is a major component
    - Treatment:
        - alkalnization of the urine (chemolysis of the stone)
        - diuretics
        - Allopurinol to lower uric acid levels
        - Removal of the stone (lithotripsy - ultrasound)

<u>Prostate enlargement (cancer of BPH - Benign Prostatic Hyperplasia)</u>

<u>Hydroneprosis</u> - water inside the kidneys; condition that typically occurs when the kidney swells due to the failure of normal drainage of urine from the kidney to the bladder

- Pinches off urinary tubule and leads to too much urine in kidney. Typically arises from VUR
- Note: Normally, urine flows from the kidneys through the ureters to the bladder. The muscles of the bladder and ureters, along with the pressure of urine in the bladder, prevent urine from flowing backward through the ureters. During development ureters will descend where bladder is developing and they need to insert at specific point in bladder and when done flap is formed in bladder and when bladder contracts flaps close and prevent back flow into ureters and it goes forward to be secreted out of body.
- Vesicourethreral reflex:
    - See this on ultrasound - two types:

    1. Primary
        - Most cases of VUR are primary and typically affect only one ureter and kidney. With primary VUR, a child is born with a ureter that did not grow long enough during the child's development in the womb. The valve formed by the ureter pressing against the bladder wall does not close properly, so urine refluxes (back-flows) from the bladder to the ureter and eventually to the kidney. This type of VUR can get better or disappear as a child gets older. As a child grows, the ureter gets longer and function of the valve improves
    2. Secondary

        - Secondary VUR occurs when a blockage in the urinary tract causes an increase in pressure and pushes urine back up into the ureters. Children with secondary VUR often have bilateral reflux. VUR caused by a physical defect typically results from an abnormal fold of tissue in the urethra that keeps uric from flowing freely out of the bladder
    - Different grades: 1-5. The more severe must be corrected with surgical approach
        - 1 - contrast appears in the non dilated ureter
        - 2 - contrast appears in the renal pelvis and calyces without dilation
        - 3 - mild to moderate dilation of the ureter, renal pelvis and calyces with minimal blunting of the famines
        - 4 - moderate ureteral tortuosity and dilation of the renal pelvis and calyces
        - 5 - Gross dilation of the ureter, renal pelvis, and calyces; loss of papillary impressions; and ureteral toruosity
- VUR can lead to CKF later in life
- Other developmental issues that can affect the kidney include:
    - Renal dysplasia— kidney consists of irregular cysts of varying sizes
    - Renal aplasia — one or both kidneys fail to develop
    - Low nephronnumber at birth ~ risk of hypertension in adults
    - Gestational diabetes or maternal diabetes = increased risk of Chronic Kidney Disease
    - Low vitamin A in diet could lead to dysplasia or aplasia

Urinary Tract Infections

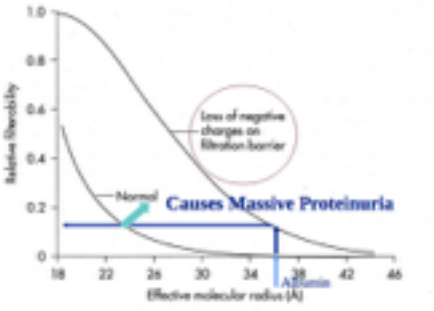
- VUR more common reasons to get these; if don;t have a lot of flow through ureters get more favourable environment for infection
- Low pH and flow rate typically discourage material growth in the urinary tract
- Risk factors:
    - More common in women
    - Reflux
    - Stones
    - Pregnancy
    - Catheters
- Typical Organisms include:
    - Gram (-) E Coli
    - Klebsiella
    - Proteus
    - Staphylococcus saprophyticus (gram +)
- Upper (pyelonephritis - febrile) vs Lower UTI (afebrile)
- Tx = antibiotics (antimicrobial prophylaxis) +/- surgery (correct VUR)

Glomerular Diseases

- Filtration barrier
- What is it and how does it become injured

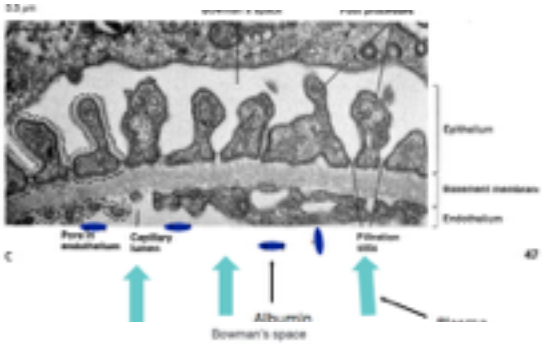
Molecular Sieving

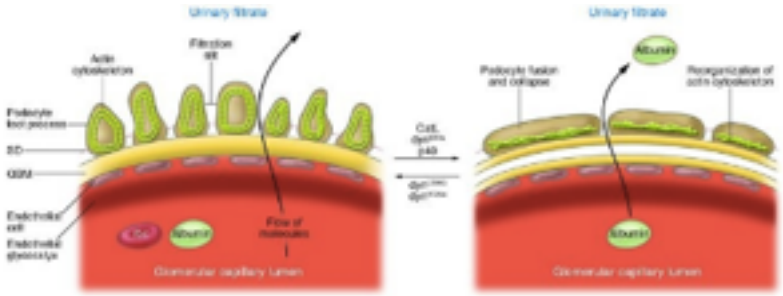
- Glomerular capillaries are molecular sieves
- Molecules > 10,000 MW are not freely filtered
- Glomerular capillary basement membrane has fixed negative charges
- Albumin is negatively charged
- Charge repulsion contributes to low albumin permeability

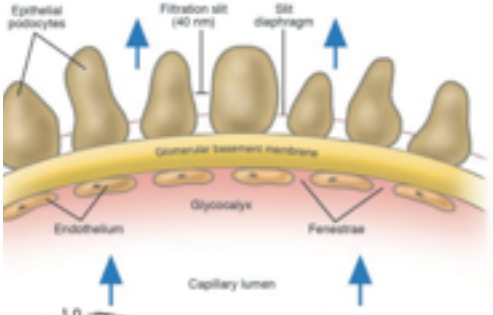


The Glomerular Filtration Barrier

- Each foot process (podocyte) sits on glomerular basement membrane
- When foot processes collapses and lie face on membrane the bridge or pore in foot processes also breaks down and this allows large pores to form and albumins

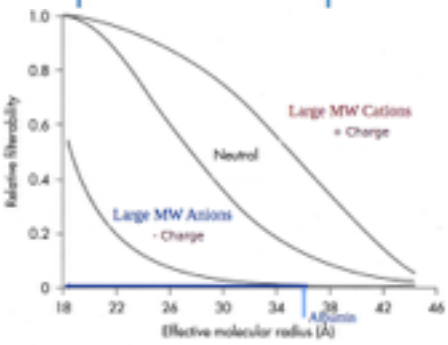






can flow through

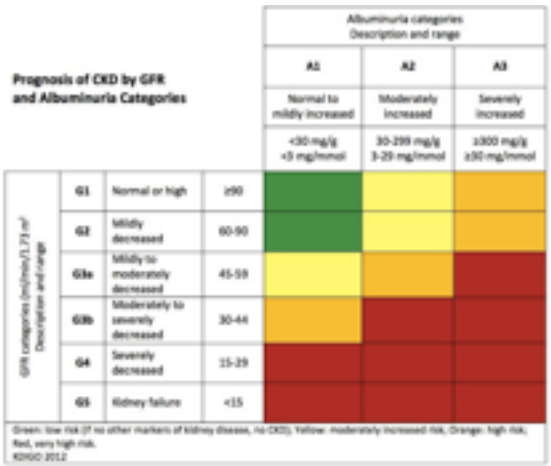
- Graph: Theoretical sense of charge and size affecting permeability. Cations more permeable than negatively charged anions and smaller molecules more permeable than large.



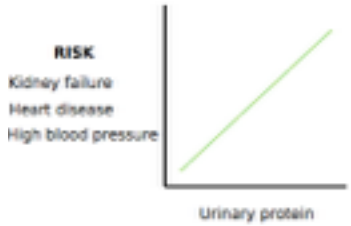
- 2nd: loss of negative charges on filtration barrier raises filterability of albumin because no repulsion from barrier — causes massive proteinuria
- Chart: Prognosis of CKD by GFR and Albuminuria
  - As GFR drops, can still have normal levels of albumin but can also have more albumin and this disrupts ratio.

Urinary Protein (proteinuria) - a risk factor

- proteinuria - presence of excess proteins (albumin) in urine
- Even in damaged glomeruli most proteins that have negative charge are still repelled but albumin is not charged and passes through



damaged filter easily



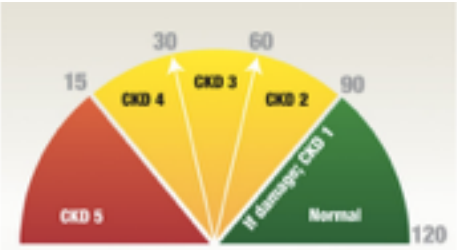
•Proteinuria & Hypertension

•Proteinuria commonly occurs in concert with hypertension in people with chronic kidney disease and is commonly the result of hypertension.

Chronic Kidney Disease

- Gradual decline in GFR that progresses over a period of years. Eventually End Stage Renal Disease (ESRD) occurs when renal function is insufficient to maintain homeostasis
- If the primary disease process causes nephron loss, one sees hyper filtration in the remaining nephrons with a continual steady reduction in the number of nephrons
- CKD may be slowed but can never be reverse

CKD Stages



Glomerulopathies - Primary & Secondary

- Primary: those disorder that affect glomerular structure/function in the absence of a multi system disorder
  - Results in: proteinuria; hematuria (allow blood cells to leak into urine); decreased GFR

Nephrotic vs Nephritic Syndromes

- Nephrotic — group of symptoms including proteinuria (more than 3.5 grams per day), low blood protein levels, high cholesterol levels, high triglyceride levels, and edema.
- Nephritic syndrome — group of disorders that cause swelling or inflammation of the internal kidney structures (specifically, the glomeruli)

Clinical Manifestation of DKD

Early in the progression of DKD, there are increased levels of protein in the urine (albuminuria) as well as an increase in the glomerular filtration rate, due to a dysregulation of afferent/efferent arteriole constriction (supplying blood to glomeruli) due to vasoactive hormones from the prostanoid/RAS systems (ANGII, PGE2, ET1)

As for renal structural abnormalities linked to DKD, the first change to be noticed is a thickening of the basement membrane (where renal epithelial cells (podocytes) adhere) and an increase in mesangial matrix deposition (from mesangial cells). As DKD progresses, glomerular lesions / scarring appear which hinder normal capillary architechture, ultimately leading to a collapsed glomerulus.
A key finding however in the last few years is the noticable decrease in podocyte number in patients with DKD.

How to deal with this epidemic?
- Prevention through education, physical activity, and better eating habits
- Treatment through: glycemic control (with diet and meds), blood pressure control with (ACEi / ARBs) and reduce proteinuria —
- Urinary protein - a risk factor
- Nephritic syndrome can be caused by: think infection or immune system (itic)
- IgA nephropathy -antiibodies come in and stick to mesengial cell

Disorders Caused by Renal Failure
1. Hyperkalemia - condition caused by abnormally high levels of potassium in the blood.
2. Edema- Generalized and Pulmonary
3. Hypertension
4. Metabolic Acidosiss
5. Uremia: Seen in AKI and End Stage CKD listed from most to least life-threatening
6. Anemia
7. Bone Disease
8. Failure to concentrate or dilute the urine

Progression of CKD
- The underlying mechanism of the remaining nephrons to adapt to nephron loss leads to further nephron loss i.e. it is a downward spiral
- concept of putting load into kidney, but decrease amount of nephrons it increases burden per nephron of remaining nephrons.
- Renin Angiotensin system - angiotensin II controls hemodynamics in glomerulus by constriction and dilation

Dilate efferent arteriole now blood will go more through to other side of capillary and this will lower glomerular hydrostatic pressure

Lecture 8 — Gastrointestinal Disorders

Digestive Processes
- Ingestion — process of taking food into digestive tract
- Propulsion (directional) — technical; move food through GI tract
  - Swallowing: initiated voluntarily
  - Peristalsis: involuntary - alternate waves of contraction & relaxation of muscles

- Mechanical Digestion — chewing, mixing with saliva (tongue), churning food in stomach, segmentation (intestines)
- Chemical Digestion — due to action of secreted enzymes; begins in mouth, completed in small intestine
- Absorption — movement of products into blood or lymph; primarily in small intestine
- Defecation — expulsion of indigestible material (feces)

Mouth + Associated Organs

- Saliva:
  - cleanses the mouth
  - dissolves food chemicals so can be tasted
  - moistens & compacts food
  - enzymes that begin digestion of starches
  - 3 pairs of extrinsic salivary glands + small intrinsic buccal glands (in cheeks)
- Control of Salivation: average output of 1000-1500 ml/day
  - stimulated primarily by PNS division of ANS (salivatory nuclei in brain stem)
  - salivation also triggered by: sight, smell, thought of food, irritation in lower GI tract (bacteria, spicy food, excess acid)
  - SNS inhibits saliva secretion

Diseases of the Oral Cavity

A. Stomatitis
  - Inflammation of one or more areas of oral mucosa
  - Can be due to microorganisms, trauma, chemo, nutritional deficiencies, occursoften in individuals with AIDS
  - Includes cold sores are caused by Herpes simplex virus (affinity for skin & nervous system); once acquired, tends to remain latent in dorsal ganglia of spinal cord & can be reactivated by stress
  - Angular stomatitis (angular cheilitis):
    - Risk factors: lack of vit. B2 (riboflavin - important in energy metabolism and to maintain mucosae) and iron-deficient anemia possibly followed by secondary opportunistic fundal or bacterial infection

B. Other Infections
  - Strawberry tongue of scarlet fever; white lesions go Candida albicans
  - Tumors uncommon, usu benign in oral mucosa, salivary glands may develop stones, infections or tumours (usu. benign)
    - Symptoms:
    - Tx:
  - Mumps: inflammation of parotid glands by myxovirus; in adult males, 25% risk that testes can be infected leading to possible infertility

Diseases of the Esophagus

A. Achalasia

- Uncommon disorder of esophageal mobility -> food stays in esophagus
  - i) dec peristalsis of esophagus
  - ii) loss of tone of GE sphincter
  - iii) dec relation of GE sphincter after swallowing
- Degeneration of esophageal ganglion cells & atrophy of smooth muscles
- Symptoms (chronic): dysphagia, vomiting, nausea, wt loss, dysphagia increased by stress, risk of pneumonia (aspiration of esophageal contents)
- Diagnosis: barium swallowing
- Tx: manage eating by small meals with lots of fluids, sleep with head elevated; also, anticholinergic drugs, Ca blockers, mechanical dilation of GE sphincter, botox

B. Gastroesophageal Reflux & Esophagitis

- GERD — Gastroesophageal reflux disease, or GERD, is a digestive disorder that affects the lower esophageal sphincter (LES), the ring of muscle between the esophagus and stomach
- Usu, P of GE sphincter & secondary persistalis prevents back flow
- Frequent/long term reflux can lead to esophagitis (inflammation of esophageal mucosa - extent of damage depends on duration/acidity of gastric contents)
- Symptoms: substernal pain; exacerbated by supine positon, pulmonary aspiration a risk; over time, damage can reach muscular
- Diagnosis: clinical manifestations, esophageal endoscopy (+biopsy); most effective tests are pH measurement in esophagus + biopsy to demonstrate inflammatory changes; barium swallow to reveal associated conditions - e.g.: distal hernia, gastric ulcers, shortened, structured &/or ulcerated esophagus
- Tx: antacids, elevation of head, weight reduction, PPIs, H2-blocker

<u>Regulation of Gastric Secretion</u>

- Neural: long (vagus nerve) & short (enteric) reflexes
- Hormonal: gastrin & histamines
- 3 types of receptors:
  - ACh — PNS; Ca++
  - Gastrin — G-cells; Ca++
  - Histamine — ECL cells; cAMP

<u>Barrett's esophagus</u>

- Serious complication of GERD
- Normal tissue lining the esophagus changes to tissue that resembles the lining of the intestine
- Symptoms similar to GERD but increased risk of developing esophageal adenocarcinoma, which is potential fatal cancer of esophagus

C. Hiatal Hernia

- Part of stomach above diaphragm

1. Sliding Hiatal Hernia: 90%; stomach slides thru esophageal hiatus when spurn or intra-abdominal P inc and slides back when standing
   - Potential causes: short esophagus, post-gastritis scarring, weakening of diaphragm muscles (P4 & pregnancy); sporadic

2. Rolling (paraesophageal) hiatal hernia: 10%; part of greater curvature of stomach protrudes through 2nd or enlarged opening in diaphragm
    - GE sphincter remains below diaphragm, so reflux uncommon; can have gastritis, ulcers in herniated region; continuous

D. Esophageal Varices
    - Protrusion of s=esophageal veins into esophageal lumen
    - A consequence of portal hypertension
    - Thing-walled veins subject to rupture leading to tremendous bleeding into G system
    - 40% mortality (even first time bleed)

E. Carcinoma of the Esophagus
    - 5-10% of GI malignancies; usu asymptomatic until unresectable
    - Are > 50, male, heavy alc intake and smoking
    - Squamous cell carcinoma in lower middle to lower 1/3 of esophagus
    - Symptoms: not much; mild dysphagia which worsens with time; weight loss
    - Diagnosis: endoscopy + biopsy; barium swallow, chest film, blood tests
    - Prognosis: poor (3-5% last past 5 yrs)

Diseases of the Stomach

- Temporary “storage tank”
- Chemical breakdown of proteins begins
- Food converted to chyme
- Digestive Processes in Stomach:
    - Just digestion of proteins - pepsin
    - Lipid-soluble drugs like aspirin, alcohol easily pass through stomach mucosa into blood; too much passage leads to gastric bleeding
    - Only stomach function essential to life — the secretion of Intrinsic factor which is required for intestinal absorption of B12 which is needed to produce RBC
- Other Influences on Stomach Acid
    1. Caffeine &nicotine increase amount & acidity of gastric secretions
    2. Alcohol increases amount of secretions
    3. Aspirin, alcohol, bile salts alter permeability of epithelial barrier
    4. Aspirin also decreases output of mucus by gastric mucosa
    5. Prolonged corticosteroids/stress increase acid/pepsinogen secretion (via histamine) and decrease blood flow to stomach wall
    6. Insulin stimulates vagus nerve- increases gastric secretions
- Emesis (Vomiting):
    - Complex reflect triggered by CNS: sequential & coordinated contraction of many muscles
    - Excessive stretching of stomach or irritants cause activation of emetic centre in medulla causing nausea, reaching (& expulsion)
    - Emetic centre -> initiates a number of motor response:

i) Skeletal muscles of abdominal wall & diaphragm contract

ii) GE sphincter relaxes

iii) Soft palate rise to close off nasal passages

- If prolonged vomiting, concerns are:

i) Dehydration

ii) Acid-base balance

- Stimuli for Emesis:
  - Drugs, toxins, preganancy, motion, alcohol, radiation, ketosis, pain, infections, psychogenic conditions, anesthesia, acute head injury, inc. intracranial pressure, brain tumours, migraine, GI tract over-distension, GI tract obstruction, vestibular disease, fever
- Gravel (dimenhydrinate) — an H1 antihistamine with some antimuscarinic properties that reduces overstimulation of vestibular and emetic centres

Alterations in Gastric Function

A. Gastritis

- Inflammation of gastric mucosa
- Can be acute or chronic; can affect fund or antrum or both

A1) Acute Gastritis:

- Erosions usu superficial
- Injury of protective mucosal barrier by drugs chemicals, helicobacter pylori
- Anti-Inflam drugs (eg: aspirin, ibuprofen, naproxen, indomethacin) -> inhibit PG release; PGs stimulate mucus secretion
- Alcohol, histamine, digitalis (5X more often in those who abuse alcohol)
- H pylori infections cause inflammation, pain, nausea, vomting
- Symptoms: vague abdominal discomfort, epigastric tenderness, bleeding
- Tx: usu spontaneous healing within days; aided by antacids, stopping problem drug, reducing acid secretion via a PPI or an H2 blocker; antibiotics if H pylori

<u>Helicobacter pylori:</u>

- Bacterium that can live & multiply in acid environment of stomach
- Embeds in mucus layer of stomach - produces urease (neutralizes acidity)
- Prince of H pylori can be shown by a breath test (urease enzyme), blood test (antibiotics) or cultures
- Infection with H pylori provokes an inflammatory reaction -> can lead to gastritis, ulcers, cancer

A2) Chronic Gastritis:

- Usu in elderly: causes thinning & degeneration of gastric wall - fundal (type A) or antral (type B)
  - Fundal: autoimmune in origin (antibodies to parietal cells, intrinsic factor, gastric cells) & there is impairment of function (production of Hal, pepsin, intrinsic factor); most rare but most severe
  - Antral: 4x more common, not associated with function losses; H pylori implicated -> persistent inflammation

- Symptoms: not indicative of disease severity; e.g. long-standing inflammation & gastric atrophy with no history of abdominal stress; H. pylori present (antral), also: anorexia, fullness, nausea, vomiting, pain, gastric bleeding
- Tx: small meals, bland diet, avoid alcohol/aspriin; antibiotics (for H.pylori)

Mrs. EA, age 48, has had difficulty swallowing for many years. She says that it often feels as though the food were stuck partway down her throat. For a while the situation was improved by including more soups in her meals, rather than solid food, but now the problem seems to be getting worse again. She has begin to lose weight because she finds she doesn't enjoy eating anymore.

Hypothesis?

Achalasia – reduced esophageal peristalsis combined with reduced ability of gastroesophageal sphincter to relax in response to swallowing

Diagnostic Tests?

Barium swallow and endoscopy

Treatment?

anticholinergics (atropine), calcium-channel blockers (nifedipine), balloon dilation, sleep with head elevated, botox

Mr. CE is a 73 year old alcoholic who has progressive difficulty in swallowing over the past several months. It began with difficulty in swallowing meat and bread, but in the past several days, he has also had difficulty swallowing liquids. He has lost 30 lbs over the past 3 months.

Hypothesis?

esophageal cancer; age + alcohol

Diagnostic Tests?

endoscopy, biopsy

Treatment?

surgery, chemotherapy, radiation

B. Peptic
Ulcer Disease (esophagus, stomach, duodenum)

- Lower esophagus, stomach, duodenum; can be acute or chronic, superficial (erosions) or deep (causin hemorrhage, even perforation)
- Peptic activity + individual susceptibility (mucus barrier weakened):
  - i) Failure to regenerate epithelium quickly enough
  - ii) Dec in quantity & quality of mucus
  - iii) Poor local mucosal blood flow (e.g. occlusion of blood vessels)
- MC site is pyloric region of duodenum (80%); risk factors include, H. pylori infection, habitual use of NSAIDS or alcohol

B1) Duodenal Ulcers:

- Tend to develop in younger ppl & ppl with type O blood (genetic link - eg: hyper secretion of pepsinogen = autosomal dominant)
- Role of chronic stress under study - is there an ulcer personality?
- H pylori infection major cause (almost 100% association, but presence of H pylori not enough); also hyper secretion of acid/pepsin and inadequate secretion of bicarbonate:
  - i) Excess parietal cells in gastric mucosa
  - ii) Prolonged high serum gastrin (can be caused by H pylori - result???)

iii) Failure of acid negative feedback on gastrin secretion

iv) Too rapid gastric emptying

v) H pylori and secretion of inflammatory/ulcerative toxins

vi) Use of NSAIDs

vii) Cigarette smoke-stimulated secretin of acid

- Symptoms: chroni, intermittent epigastric pain (30min-2h after eating); pain relieve by food/antacids; with some (esp. elderly) no pain & first sign is hemmorhage r perforation -> risk of peritonitis
- Evaluation: want to differentiate from gastric ulcers/carcinoma with barium x-ray films for anatomical deformity at beginning of duodenum; flexible endoscopy, gastric biopsy to detect H pylori
- Tx: antacids (pH, activate pepsin, relieve pain), PPIs or H2 blockers, antibiotics, ulcer coating agents (sucrafate, colloidal bismuth) for healing, anticholinergics to decrease gastric secretion, suppress gastric motility, slow emptying

B2) Gastric Ulcers (see flow chart):

- Typical ages 55-65; ~1/4 as common as duodenal ulcers
- Primary defect is abnormality that increases mucosal barrier's permeability; gastric secretion can be normal or even less than normal
- Usu associated with gastric atrophy; secretions are mostly water with a little mucus; intrinsic factor may be lacking
- association with H pylori & gastritis; bleeding possible if sufficiently deep
- Gastric ulcers frequently transform into malignant tutors
- SymptomsL: similar pattern of cyclical pain, food, relief as with duodenal ulcers, but pain may occur right after eating; other difference is that gastric ulcers tend to be chronic rather than periods of remission/exacerbation - cause more anorexia, vomiting, weight loss than duodenal ulcers
- Evaluation & Tx: as for duodenal ulcers

C. Gastric Carcinoma

- 90-95% of stomach malignancies are carcinoma frequency declining in US since 1930s (decreased consumption of smoked foods?)
- Usu ages 60-65; (less than 15% service past 5 years)
- Risk Factors: diet (nitrates -> nitrites -> nitrosamine =carcinogen); genetics (family hisotry, blood type A)
- Begin as lesions in mucosa/submucosa - can spread to regional lymph nodes
- Distant metastases (liver, lungs, ovaries, peritoneum) often when diagnosed
- Symptoms: Vague, nonspecific, early satiety loss of appetite, weight loss, abdominal pain, vomiting, bleeding
- Only definitive diagnosis is gastric biopsy

<u>Summary: H. pylori & the GI Tract</u>

- currently 35-40% Canadian population infected (family clustering – eg: study in TO; incidence considerably higher in aboriginal populations and, globally, in developing nations – possibly linked to transmission via contaminated water
- Frequency of infection increases 8% for each 10 yr of life

- Mode of transmission not 100% clear; bacterium doesn't do well outside of acidic gastric environment
- Effects of H. pylori:

    i) Linked with gastritis; increased risk of ulcers and cancer

    ii) Provokes inflammatory response - but symptoms with initial infection can be mild; damage results due to an inability to eradicate the bacterium but continuing inflammatory response damages mucosal cells

    iii) Mucus barrier compromised

    iv) Antibiotics needed to cure the infection — often a long course needed with multiple antibiotics

The Liver & Gallbladder

- Digestive function of the liver is to produce blue for export to duodenum
- Bile is a fat emulsifier; renders fats more accessible to pancreatic lipase
- Digestion not occurring: bile stored & concentrated in gallbladder

A. Gallstones
    - Inadequate bile salts or excessive intake of cholesterol -> crystallizes to form biliary calculi or gallstones
    - Obstruct flow of bile from gallbladder; pain occurs when gallbladder congrats
    - Obstructive jaundice: yellow bile pigments to blood then to skin
    - Tx: dissolution with drugs, pulverize by US, vaporize lasers, surgical removal of gallbladder (bile duct enlarges for storage)

B. Cirrhosis of the Liver
    - Chronic liver injury -> extensive fibrosis & regenerative nodules
    - Ends in liver failure = 9th leading cause of death in US (45% - alcohol abuse)
    - Progression to cirrhosis not totally understood; with alcohol, known to cause:

        i) Alteration if metabolic pathways (alcohol becomes primary metabolic fuel)

        ii) Direct effects in cellular & organelle membranes & mitochondria function

        iii) Generation of reactive oxygen species

        iv) Often concurrent with malnutrition, which exacerbates problem

- Fibrosis due to increased production of ECM components (can get 6X normal deposition of collagen) -> bands of scar tissue

The Pancreas

- Produces a range of enzymes delivered to duodenum to digest all types of nutrients
- Exocrine function associated with acini = groups of secretary cells grounded around ducts
- Cystic Fibrosis and the Exocrine Pancreas:
    - Changes begin during fetal development and are often severe enough by birth to prevent exocrine secretions from reaching duodenum
    - Defective gene for CFTR (cystic fibrosis transmembrane conductance regulator; chromosome #7) - a chloride channel

- Accumulation of mucus - get blockage of collecting ducts -> fibrosis and degeneration of secretory tissue -> absence of pancreatic enzymes in duodenum -> incomplete digestion -> malabsorption & nutritional deficiencies

The Small Intestine

- Intolerance of lactose (NOT a disease):
  - Deficient lactase enzyme (produced by cells that line small intestine ; enemy digests sugar molecule lactose into simpler molecules glucose and galactose.)
  - Lactose creates osmotic gradients leading to diarrhea (all water absorbed my small intestine to try to dilute indigestible lactose)
  - Bacterial metabolism of lactose leads to gas and bloating
  - Solution: Lactase enzymes drops or pills before ingesting dairy products
  - In most human populations, the manufacture of the lactase enzyme is “turned off” by around 4 years of age

Alterations in the Small Intestine

A. Diarrhea
  - Large volume diarrhea can be osmotic, secretory, mixed (motility):

    i) Osmotic: non-absorbable substance (eg. lactose in lactase deficiency) in intestine draws water into lumen by osmosis

    ii) Secretory: due to excessive secretion of fluid & electrolytes into intestinal lumen or inhibition of Na/Cl absorption — primary causes are: bacterial endotoxins (eg. cholera toxin) & neoplasms (produce hormones that stimulate secretions

    iii) Mixed (motility): for some reason, rate of transit thru intestine increased so that not enough time for water reabsorption
  - Small volume diarrhea (exudative): inflammatory disorders of intestine (ulcerative coltis, Chron’s disease)
  - Evaluation& Tx:
    - Determine cause — travel, drug therapy, still culture, examination of still specimens for blood, abdominal x-ray, intestinal biopsy
    - Tx includes restoration of fluids & electrolytes ; management of symptoms & treatment of causal factor

B. Malabsorption
  - Can be due to:

    i) Problems with digestion so that nutrients can be absorbed - eg: changes in pancreatic enzymes & secretion, in billiard secretions

    ii) Difficulty with absorption through intestinal wall — can be a single substance (eg: vitamin B12) or many nutrient groups
  - Generalized malabsorption leads to weight loss and malnutrition

C. Gluten-Sensitive Enteropathy (Celiac Disease)
  - Loss of villous epithelium due to ingestion of gluten, protein found in cereal grains - toxic to intestinal epithelium of genetically susceptible individuals
  - Occurs more often in women than men; onset in round adulthood
  - Gluten proteins have antigenic properties and intolerance relates to activation of the immune system (antigladin antibodies)

- Pathological changes:
  - Villi flattened or absent
  - Epithelium disorganized & cuboidal rather than columnar
  - Brush border thickened & infiltrated with inflammatory cells… ALL leading to malabsorption of almost everything
- Clinical signs: frequency, foul-smelling stools containing fats, weight loss, malabsorption of fat-soluble vitamins; muscle wasting; hypoproteinemia, failure to thrive
- Diagnosis: blood work to look for antibodies (e.g. anti-tissue transglutaminase - involved in destruction of villous ECM); definitive diagnosis is an intestinal biopsy
- Tx: Remove barley, wheat, rye from diet (rice and oats are OK); ;actose intolerance also presumed; tolerance of lactose restored with epithelium repair

D. Chron's Disease (Inflammatory Bowel Disease #1)

- Idiopathic, chronic, inflammatory bowel disease —any segment of GI tract
- Incidence equal between men & women; exhibits familial predisposition
- Onset between 15 & 20 years; secondary peak between 55 & 60 yrs
- Chron disease & ulcerative colitis are similar; grouped as inflammatory bowel disease - origins can be infectious, auto-immune, psychosomatic, dietary, hormonal, unknown; genetics also involved
- Clinical signs: "irritable bowel" for several years: diarrhea; can have tenderness in lower right side (inflamed ileum); malabsorption of vitamin B12 (if ileum involved); with time, weight loss, blood in feces, nausea & vomiting; intestinal obstruction/rupture of fistulas possible; increased risk of intestinal adenocarcinoma; correlated with several autoimmune diseases
- Skip lesions — damage to mucosa and deeper; cobblestone appearance; bowel wall becomes congested, thickened & rigid
- Evaluation & Tx: medical history 7 clinical signs; radiography shows narrowing
- Treatment: suppress immune response (e.g. corticosteroids, but most recently using methotrexate, even anti-TNF alpha {[TNF = tutor necrosis factor] with some patients); surgery to manage complications (eg: structures, abscesses, relieve obstruction)

Large Intestine

Bacterial Flora of Large Intestine

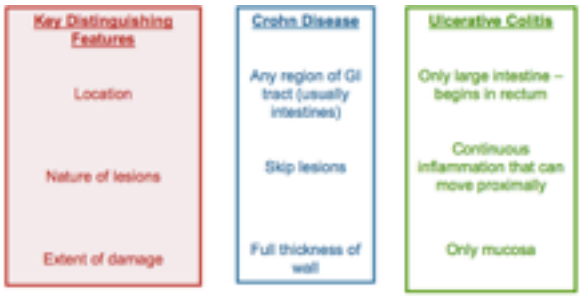
- Ferment indigestible carbohydrates; release acids & gases (~500 ml/day)
- Synthesize B complex vitamins & vitamin K
- There are more bacteria busily living in 1cm of the lower colon that there have been people in the world
- 99% of your DNA genes are in microbe cells not human cells
- Diarrhea: already discussed
- Constipation: too much water absorbed - stool difficult to pass; lack of finer, don't heed need to defecate, lack of exercise, emotional upset laxative abuse
- Diverticulitis: When pushes form in the wall of the colon, if these pushes get inflamed or infected called diverticulitis. Possible consequence of lack of dietary fibre. Why?

Alterations in the Large Intestine

A. Intestinal Obstruction
   - Blockage of lumen of bowel by mechanical obstruction
   - Blockage -> gas is primary bowel distended proximal to blockage -> gastric, biliary, pancreatic secretions accumulate, plasma volume decreases
   - Bowel wall edema also decreases blood supply to tissues
   - Risk of necrosis, perforation, peritonitis; also sepsis
   - Clinical signs: acute, severe cramping pain, vomiting, diarrhea (if obstruction not complete), risk of hypovolemic shock, septic shock

B. Haemorrhoids
   - dilatations of venous plexus surrounding rectal/anal areas; very common; often related to other abnormalities such as varicose veins
   - precipitating factors: constipation, pregnancy
   - can be painful, irritating, bleeding during defecation; blood loss usually insignificant

C. Ulcerative Colitis Inflammatory bowel disease #2)
   - Chronic inflammatory disease of colon; jus recut or extending into colon
   - Disease appears in susceptible individuals between 20 & 40 years
   - Risk factors: family history, Jewish descent, more prevalent among whites
   - Bowel fills with bloody, mucoid secretion -> crampls, rectal urgency, diarrhea
   - Clinical signs: depend on severity/extent of disease - periods of exacerbation & remission; increased frequency of bowel movements, bleeding, pain - if severe, fever & other symptoms intensified



Both Crohn disease and ulcerative colitis are classified as chronic inflammatory bowel diseases and are associated with increased risk of colorectal cancer (most extensively studied: ulcerative colitis)

   - Diagnosis: medical history, sigmoidoscopy, barium x-ray (loss of haustra), ulceration, irregular mucosa; rule out infectious agents by stool culture
   - Treatment: suppress inflammation, antibiotics if needed, IV fluids/nutrients if disease severe; surgery is disease unresponsive

D. Irritable Bowel
   - A common complaint accompanied by abdominal pain and problems with constipation or diarrhea or one followed by other (affects colon); also can have a bloated feeling, abdominal pain or cramping
   - Affects 7-20% of the population; more common in females and can accompany depression and/or anxiety
   - It is important to distinguish between colitis and irritable bowel:
     - Irritable bowel doesn't damage the intestinal wall
     - irritable bowel is not linked to an increased risk of colorectal cancer
   - Possible triggers that alter intestinal motility:
     - Intestinal infection or overgrowth of intestinal bacteria

- Food allergy (eg. chocolate, fats, fruits, beans, cabbage, cauliflower, broccoli, milk, carbonated beverages, alcohol)
- Stress can aggravate symptoms
- Hormones (esp. females toward end of luteal phase of cycle — two times more common in females)
- Still poorly understood and cannot be cured; but the severity of the symptom can be managed by recognizing and avoiding triggers and managing severity of symptoms

E. Appendicitis

- Inflammation of vermiform appendix; most common surgical emergency of abdomen; affects 7-12% of population (usu. 20-30 yrs of age)
- Pathology: obstruction: appendix can't drain leading to inc pressure and decreases blood flow -> hypoxia, ulceration, more inflammation, perforation
- Clinical signs: pain (lower right quadrant), nausea, vomiting, low-grade fever
- Evaluation & Tx: rebound tenderness, inc. WBC count leading to appendectomy

F. Cancer of the Colon & Rectum

- 10-15% cancer deaths; onset usu after 50
- Genetic link, but risk increased by diet (high fat, low finer, low calcium(- anything that increases contact time between fecal mass & colon mucosa
- Polyps associated with increased risk: most polyps benign but once traverse muscular mucosal, become malignant & highly invasive
- Most cancers are adenocarcinomas - long pre-invasive phase & grow slowly
- Diagnosis & Tx: family history of polyps, screen by colonoscopy & remove; DIET (fiber, calcium low fat); prep testing to detect liver enlargement, ascites, lymph nodes, barium enema, always surgery; radiation, chemotherapy

Stage A	Stage B1	Stage B2	Stage C1	Stage C2	Stage D
confined to mucosa	muscularis but not to serosa	to serosa, not lymph nodes	B1 to regional lymph nodes	B2 to regional lymph nodes	metastases extends to distant sites

Laxatives

- 3 kinds:

1. Bulk forming laxatives that act like finer to move more water into the intestines
2. Stimulant laxatives that speed up mobility
3. Osmotic laxatives that hold more water in the intestines

Lecture 8 — Diabetes

History of Diabetes: Milestones

Case history: Type 1 Diabetes (IDDM)

Type 1 diabetes

•Pts need insulin replacement to live (no C-peptide)

•Prevalence ~0.5%; geographical distribution

•Incidence in Canada: 20/100,000 / yr; increasing by 3-4%/yr

•Acute presentation:

•hyperglycemia, tiredness, weight loss, polyuria, thirst,

polydipsia

- nausea and vomiting signal impending ketoacidosis

- Honeymoon period: temporary remission in some
- Complication over time (major problem = mortality increased 4-7x)
  - Microvascular: nephropathy, neuropathy, retinopathy (major cause blindness)
  - Macro-vascular: CHD

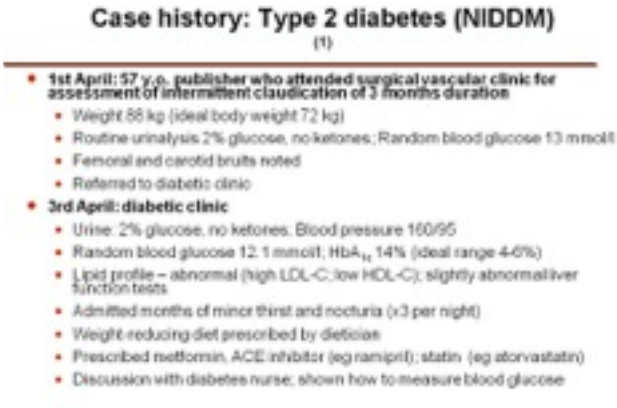
Case history: Type 2 Diabetes (NIDDM)

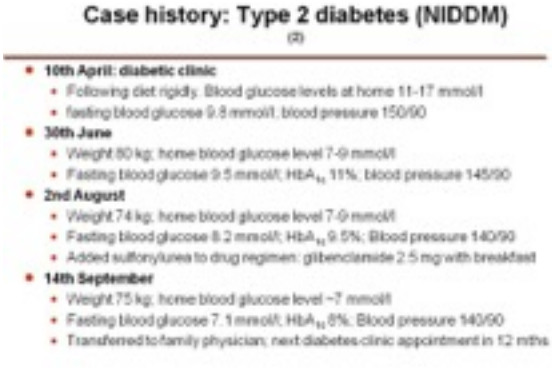
- Note: intermittent claudication = calf pain while walking

Non-insulin dependent diabetes mellitus

- Its survive without (therapeutic) insulin, although this may improve control (C-peptide present)

- Represents at least 90% of diabetic population
- Its mostly older and obese (although increasingly in children)

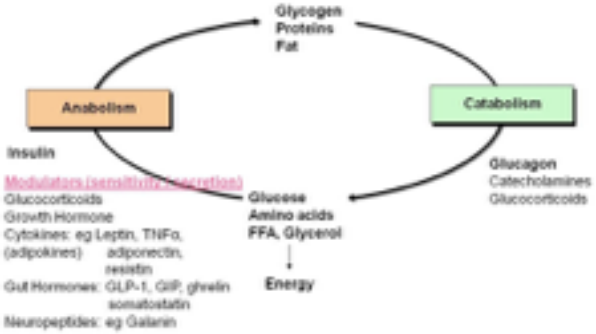




•Insidious onset of tiredness, thirst, polyuria, nocturne

- Cause: impaired insulin secretion and tissue insensitivity to insulin; strong genetic predisposition
- High risk of atherosclerosis; commonly associated hypertension, hyperlipidemia and obesity may contribute (metabolic syndrome X); myocardial infarction also more common
- Microvascular complications less common than in Type I
- Mortality increased 2-3x; life expectancy reduced by5-10yrs

Glucose Homeostasis



- When increase in blood glucose level after eating: high level in blood stimulates increased secretion of insulin from pancreas B cells, which causes a decrease in glucose production and an increase in glucose uptake from peripheral tissues — overall leading to a decrease in blood glucose levels
- When there is a decrease in blood glucose levels between meals: low level in blood stimulates secretion of glucagon from pancreatic alpha cells. This causes an increase in glycogenesolysis and gluconeogenesis leasing to an overall increase in blood glucose levels
- Note:
  - glycogenesolysis — breakdown of glycogen into glucose
  - gluconeogeneis — generation of glucose from non-carbohydrate carbon substances

Insulin Action: General

- Note: Modulators balance level of anabolism and catabolism of glucose and glycogen. —>

Pancreas: Anatomy

- Retroperitoneal gland: 80% exocrine; embedded endocrine islets (2 million)

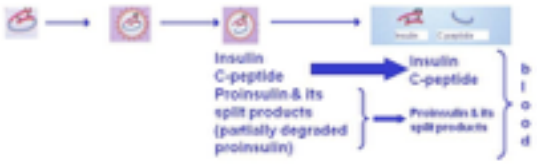
- Upper portion of posterior abdominal wall
- Head and neck in the C-shaped curve of the duodenum (1st-3rd parts)
- Body behind the stomach and tail touches spleen
- Venous drainage of pancreas is into the portal vein

Structure of a Pancreatic Islet

- B-cell core: secrete insulin into blood vessels which then perfuse the outer islet
- Cortex of other cells in which A-cells predominate: these secrete glucagon
- D-cells secrete somatostatin and PP cells, pancreatic polypeptide
- Insulin inhibits glucagon
- Somatostatin inhibits insulin and glucagon
- Islets are richly innervated

Insulin Secretion in the Beta Cell (non-diabetic)

1. Rough ER — mRNA transcription for prepro- to proinsulin insulin
2. Golgi apparatus — Secretory Granule Formation
3. Secretory Granule — Prohormone convertases/ carboxypeptidase = cleavage of proinsulin
4. Secretory granule / cell membrane / circulation
    - Glucose metabolism
    - Inc ATP/ADP
    - K pump inhibition
    - Ca++ channel opens
    - Sec. granule-membrane fusion



Primary Structure of Insulin

- A chain: 21 a.a.
- B chain: 30 a.a.
- The chains are linked by two disulfide bridges
- Human, pork and beef insulin are very similar
- Nevertheless, antibodies to foreign insulin can modify kinetics

The Insulin Hexamer

- In dilute solution: insulin exists as a single molecule (ie. a monomer)
- In concentrated solution and crystals: 6 insulin molecules and 2 zinc ions form a hexameter
- This is a compact storage form designed for the storage granules. Also in concentrated solutions for injection: delays absorption from s/c injection sites

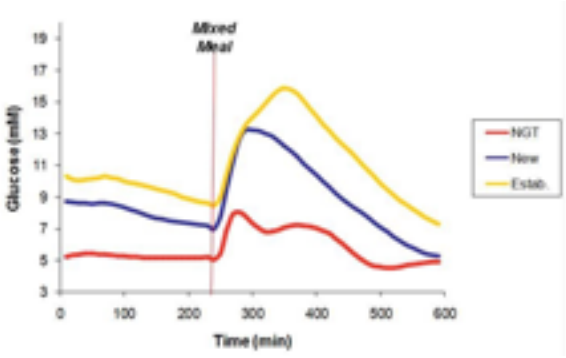
Glucose and Insulin Release

- Glucose is the primary stimulus for insulin secretion
- Under normal circumstances the secretion occurs in 2 phases
- In type 2 diabetes, even though a lot of insulin secretion occurs the first phase is lost
- This has a major detrimental effect on insulin action

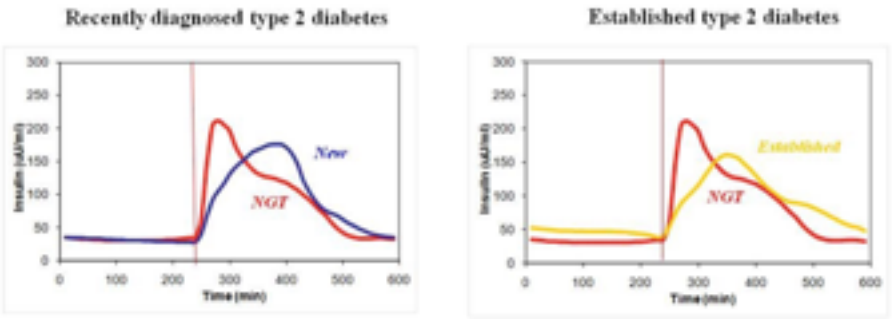
Determinants of (Oral) Glucose Tolerance

Plasma Glucose Concentrations

- Dependent on insulin resistance and insulin secretion



•NGT (red): normal glucose tolerance
•New(blue): newly diagnosed type 2 diabetes;
•Established(yellow): longstanding diabetes



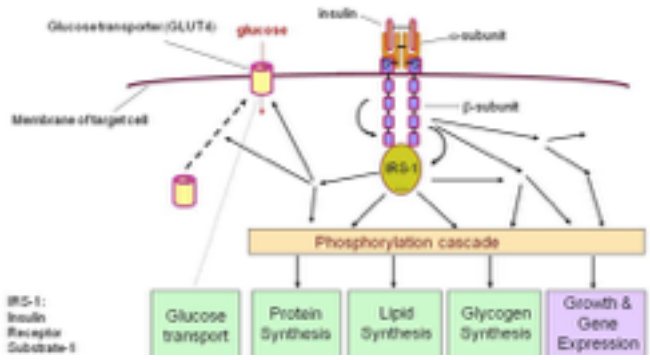
• New - slower (more time) to reach peak glucose level and decreases more rapidly

•Established: Takes less time to reach peak glucose level and decreases more gradually (insulin getting less compatible with peripheral tissues)

Factors which (acutely) Regulate Insulin Secretion

- Nutrients and metabolites:
  - Glucose and sugars increase
  - Free fatty acids increase
  - Ketone bodies increase
  - A.a. increase
- Islet hormones/peptides
  - Insulin decrease
  - Glucagon increase
  - Somatostatin decrease
- Entroinsular hormones
  - Glucagon-like peptide 1 (GLP-1) increase
  - Gastric inhibitory polypeptide (GIP) increase
- Other hormones — e.g. adrenaline decrease
- Autonomic nn: sympathetic decrease — Noradrenaline (NA)
- Autonomic nn: PNS increase — acetylcholine (ACh)

Insulin Action: Signal Transduction



Insulin Receptor Internalization

•Insulin binds to receptor

- Insulin-receptor complex enters cell
- Receptors are recycled to the cell surface
- Insulin is largely degraded in lysosomes and its action stopped
- High insulin levels (eg. obesity) may “down-refulate) the number of receptors, and therefore the insulin signal

Insulin Regulation of Glucose Transport

- The glucose transporter (GLUT-4) is normally located inside the cell, in the cytoplasm
- Insulin and exercise both (independently) cause the movement of the transporters to cell surface, where they move glucose into the cell
- This is part of the reason why exercise has always been used in diabetes treatment and prevention

Insulin Regulation of CHO Metabolism

- CHO = carbohydrate
- In CNS:
  - Non-insulin-dependent glucose uptake into CNS through GLUT 1 then glucose split into ATP and Co2 and H2O.

- In Adipose Tissue (Ins = insulin)
  - Non-insulin dependent glucose uptake into fat tissue - though GLUT 1
  - Insulin-dependent glucose uptake into fat tissue - through GLUT 4 (requires insulin)
    - Once in Adipose tissue: Insulin required to breakdown glucose in FFA; Glycerol and Pyruvate/lactate and CO2 and H2O
    - Pyruvate/lactate + CO2 + H2O can be made into Glycerol
    - Glycerol and FFA further broken down by insulin into triglycerides

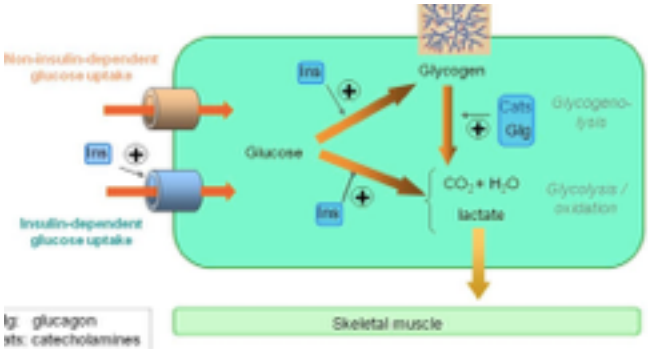
Regulation of CHO Metabolism: Adipose Tissue

- Insulin stimulates:
  - Glucose uptake (transport) into adipocytes

    - Glycolysis and glucose conversion to glycerol
    - The incorporation of glucose carbon into fatty acids
    - Lipogenesis via increases in several lipogenic enzymes
- Glucose is the major source of the glycerol backbone of the triglyceride molecule and therefore a critical factors in the insulin-stimulated increase in fat synthesis (either conversion to glycerol directly via glyceroneogenesis)
- Some drugs (thiazolidinediones) work partly by increasing glucose uptake by adipocytes (and therefore decreasing uptake by other tissues where it is harmful, e.g. muscle)

Insulin Regulation of CHO Metabolism

- In Skeletal Muscle (Glg: glucagon; and Cats: catecholamines)
    - Non-insulin-dependent glucose uptake - doesn't require insulin though GLUT-1
    - Insulin-Decedent glucose uptake - via insulin through GLUT-4
        - Once glucose in cell insulin stimulates breakdown to either:
            - CO2 +H2O & lactate (via glycolysis - more direct than glycogenolysis) OR
            - Glycogen
                - Stimulated by Cats and Glg to undergo glycogenolysis into CO2 + H2O and lactate



Insulin Regulation of CHO Metabolism: Muscle

- Increases in insulin levels cause:
    - "Translocation" of glucose transporters to cell surface: this appears to be the main effect
    - Increased net synthesis of glycogen (storage form of glucose)
        - Muscle glycogen is major site of postprandial glucose disposal
        - Changes (mutations) in the enzyme (glycogen synthatse) have been suspected as a potential cause of Type 2 diabetes
        - Note: postprandial is after a meal
    - Increased glycolysis (lactate formation) and glucose oxidation
- Increases in Catecholamines cause:
    - Glycogen breakdown and the increased availability of the glucose units for energy, eg. in exercise

Regulation of CHO Metabolism: Liver

- Note: Glg = glucagon and cort = corticosteroids
- Non-insulin-dependent glucose transfer into liver; no insulin required; enters via GLUT-2 transporter
- Blood-Glucose levels high: Glucose the influence by insulin to:
    - Glycogenesis — form glycogen to be stored
    - Glycolysis — Glucose form lactate and CO2 as waste products to exit liver
- Blood-Glucose levels low: Glucagon (Glg) stimulates:

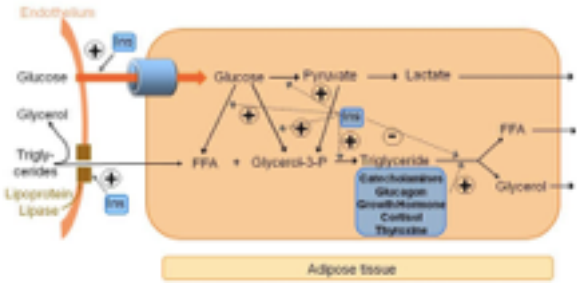
- Glycogenolysis — breakdown of glycogen to form glucose stimulated by glucagon and corticosteroids. Glucose exits liver cells via GLUT-2
- Gluconeogenesis — formation of glucose from non-carbohydrate carbons like glycerol, lactate and a.a. They enter liver cells via stimulating from glucagon and gluconeogenesis is further stimulated by Glg, Cats, and Cort.
  - Note: Insulin inhibits gluconeogenesis when present.

Regulation of CHO Metabolism: Liver

- Glycogen:
  - is the storage form of glucose, consists of a large number of glucose molecules in a branched structure
  - It is primarily formed after meals from absorbed glucose and primarily broken down during fasting
  - Insulin stimulates its formation and inhibits its breakdown to glucose
  - Glucagon and catecholamines stimulate glycogen breakdown and overall glucose production by the liver
- Gluconeogenesis:
  - The process by which circulating glucose is made from non-glucose molecules (substrates):
    - Lactate which is formed mainly from incomplete metabolism of glucose and glycogen (Cori cycle - also called lactic acid cycle)
    - A.a. arise from the breakdown of ingested and endogenous protein
    - Glycerol, from fat breakdown, also contributes but is quantitatively less important (except when lipolysis is stimulated)
  - Is stimulated acutely by catecholamines, glucagon, and more chronically, cortisol
  - Is inhibited by insulin
  - Also in the kidney- which becomes important in starvation

Insulin Regulation of Fat Metabolism: Adipose Tissue (1)

- Insulin stimulates:
  - The hydrolysis of circulating triglyceride-containing lipoproteins (VLDL from liver and chylomicrons from the gut) by lipoprotein lipase at capillary endothelial surface
  - Glucose uptake and conversion to glycerol
  - Incorporation of glucose carbon into fatty acids
  - Lipogenesis (increase in enzyme activities



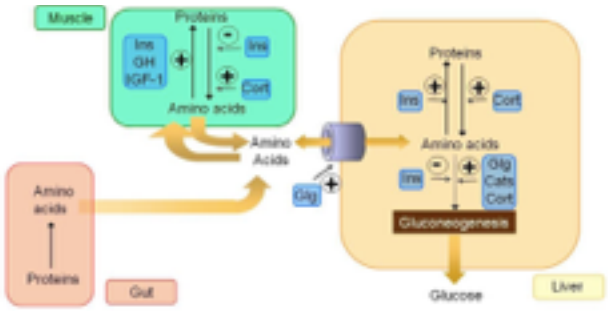
- Insulin inhibits:
  - Lipolysis (fat breakdown)
- Free fatty acids (FFA)
  - Products of lipolysis
  - Interfere with many of the actions of insulin, causing insulin resistance
- Lipolysis is stimulated by:
  - Catecholamines

- Glucagon
- Cortisol (permissive effect on hormones and thyroxine, needs to be present in great enough concentration to influence CH and thyroxine)
- Growth hormone and thyroxine (delayed - hormones are slower mechanism)

- Abdominal (visceral) fat:
  - More sensitive to lipolytic stimuli
  - May release more FFA into portal vein which could, in turn, directly impact the lover and stimulate glucose production (energy substrate competition) and thus increase circulating glucose concentrations
  - Increased abdominal fat highly correlated to insulin resistance and type 2 diabetes

Regulation of Protein Metabolism

- Circulating a.a. arise from ingested proteins and from breakdown of endogenous protein
- Different proteins turn over at different rates
  - Overall avenger is ~250-300g per day
  - It is reflected in urinary urea (elimination of nitrogen from amino acids)
  - Insulin stimulates protein formation and inhibits its breakdown. Inmuscle growth hormone and IGF-1(Insulin-like growth factor 1) also stimulate protein formation
  - Cortisol stimulates protein breakdown



Energy Metabolism: The Fed State

- G = glucose
- Inc G from GI tract (absorbed from food) causing increased G concentration in blood
- Pancreas secretes insulin into blood stream causing
- Liver, adipose and muscle tissue and neural tissue to uptake glucose

Energy Metabolism: The Fasted State

- G = glycose
- FFA = free fatty acids
- No food or glucose getting absorbed by GI tract causing decrease in blood-G concentration
- This stimulates pancreas to release glucagon
- Glucagon acts on liver and liver performs glycogenolysis and gluconeogenesis. Also acts on adipose tissue to release FFA.
- Pancreas also releases little insulin to stimulate uptake of G and FFA - given by liver and adipose tissue - by neural and muscle tissue

Energy Metabolism: Exercise

- Neural tissue stimulates release of glucagon from pancreas to be viable to breakdown glycogen from liver into a lot glucose and a lot of FFA from adipose
- To be used for energy by muscle tissue - insulin also secreted in smaller amount to allow uptake and breakdown of FFA and G mostly by muscle tissue but little by neural tissue

Type 1 Diabetes: Etiology

- Environmental factors and Genetic predisposition lead to:

    - T-cell mediated autoimmune destruction of beta cells ->
        - Insulin deficiency ->
            - Other metabolic disturbances and hyperglycaemia
- Inherited susceptibility — strongest link
    - Polymorphisms of human leucocyte antigen genes in the MHC (major histocompatibility comples)
    - 95% Type 1 diabetes carry the antigen (decreasing)
    - Other weaker links found (~60)
- Type 1 diabetes associated autoantibodies
    - Islet cell antibodies: a specific and sensitive predictive marker for the development of Type 1 diabetes
    - Antibodies to insulin: most common ins ome studies
    - Others
- Increasing prevalence
    - Could be proliferation of susceptibility genes in population since natural selection bypassed with insulin treatment
    - Environmental effects

Gene-Environment interactions

- Diabetogenic viruses
    - Infection of B-cells — cytomegalovirus (CMV)
    - Systemic infection with cross-reacting immune response — mumps, cocasckie B, measles, chickenpox, Rubella
- Dietary factors (early weaning)
    - Cow milk proteins (TRIGR) — bovine serum albumin sequence (molecular mimicry)
    - Other dietary components, eg. wheat (gluten): mainly in animal models
    - Decreased vitamin D (decreased exposure to sun)
- Micro biome — alterations to gut bacterial population and production of metabolites - may impact autoimmunity
- Epigenome — mediates dietary/bacterial effects by modifying DNA transcription (.> autoimmunity)

Pathophysiology of Energy Metabolism: Type 1 Diabetes - untreated

- KA: keto acids
- G absorbed from GI tract increased blood glucose concentration
- No insulin able to be produced
- Pancreas still produces glucagon stimulation G and KA release from liver and FFA uptake by liver (to make more LDLs and VLDLS)
- Glucagon also stimulates Adipose tissue to release more FFA.
- KA and G are absorbed by Neural tissue
- FFA and KA are absorbed by muscle tissue

Lecture 9 — Nervous System I

Approach to the Patient with Neurologic Illness

Formulate a Diagnosis

- History & physical examination -> note symptoms and signs
- Interpret in terms of physiology and anatomy
  - Anatomic diagnosis : localize disease process
  - Syndromic diagnosis: characteristic clustering of symptoms/signs
- Think flexibly: initially incorrect impression -> selectively ignoring data
- Assess other data:
  - Mode of onset/speed of evolution
  - Involvement of non-neurologic organ systems
  - Relevant past and family medical histories
  - Lab findings
- Epand formulation:
  - Pathologic diagnosis: identify the disease
  - Etiologic diagnosis: mechanism and causation of disease
  - Functional diagnosis: degree of disability, temporary/permanent, potential for restoration of function

The Neuro Exam

- Mental Status Exam — 10/15 min
  - Observe pt during history: test higher cortical functioning
  - Psychiatric aspects: mood, thought processes/content
  - Cognitive: level of consciousness, attention, understanding, language & speech, memory, visuospatial (perception of environment)
- Testing of Cranial Nerves
  - Sense of smell
  - Visual field, pupil size/reactivity, eyelid position, range of ocular movements (ROM), corneal reflexes
  - Sensation over face, facial movements
  - Ears: otoscope, tuning fork (test hearing loss)
  - Tongue (atrophy/fasciculations), pharyngeal elevation (symmetrical)
  - Inspect vocal cords (special instruments) if hoarseness
  - Pronunciation of words
  - Reflexes: jaw jerk, snout, buccal, sucking reflexes
- Testing of Motor function — check their movements, compare let to right. Figure out where in brain/body that problem lies. Look for tremor or twitching, finger to nose test
  - speed and strength of movements; Muscle bulk (atophy), tone, and coordination (arms, legs)
  - Limb tremor or fasciculations (twitching
  - Abnormalities of movement (finger-to-nose/toe-to-finger/heel-to-knee
- Testing of Reflexes
  - Biceps, triceps, supinaor-brachioradialis, patellar, Achilles, cutaneous abdominal

    - Plantar — should curl in, babinski sign if fan out. Bad in adults but common in babies in 1st year of life
- Testing of Sensory Function
    - Subjective pt responses require cooperation
    - Subject to over interpretation and suggestibility
    - Quick survey of face/neck/arms/trunk/legs with pin (L/R differences, level lost, zone insensitivity/hypersensitivity, vibration)
- Testing of Gait and Stance/Posture
    - Observe pt arise from a chair, stand and walk, tandem walk (feel-to-toe), hopping/standing on one foot, Romberg test (balance when standing with feet together, eyes closed)
- Screening neurologic exam — who they are, the date, do they understand what's going on with their illness, check language fluency, check pupils with pen light to check accomodation, watch eyes move. Ask to follow finger, ask to stick out tongue. Hold you hands out. Looking for symmetry
    - Watch legs move as extend and flex hips, more reflexes, do they have vibration can they sense tuning fork in extremities

Working Knowledge of NS

- Anatomy — coritcospinal tract, motor unit, basal gnaglia/cerebellar motor corrections, sensory pathways, cranial nerves, hypothalamus/pituary, reticular formation of brainstem and thalamus; limbic system, cortex areas/connections, visual/auditory/auntomic systems, CSF pathways
- Neurophysiology — neural excitability, nerve impulse propagation, neuromuscular transmission, muscle contractions, spinal reflexes, central neurotransmission, neuronal excitation/inhibitions, cortical activation, seizure production
- Pathologic anatomy/physiology — clinical features to expect/inconsistent with particular diagnosis
- Genetics (Medndelian and mitochondrial): terminology, main genetic aberrations -> neurologic disease
    - Put this theory into practice:
        - Imaging (see below)
        - Other lab studies
        - <u>But only after rigorous physical exam</u> — lab tests should be icing on the cake! Should already have good idea of what they have and test just to confirm it.\

Temporal Course of Illness

- Change in symptoms over times gives clinician clues on probable mechanism of NS dysfunction/which disease to excludes. <u>Also helps with prognosis</u>
- <u>Terms:</u>
    - Transient focal (+/- recurrent): Ischemia/migraine/seizure
    - Sudden-onset: ischemia or hemorrhage
    - Progressive focal: compressive, inflammatory or infectious
    - Progressive diffuse: degenerative (over years), inflammatory, metabolic (over days)
    - Waxing/waning focal: Ishcemia or compressive

- Waxing/waning diffuse: toxic or metabolic processes

Imaging, Electrophysiologic, and Lab Techniques for Neurologic Diagnosis

- CSF
  - Crucial in diagnosis of infectious and inflammatory conditions, subarachnoid hemorrhage, and processes that alter intracranial pressure.
  - CSF gives a wealth of information
    - Normal findings: Lecture 1 Notes (p3-4). Normal CSF clear & colourless
    - Abnormal findings: next slide
  - Foramen magnum — hole in skull, in buildup of intracranial pressure brain will be pushed through this and it will herniate. If suspect bleed, defer LP (take 15 min to do) and take to CT to locate bleed (blood work on the brain - giving ton of info on blood bacteria, white cells infection organisms, cancer cells, etc.
- Plain X-rays (early 20th century):
  - Cranium: Yield of useful information relatively small (eg. skull fracture in 1/16 cases), at a cost of thousands of dollars per fracture, small risk from radiation exposure
  - Spine: destructive lesions (eg. degenerative processes/cancer/infection), fractures
- Computed Tomography (early 1970s)
  - Precise size & position of cortex/sulci/some brain structures (eg. thalamus, brain stem, cerebellum, optic nerves), ventricles, spinal cord, peripheral nerves
  - See hemorrhage, infarcted/bruised/edematous brain, abscess, tutor tissue
  - Looks inside skull; slices of brain
- Magnetic Resonance Imaging (late 1970s)
  - Images in plane. Non ionizing energy
  - Higher Resolution views, and improved contrast between different structures. Preferred procedure
- Positron Emission Tomography
  - PET images reflect regional levels of administered radioactive compounds, eg. glucose, NT, the receptor binders
  - Local cerebral blood flow, O2/glucose utilization
  - Brian tumors, epileptic foci degenerative disease
  - Alzheimer/PK disease: understand/follow/forecast
- Functional Magnetic Resonance imaging
  - Tissue concentrations of cellular metabolites show activation of regions of cerebral cortex during mental and physical activities
  - Similar practical uses as PET
- Ultrasonography
  - In recent years technique refined to the point where it has become a principal methodology for clinical study of the fetal and neonatal brain
  - Important ancillary test for evaluating cerebral vessels in adults
    - Intracerebral/subdural hemorrhages, mass lesions can readily be visualized
- Electroencephalography (EEG)

- 8-32 electrode discs attached to scalp with conductive waste, record spontaneous electrical activity from cerebral cortex
- Essential for assessing seizures (paraoxysmal spikes/sharp/fast/slow wave), brain death (electrocerebral silence), sleep (polyomnography)
- Also cerebral effect son systemic metabolic disease, level of consciousness, drug intoxication (eg. barbiturates), hypothermia, cerebral hypoxia, CNS infections
- Replaced by CT/MRI for localizing structural lesions
- No help diagnosing
- Gold standard for diagnosing epilepsy; electrical beat of the brain. Pretty much useless for any other CNS problem.
- To assess brain death, flat EEG, medical legal criterion for brain death. Also used in sleep studies
- EEG abnormal with epilepsy (gold standard) provided it is being recorded at time of seizure: “spikes” and “sharp waves” diagnostic
- False negatives common:
  - Between seizures, single EEG normal in 30% with absence seizures, 50% with generalized tonic-clonic (grand mal) epilepsy
  - Another 30-40% with epilepsy have abnormal but “non-specific” EEGs between seizures
- If seizure originates in deep temporal, medial or orbital frontal focus, need depth electrodes (through skull) to detect
- Normal EEG during a “convulsion” indicates a pseuodoseizure (psychogenic non epileptic seizure, a “non-epileptic behavioural event”

- Evoked Potentials
  - Distinct from spontaneous potential detected by EEG
  - Via external stimulation of visual/auditory/somatosensory sense organs or peripheral nerves
  - Electrical response in cortex measured
  - Abnormal: prolonged latency of response
- Genetic Testing
  - Genetic marker son hereditary disease now available: greatly advanced diagnosis and categorization of neurologic disease
  - Eg. muscular dystrophy, spinocerebellar atrophies, some polyneuropathies, Huntington chorea
- Biopsy
  - Examination of exited sample of tissue via eg. microscopy. Very invasive task, cut out piece of brain
  - Eg. brain tuours, vasculitis, sarcoidosis, infections (encephalitis, infectious abscesses)

Cardinal Manifestations of Neurologic Disease

Disorders of Motility

Motor Paralysis

- Motor system: motor cortex, basal ganglia, cerebellum, and upper/lower motor neurone in brain and spinal cord

- Lesions can result in full paralysis or partial paresis loss of movement

Motor Apraxia

- Disorder in which an attentive pt loses ability to execute previously learned complex activities in absence of a derangement (weaknes,, ataxia sensory loss) that would be adequate to explain the deficit
    - Cause: lesion erases memory of pattern of movements necessary for an intended act

Patterns of Paralysis

1. Monoplegia: all muscles of 1 leg/arm
2. Hemiplegia: arm + leg + face on 1 side of body
3. Paraplegia: both legs
4. Quadriplegia: all four extremities
5. Isolated to >/= to 1 muscle group
6. Non paralytic disorders: apraxia, ataxia
7. Hysterical: psychological cause; doesn't fit with any atomic lesion.

Basal Ganglia: Movement Abnormalities

- Also known as extrapyramidal motor system abnormalities
- Influence derangements of basal ganglia and related thalamic and brainstem nuclei
- Regulate posture, automatic movement (like walking)
- Result: disorder of automatic, static, postural and some other motor activities

Symptoms of Basal Ganglia Disease:

- Negative symptoms (functional deficits): bradykinesia, hypokinesia, and loss of normal postural reflexes
- Positive symptoms (excessive motor activity) from "release"/disinhibition of undamaged parts: tremor, rigidity, dyskinesias (chorea, athetosis, ballismus and dystonia)
- Disorders of Postural Fixation, Equilibrium, and Righting:
    - Demonstrated most clearly in Parkinsonian patient
        - Involuntary flexion of trunk/limbs/neck
        - Righting reflexes impaired: gentle push on sternum -> fall
        - Series of small corrective steps when walking (festination)
- Hypokinesia, Akinesia, Bradykinesia (eg. Parkinson Disease)
    - Poverty of movement: autonomic, habitual movements absent
    - Blinking infrequent. Saliva not swallowed fast enough -> drooling results
    - Masked facies
    - Speech rapid/mumbling/monotonic, voice soft
- *Rigidity and Alterations in Muscle Tone*
- Rigidity
    - Muscles continuously/intermittently firm & tense
    - Seen in Parkinson and Wilson disease, progressive supra nuclear palsy (PSP), and from exposure to antipsychotic drugs ("neuroleptics")
    - Sometimes treatable

- Gegenhalten/paratonia/oppositional resistance:
  - Pt appears to actively resist when limb muscles passively stretched
  - No Tx
- Waxy Flexibility
  - Limb placed in suspended position, maintained there for minutes (possibly hours)
  - Seen in psychotic “catatonic” pts
  - Tx available
- Dyskinesias
  - Common “ambiguous” clinical term
  - All active movement phenomena that are a consequence of disease of basal ganglia, undifferentiated excessive movements induced in PK disease its from L-dopa Rx.
  - May follow the use of antipsychotic drugs (tardive dyskinesias - no pain and they aren’t
- Chorea
  - Involuntary arrhythmic movements of a forcible, rapid, jerky type.
  - From simple to quite elaborate
  - Although purposeless, pt may incorporate them into a deliberate act to make them less noticeable
  - Can appear exaggerated and bizarre
  - Grimacing and peculiar respiratory sounds
  - Certain drugs (eg. antipsychotics, oral contraceptives, some anti epileptic drugs, cocaine) can induce Chorea
- Athetosis
  - Cant; sustain fingers/toes/tongue — any body part — in 1 position
  - Slow, sinuous, purposeless movements
  - Eversion/inversion of foot, retraction/pursing of lips, twisting neck/torso, wrinkling of forehead, forceful opening/closing of eyelids
  - Slower than chorea, but can be impossible to distinguish
  - Choreoathetosis of all four limbs in Huntingtons disease. Totally inherited, non-treatable, congenital. Psychosis, disintegration of personality
- Ballismus
  - Uncontrollable, poorly patterned flinging movement of an entire limb
  - Closely related to chorea and athetosis
  - Usu unilateral (hemiballismus)
  - Flinging movements continuous/intermittent, (several/min)
    - Of such dramatic appearance that it is not unusual for them to be regarded as hysterical (psychologically caused in nature)
    - No tx
- Dystonia
  - Unnatural spasmodic movement of posture - limb twister

- Overextension/over-flexion of hand, inversion of foot, lateral flexion/retroflexion of head, force extension of neck, torsion of spine, arching/twisting of back (opisthotonos), forceful closure of eyes, fixed grimace
- Frequent cause: antipsychotic drugs, even - although marketed as non-contributory - the newer agents called olanzapine.
- Treatable

Note: Role for basal ganglia in cognitive function & abnormal behaviour seen PK disease, PSP, Tourette syndrome and others, e.g.. slowness in thinking (bradyphrenia)

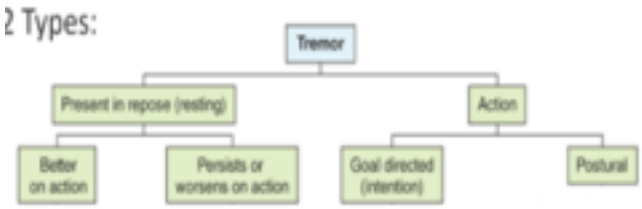
*Bradyphrenia — slowness in thinking

Cerebellar Dysfunction

- Ataxic Incoordination
  - Abnormalities of intend (volitional) movement
  - Speed of initiating, sustaining, accelerating/decelerating movement all slow
  - Impart a highly characteristic clumsiness
  - Velocity/forces of movement not checked: arrested prematurely or target overshot
  - Corrected closely (jerky movements, finger sways around target before coming, moves side-to-side on target (intention tremor)
- Tremor
  - Coarse irregular, wide-range, resting quivering
  - If rhythmic of head.upper trunk (titubation)
- Cerebellar Disease
  - Disorder of speech
  - Either slowed/slurred or
  - Scanning dysarthria: words broken up into syllables, each uttered with unnaturally less/ more forces (explosive speech)
- Eye Movement Abnormalities
  - Pts can't hold eccentric positions of gaze (look sideways) without rapid repetitive saccades (jerks) - horizontal _____
  - Same fro pursuit movements (following moving target)
- Disorders of Equilibrium and Gait
  - Difficulty standing and walking
  - Stand with feet together - pieces to one side/backward
  - Walking -> lurching: steps uneven, foot placement misaligned
- Hypotonia
  - Normal muscle resistance to passive flexion/extension dec d
  - Failure to check a movements: after strongly flexing one arm against a resistance suddenly released, pt's arm may strike face

Tremor

- Involuntary rhythmic oscillatory movement: alternating/irregularly synchronous contractors of reciprocally



innervated muscles

- Normal/physiologic. Almost invisible
- Abnormal. 2 Types
  - Action: Goal directed atactic action tremor (cerebellar, see below)
    - Postural (aka essential): upper limbs, head, L/R or Up/Down, chin/jaw/lips/tongue, larynx (causing voice tremor
  - Resting (when “in repose”)
    - Eg. Parkinson disease hand “pill-rolling” tremorWalking, jaw/lips/tomgue, eyelids (“blepharoclonus”)
- Primary Orthostatic Tremor — rare. In legs, but only when standing and disappears on walking
- Psychogenic (“hysterical”) Termor — stimulates many “organic” tremors
  - Atypical presentation (see notes)
  - Inconsistent symptoms: wide variation, from exaggerated to complete remission
  - Psychiatrically unexplained: no stressors, psychiatrist can’t make alternative diagnosis
- Asterixis
  - Flapping tremor
  - Seen with metabolic/toxic encephalopathies (liver, lung and kidney disease)

Clonus

- Unidirectional Gross Teror
  - Tremors are faster, bidirectional
  - Always in CNS pathology sign (eg stroke(
  - includes “restless legs syndrome”. Its march in place and rock their bodies during sleep
  - Can also be seen in daytime

Pathological Startle Syndromes

- Greatly exaggerated normal (adaptive) response to unexpected threat
  - Elicit by e.g. sudden sound, light flash, tao on body, person’s presence
  - Contraction of obicularis (close eye/mouth), neck spine, leg muscles
  - Jump, shout, fall

Spastic Torticollis/Focal Dystonias

- Intermittent Brief or Prolonged Muscle Spasms
  - If neck muscles involved, head hyperextends and twists
  - Can also involve e.g. eye, mouth/jaw/tongue
  - Rx: Parkinson meds fail. Use botox and deep brains stimulation

Blepharospasm

- Inability to Keep eyes Open b/o Involuntary Eyelid Closure
  - Can’t read, watch Tv - intermittently
  - Not due to ocular irritation or photophobia; persists in dim light
  - Extra-ocular movements OK. No neuropathological lesion

- Biofeedback/hypnosis/psychotherapy fail
- Rx: botulinum toxin

Other Head/Neck Muscle Spasms

- Lingual, Facial and Oromandibular Spasms
  - Jaw forced open/clamped shut, retraction/pursing of lips, platysma/neck muscle spasm (toricollis), protrusion of tongue
  - Merge or Brueghel syndrome

Task-Specific Dystonias

- Muscle Spasm with Highly-Skilled Motor Act
  - Can involve hands (eg. writer's cramp, paino/violin playing), "loss of lip" (trombonists, etc)
  - Delicate motor skill perfected by years of practice.performance, suddenly requires continuous and laboured effort
  - Rx: botox

Drug-Induced Tardive Dyskinesias

- "Dyskinesia": involuntayr hyperkinetic movements eg. chorea, athetosis
- "Tardive" (TD): from antipsychotic drugs after yrs of use
  - Often irreversible even after drug stopped
  - Worsened by high doses, prolonged use
  - Myth: newer 2nd generations won't cause
  - Also from non-psychiatric meds of similar structure
  - Rx: nothing really proven to work

Tics and Habit Spasms

- Gestures and Mannerisms
  - More than normal fidgeting, range from bei=nign - intrusive
  - Eg. Idiosyncratic lip movements - repetitive sniffing or blinking
  - Latter stereotyped, irresistible (relieve tension) - stop only breieflt
  - Pathologic anatomy not down
  - More common in children but usually self-limiting
  - In developmentally delayed: rocking, head bobbing, hand-wringing
  - Most severe: Gilles de la Tourette syndrome
    - Sniff, snort, jump, quit, twirl, aggressive impulses (touch), word repetition, vocalizations (repeat, utter swear words — coprolalia)
    - Cause unknown: PANDAS? - paediatric autoimmune neuropsychiatric disorders with streptococcal infection
    - Rx available

Akathisia

- Motor restlessness, inability to sit still, compulsion to move
  - When sitting, shift body, cross/uncross, move legs. Standing — pace and run in place
  - Affects concentration

- Seen in Parkinson/Alxhiemer disease
- most commonly as antipsychotic drug side effect
- Rx: difficult to stop. Try bensodiazpines, anticholinergics, amantadine, B-blockers; lower dose of neuroleptic

Cerebellar Dysfunction: Stance/Gait

Normal Gait and Stance:

- Body erect, head straight, arms loose and graceful — moving forward with opposite leg, steps equal legs almost touch coordinated hip/knee flexion, foot clear ground, thorax advance on side opposite lower limb, head stakes grounded first
- Requirements for walking upright:
  1. Antigravity support of body
  2. Stepping
  3. Maintenance of equilibrium
  4. Means of Propulsion
- Equilibrium/balance: postural righting reflexes (peripheral stretch, central vestibulocerebellar) react to constantly changing centre of gravity. Intact vision/vesitbular function/proprioception required
- Propulsion: walking — slightly leaning forward and falling;
  - running — forward drive or thrust by the trailing leg

Abnormal Gaits:

- Blind individuals moves cautiously: arms forward, steps shortened, gait stiff
- Vestibulopathy (inner ear dysfunction -> loss of equilibrium:
  - Unsteadiness standing/walking/running/turning/driving/reading while moving. Can't focus on moving target, which blurs/jiggles (vestibular-occular reflex)
- Loss of proprioception: abolishes/seriously impairs capacity for locomotion
  - Pt can't inmate gait/walk forward
  - Hands held in front, body bent/rocking, head forward, wide-based irregular walk, uneven steps
- Can't compensate if tilted to one side, stand after falling, even unable to crawl. Difficulty getting up from a chair
- Sway and fall in standing and close eyes (Rhomberg sign)

A. Reeling Gait of Intoxication
   - From e.g. alcohol, sedatives, and antipileptic drugs
   - Pt totters, reels, tips forward and then backward, on verge of losing balance and falling
   - Control over trunk and legs impaired. Steps irregular/uncertain
   - No effort to correct staggering by watching his legs ground

B. Choreoathetotic and Dystonic Gaits
   - With each step, pt resembles a marionette. Trunk/limbs twist
   - One arm thirst aloft, other behind body. Head inclined
   - Leg movements slow/awkward, wt carried on toes

- Leg suspense in air -> waltzing gait/twists trunk violently -> falls

C. Primary Orthostatic Tremor
   - Fast leg tremor on standing
   - Ceases upon walking

D. Gaits of the Developmentally Delayed
   - Defy easy analysis - -wide individual variation, yet stereotyped
   - Ungainly/ungraceful/maladroit: head too far forward/back. Arms in odd positions/waving. Awkward, lurking gait. Feet stomping, hand clapping, rhythmic rocking, etc.

E. Hysterical Gait (Atasia-Abasia):
   - Psychogenic (psychological not physical origin): pt unable to stand/walk (notes give examples) but normal use of legs in bed and neurologic examination otherwise normal
      - Note: Must rule out anterosuperior cerebellar vermis lesions, NPH, frontal lobe disease, intoxication, peripheral neuropathy
   - Can be accompanied by exaggerated movements of arms (show great effort required to walk/maintain balance), abnormalities of voice/visual fields, tremors, etc.
   - Explanations: complex province of psychiatry, eg. _____ (patient feigns/exaggerates illness for secondary gain, e.g.. win a legal judgement or in order to escape duty or work

Pain and Other Disorders of Somatic Sensation

Pain

- Pain important sign illness. MC medical symptom
- Preeminent sensory experience by which humans judge existence of disease within themselves
- Wide range of pain patients:
   - First rumblings of discomfort. No other symptoms/signs
   - Pain that appears to no structural bias: worry/depression has aggravated minor ache
   - No amount of investigation brings to light ether medical or psychiatric illness
   - Require relief from intractable pain from established/incurable disease
   - Seeking attention, drugs or monetary compensation
- Much known about anatomy/physiology of pain, relatively little known about who should be given meds and or surgery
   - High level of knowledge of neurology, psychiatry and general medicine required

Skin Pain and Deep Sensibility

- Skin Pain of 2 types: immediate pricking pain from a needle stick or stinging/bruning pain that follows in 1-2 seconds
- Both precisely localized
- Deeds pain from visceral and skeletomuscular structures: usually aching, may be sharp & penetrating (knife-like), or burning)
   - Felt as deep inside the body, but diffuse/poorly localized
   - Relatively few nerve endings

Referred Pain

- Deep pain not felt to be from a viscera of origin, protected to other areas distant from source but innervated by same spinal nerves
- Eg. afferent pain fibers from cardiac structures, distributed through segments T1 to T4, projected to inner side of left arm and hand and arm as well as over the heart (percordium)

Headache:

- Most common painful state
- Rivals backache as most common reason to seak medical care
- Caused by general medical as well as neurological problems
- Many valuable and delicate structures in head – therefore many pain receptors, but none in the brain itself
    - A headache is not the brain
- Diagnosis
    - determine quality, severity, location, onset, duration
    - Patients assessment of pain is unreliable, very subjective and many interpersonal differences
    - Physical exam is less important – informative if large arteriovenous malformation,

Mechanisms of Cranial Pain:

- intracranial mass lesions
    - only if deform, displace, stretch vessels/ structures at brain base
    - increased intracranial pressure itself doesn't cause pain
- dilation of intra/extra-cranial arteries
    - eg: following a seizure, high fever
    - same mechanisms for extremely rapid rises in BP
        - mild/ moderate HTN does not cause H/A
    - some mechanism for cough and exertional H/A
    - formerly believed that migraine is due to dilation of extracranial arteries – now is believed that migraine is more complex
- ischemic (not hemorrhagic, vaso-occulusive) strokes except in a few sites do not cause H/A
    - blockage of paranasal sinuses
- ocular H/A from prolonged use of eye
- diseases of ligaments, muscles and joints of upper cervical spine
- fibromyalgia – chronic widespread pain
- meningeal irritation from infection/ hemorrhage
- subarachnoid hemorrhage
    - intense, sudden, thunderclap H/A
    - accompanied by vomiting and neck stiffness
- low CSF pressure
    - eg. Following a lumbar puncture
        - orthostatic begins when patient stands up too soon after a lumbar puncture
            - Head ache when lying down are from subdural hematoma

Migraine Headache

- Periodic, unilateral, pulsatile
- Begin in childhood, decrease with age
- Familial
- Preceded by changes in mood/ appetite
- Classic/ neurologic migraine
    - Accompanied by an aura
    - Followed in min/hr by headache, nausea, +/- vomiting hrs-days
- Common migraine: no aura, headache buids up over a few mins, follows same time course
- Sensitivity to light, noise and smells
- Worsens with head movement
- Pt lied down in quiet, darl room and tries to sleep
- Can be switching from one attack to the next
- With females: can worsen premenstrually, in 1st trimester, on bc, and for premenstrual women
- Some link headaches with certain foods, strong stimuli, glare, head jarring, but trials don't replicate or back this thought up
- Migrainous personality is no longer a valid concept – tense, rigid
- Migraine – epilepsy relationship "tenuous"
- Causes and pathogenesis:
    - No agreed on unifying theory except genetics

<u>Treatment:</u>

- Control of an individual attack:
    - Begins during prodrome or at start of a H/A attack
    - For mild heard attach use acetaminophen, asprine, other NSAID
    - Can add codeine/ oxycodone
    - Avoid barbiturates – less effective and habit forming (oxycodone)
    - Numerous other medications used by MDs and pts
    - For severe attacks: sumatriptan/ other serotonin agonist, ergot alkoids, IV metoclopramide, many others
    - Last resort: opioids and corticosteroids
- <u>Preventive</u>
    - B-blockers, certain antiepileptic drugs, tricyclic antidepressants
    - Calcium channel blockers, indomethacin, cyproheptadine
    - Newest: botulinum tocin injections in cranial muscles
    - Diet may help
    - Psychotherapy, chiropracty, meditation, massage, biofeedback

Tension headache:

- Most common variety
- Usually bilateral

- Dull, aching pain and fullness/tightness/ pressure
- Throbbing, nausea, photo/phonophobia of migraine not seen
- Don't seriously interfere with daily activities, unlike, migraine
- Onset more gradual than with migraine
- Can last much longer than migraine: days, weeks, months, years
- Not more than 1-2/1000 with have an intracranial tumor
- Cause:
    - Not from contraction of craniocervical muscles and constriction of scalp muscles – as once believed
    - Pericranial and trampezius muscles harden
    - Nitric oxide – central sensitization to sensory stimuli
        - Promising drugs are NO inhibitors
    - Rx: OTC analgesics, low dose antidepressants,
    - avoid migraine meds!!!!

Disorders of Special Senses

Smell and taste:

- both modalities respond to chemical stimuli
- interdependent: appreciation of food depends on their aroma
- less critical in life than sight hearing
- but importance chemical stimuli intr-and interpersonally just beginning to be appreciated
    - eg. Pheromones for sexual attraction, key role in animal defenses
    - protective against noxious odors and poisons in humans, can distinguish between 1trill
- important to assess clinically: loss of taste/ smell can signify a number of intracranial, neuro and systemic disorders
- both modalities diminish with age as receptor neurons no longer replaced

Olfactory Lesions

- 4 types of clinical abnormalities:
    - quantitative:
        - Lost – Anosmia
        - Reduced – Hyposmia
        - Increased – hyperosmia
        - Latter chemo-sensitivity may not exist
    - Qualitative: distortions. Illusions of smell
    - Olfactory hallucinations and delusions
    - High order loss of olfactory discrimination – olfactory agnosia
- <u>Anosmia:</u> loss of sense of smell:
    - Pt only aware if bilateral, but clinician must detect and also decide if taste is lost as well
    - Causes:

        - Nasal, olfactory epithelium disorders (head injury), metabolic disease, tumours, degenerative disease, temporal lobe epilepsy
- Dysosmia / parosmia:
    - Distortions of odour perception hen an odour is present
    - Psychotic/ depressive illness: all food has very bad odour
    - Olfactory bulb injuries can have same effect
- Olfactory hallucinations:
    - Report an odour without any stimulus
    - With temporal lobe epilepsy
    - Can become a delusion if meaning attributed to hallucination: “I smell martians in my closet”
        - With depression, psychosis, Alzheimer disease
- Causes of loss of taste:
    - Aging, smoking, drying tongue, dry mouth, neck/ head irradiation, familial dysautonomia, bell palsy, post-influenza, scleroderma, acute hepatitis, viral encephalitis, myxedema, adrenal insufficiency, malignancy, deficiency of vitamin B and A, administration of a wide variety of drugs
    - Aside: gustatory hallucinations from temporal lobe epilepsy much less common than olfactory hallucinations

Disorders of special senses: Vision

- Physiology of vision well understood
    - Specialized pigments in photoreceptor cells – rods and cones – of retina absorb light energy and transform it into e_____ signals
    - Transmitted – bipolar cells – ganglion cells – optic nerves
    - Optic tracts pass through optic C____ -- lateral geniculate nuclei
    - Then:
        - Superior colliculi to midbrain pretectum – Suprac_____ nucleus of hypothalamus
        - Visual striate cortex of occipital lobe
        - Pretetum to control p____ constriction/ accommodation

Reduced vision: neurologic causes:

- A lesion in one optic nerve: complete blindness in that eye
- In optic chiasm: nasal retina fibers cross, continue with uncrossed temporal fibers of other eye
- Lesions here: contralateral super temporal quadrant defect + central scotoma in ipsilateral eye
- Optic chiasm lesion: bitemporal hemianopia
- Interruption of left optic tract: homonymous – L-nasal/ R-temporal field defect
- Temporal lobe lesions fibers from lower and upper quadrants of retina
- Lesions of visual pathway behind chiasm: homonymous hemianopia – vision loss in corresponding halves visual fields

Cerebral blindness/ visual a___

- Recognize objects/ words visually: visual pathways and visual cortex
- C___/ cerebral blindness results when latter destroyed
    - A__ syndrome: pt denies/ oblivious
- Visual a___: pt can't understand meaning of what is seen, even though primary visual perception intact, pt can accurately describe shape/ color/ size and draw object. Can't identify unless hears/ smells/ tests/ palpates
- Visual verbal agnosia/ alexia: limited to words
- Simultanagnosia: cant understand meaning of what is seen, even though some parts recognized
- P___: cant recognize familiar faces
- Teleopasia: images recede into the distances
- M__opsia/M___opsia: images appear too small/ large
- Palinopsia: persistence of repetitive afterimages
- T___: objects appear tilted/ upside down, straight liens are curved

Lecture 10 — NS II

Epilepsy

- Affects 200,000 in Canada 4.4 new cases/100,000 persons/ year o ~1 percent will have epilepsy by the age of 20 years
  o 2/3 begin in childhood; incidence increases again > 60 yo
  o 80-90% in developing world never receive RX

▪ Definitions:

1. *Convulsion* – intense paroxysm of involuntary repetitive muscular

contractions (*aka motor* or *convulsive seizure*
o *Seizure* – all paroxysmal electrical discharges of brain

2. Seizure — all paroxysmal electrical discharges of brain
3. *Epilepsy* – recurrent seizures

• Unpleasant connotations; use advisedly with pts
o *Nonconvulsive seizure* – impaired consciousness, but no

abnormal bodily movement

- Its sudden and sporadic
- Epilepsy ; an excessive and disorderly discharge of cerebral nervous tissue on muscles (John Jackson 1870) Previously “falling sickness” or “falling evil”

Classification

1. Generalized seizures ;
   A. Tonic, Clonic, or Tonic-clonic (grand mal)
   B. Absence
      i) Typical
      ii) Atypical
      iii) Special features
         - Eyelid myoclonia
         - Myoclonic absence
   C. Clonic
   D. Tonic
   E. Atonic
   F. Myoclonic inclding Atonic Types
2. Focal (formeyly “partial”) Characterized by main feature
   A. Simple (no loss of consciousness or alteration in psychic function)
      - Aura ; somatosensory or special sensory (visual, auditody, olfactory, gustatory, vertiginous)
      - Motor
      - Autonomic
      - Awareness retained (formed “simple) or impaired (formely “complex)

3. Unclassifiable; cannot be characterized as focal,g generalized or both, including epileptic spasms

Focal seizures with Altered Consciousness

- Affects the upper cortex
- Illusions, hallucination – temporal neocortex or amygdaloid-hippocampal complex
- Dyscognitive experiences (jeda vu, dreamy states, depersonalization)
- Affective states (fear, depression or elation) ; temporal

- Automatism (ictal and postical) ; temporal and frontal
- Staring; frontal cortex, amygdaloid-hippocampal complex, reticular-cortical system

Somatic and special sensory (auras)

- Somatosensory ; contralateral postrolandic
- Unformed images, lights, patterns, ; occipital
- Auditory ; heschl gyri
- Vertiginous ; superior temporal
- Olfactory ; mesial temporal
- Gustatory ; insula
- Visceral ; autonomic ; insular-orbital –frontal cortex

Generalized Tonic – Clonic (grand Mal) Seizures

- Little/no warning. *Prodrome* (hrs): apathetic/ depressed/ irritable, ecstatic; myoclonic jerks.Brief *aura* – focal seizure (see below)
  - Some movement (few sec) consciousness lost (turn head/ eye/ whole body, limb jerking)
- Lose consciousness and loss of movement in every part of body
- Chronic Phase ; (30 sec): mild generalized tremor
  brief, violent flexor whole body spasms/jerks; face violet, grimacing; pulse rapid, BPá, pupils dilated, salivate, sweat, — bladder pressure; apneic -> deep inspiration
- Tonic Phase ; (10-20 seconds) ; *Tonic phase* (10-20 sec): trunk flexion; mouth/eyelids open, eyes deviate up; arms up/abducted, elbows semi-flexed; protracted back & neck extension, then arms & legs; piercing cry; all muscles spasm; tongue biting; breathing suspended, skin/lips cyanotic; pupils dilated/unreactive; bladder emptying
- Terminal Phase ; pt motionless/limp, in deep coma x several min; pupils react to light; breathing quiet or noisyèpt opens eyes, looks about, bewildered & confused, ± agitated; drowsy/falls asleep x several hr, wakes with headache. When fully recovered, no memory of event but sore tongue/aching muscles/shoulder dislocation/ fractures/ periorbital hemorrhages/subdural hematoma/burns
- ▪ *Status epilepticus*: 5-8% will have prolonged series of such seizures without resumption of consciousness between them .. where the status keeps going on.. (11 EMERGENCY

Absence Petit Mal Seizures

- last typically seconds, usually in kids, can have 100s a day, individual doesn't know they're having one, and the outside observer, it looks like the kid is day dreaming or spaced out for a second, may be some fine motour movements , automatic; repetitive muscle movements, posture may be slightly affected
- you can be walking and have a absence seizure, and do things completely normal, be riding your bike and wont be falling off your bike
- Unlike grand mal seizures, notable for brevity/rapid onset/cessation/ frequency/paucity of motor activity. No warning. Up to hundreds/day
- ▪ Pts themselves sometimes unaware; onlookers see moment of absentmindedness/ daydreaming.

- ▪ Sudden interruption of consciousness. Pt stares, briefly stops talking/ ceases to respond. ~10% completely motionless; 90% brief burst of fine myoclonic movement of eyelids/facial muscles/fingers/arms
- Minor *automatisms* common but subtle: lip-smacking/chewing/fumbling fingers. Postural tone slightly á/â; mild vasomotor disorder. Pts usually don't fall; may continue complex acts, *eg* walking/riding bicycle
- In ~2-10 s, pt reestablishes full contact with environment, resumes preseizure activity. Only loss of thread of conversation/place in reading betrays the *absence* – momentary 'blank' period
- Primarily in children, usually cease in early teens

Focal/Partial Seizures

- localized to a certain part of the cortex, not bilateral and not diffuse
- location of the focus defines the symptoms
- simple or partial complex, depending on if theres any interrupt on level of consciousness
- Clinical/EEG manifestations show seizure localized to some part of cerebral cortex, not bilateral and diffuse
- ▪ Vary with locale of lesion; named from specific clinical characteristics and whether consciousness is retained ('*simple partial*') or impaired ('*complex partial*'). Both occur in many forms
- Focal seizures with sensory or motor features at the onset most often arise from foci in the sensorimotor cortex
- Impairment of consciousness – focus in limbic and autonomic areas or temporal lobe, sometimes frontal localization
- Relatively few focal seizures can be pinpointed from clinical data alone. However, when combined with scalp and intracranial EEG recording & MRI, a reasonably accurate localization can be given
- Surgical treatments where finding the focus is extremely important cause the object is the find and remove the focus

Frontal Lobe (Focal Motor/Jacksonian Seizures)

- talk about a march
- you can see the seizure involving different parts of the motor cortex, can start in the hand, move up the arm, go in the face, then down the arm and into the leg
- Discharging lesion of frontal lobe
  ▪ Most common type: turning of head & eyes to side opposite
- (contralateral) focus, often associated with tonic extension of limbs
- to same side. May be followed by generalized clonic movements. ▪ *Jacksonian motor seizure*: tonic contractionèclonic movements
- of fingers of one hand/face on one side/muscles of one foot in these parts in a fashion. Movements spread ("march") from the part first affected to other muscles on same side of body, *eg* hand, up the arm, to the face, and down the leg, usually lasts 20-30 s.

Other Types of Focal Sensory Seizures

***Somatosensory seizures*:**

- Focal or 'march' to other parts of body on one side o Numbness/tingling/"pins-and-needles"/ crawling

- (formication)/electricity, or movement o Pain/thermal sensation exceedingly rare

Olfactory and Gustatory Hallucinations

- *S*ignify localization to inferior/medial temporal lobe
  o Perceived odour 'exteriorized.' Described as disagreeable/foul (eg
- "garbage, rotten eggs")
  o *Gustatory hallucinations* - rarer – give peculiar sensations of taste

Visual Seizures

- Occipital lobe: elemental visual sensations: darkness/sparks/light; flashes of light, stationary/colourless, temporary blindness
- Temporal lobe origin, more complex/formed visual/ auditory hallucinations

***Auditory hallucinations*:**

- Temporal lobe seizure: buzzing/roaring or unrecognizable words, music
- Usually from a psychotic disorder (*eg* schizophrenia, psychotic depression) – fully formed voice(s), often commenting critically or issuing bizarre commands

***Vertiginous sensations (dizziness)*:**
o Rarely first symptom of a seizure. Usually inner ear problem

***Visceral sensations*:**
o Vague, indefinable feelings from thorax/epigastrium/abdomen,

heart palpitations/acceleration of heart rate

Focal Seizures with Altered Awareness/responsiveness

- *Aka* complex partial/psychomotor/temporal lobe seizures
- Period of altered behaviour and consciousness, for which patient later amnesic [NFF ??]
- Illusions, hallucinations, depersonalization, affective experiences
- Typically last 1-2 minutes
- To name a few:

  - Objects/persons in the environment may shrink or recede into the distance, or may enlarge (micropsia and macropsia), or persist as head moved (palinopsia) or tilt
  - Formed/unformed visual images, sounds, and voices; olfactory/gustatory/vertiginous
  - Altered psychic states: déjà/jamais vu (familiar with an unfamiliar circumstance/*vice versa*), depersonalization/dream- like state (patient views self as external observer), old memories
    resurface with striking clarity or abrupt interruption of memory,
    transient episodes of amnesia
  - Focal seizure that causes depression lasts 1-2 minutes
  - Need several ECG's to pin this down
  - Its usually not direction oppositional resistance to strength ; outbursts of rage is very unusual
  - Dramatic emotional experiences: fear, sadness, loneliness, anger, happiness, and sexual excitement. Laughter (rarely crying)

- Motor *automatisms*: lip-smacking/chewing/swallowing/salivation, fumbling hands/ shuffling of the feet, walking around in daze, act inappropriately (*eg* undressing in public)
- Complex acts from before seizure (*eg* walking, driving) may continue; but pt can't answer questions/follow commands
- Walk repetitively in small circles (*volvular epilepsy*), run (*epilepsia procursiva*), wander aimlessly
- Pt may strike out, but in nondirected oppositional resistance to restraint
- Unprovoked assault or outbursts of intense rage very unusual
- Exceedingly unlikely that an organized violent act requiring several sequential steps in its performance, such as obtaining a weapon and using it in a directed manner, could represent a temporal lobe seizure

Behavioral/Psychiatric Disorders with Temporal Love Epilepsy

- Some pts with temporal lobe seizures may exhibit: slow/rigid thinking, verbose/ circumstantial/ tedious conversation, be inclined to mysticism/naive religious & philosophical ideas, obsessionalism, humorless sobriety, mood swings/sadness/ anger, tendency to paranoia, diminished sexual interest(hyposexuality)/potency in men
- Geschwind 'interictal personality': hyposexuality, hypergraphia, hyperreligiosity, circumstantiality, intense mental life (1973-84)
- Now deemphasized, having in the past been imputed to these patients by societal and medical biases
- Talking on and on, never getting to the point
- "Postictal state rarely incorporates a protracted *paranoid- delusional* or *amnesic psychosis* lasting days-weeks. EEG during this period may show no seizure discharge, although this does not exclude repeated seizures in temporal lobe structures remote from the recording electrodes. This disorder, virtually indistinguishable from psychosis, may also present in the interictal period"

Psychogenic Non-epileptic Seizures

- *aka* 'Pseudoseizures.' Common. Simulate convulsive/non-convulsive seizures but no abnormal neuronal discharge
- 70% of people diagnosed with PNES previously diagnosed/treated (unsuccessfully!) for epilepsy
- Note: Patients with true epileptic seizures can also exhibit psychogenic ones as well, so very difficult to distinguish between the two
- Felt to be a behavioural response to "emotional/psychological distress, perhaps physical, sexual, and mental abuse during childhood" allied with hysteria (*Briquet disease, conversion disorder*) or, less commonly, malingering".
- Motor display atypical is sufficient to identify pseudo seizures (Notes *p* 11)
- Second line of evidence: highly resistant epilepsy in individual with normal intellect and normal brain imaging; background of unexplained medical problems, previous psychological problems (depression, panic disorder, overdose, self harm, addiction), and a life story that includes intense emotional trauma
- usually brought to a hospital, hooked up to a bed, and hooked up to ECG and its completely normal, but they have them video surveillance, because you can see that they have seizures but their ECG's are COMPLETELY normal

EEG AND LAB TESTING FOR EPILEPSY

EEG (*see above*) most sensitive – indispensable – for diagnosis

- Must be used in conjunction with clinical data
- False negatives (known epileptic pts with normal interictal EEGs) and false positives (interictal spike-and-wave abnormalities with no seizure activity) common. With former, up to 70%
- Standard scalp recording may miss seizure spikes during the experiential aura of a simple or complex partial seizure
- 2-3% of healthy persons show paroxysmal EEG abnormalities
- Long-term in hospital EEG monitoring (24-48 h) combined with audiovisual recording: seizure phenomena synchronized with EEG
- At home small digital EEG machine worn by the patient at home and at work ("ambulatory EEG"). Pt instructed to push a button if an 'event' experienced, can later be correlated with EEG activity.
- Laboratory abnormalities associated with seizures can be detected via MRI, cerebral angiography, perfusion imaging, CSF analysis, measurement of serum pH and serum prolactin/ACTH level
- the scalp recording can be missed, and don't show on ECG but can have epilepsy
- after seizure check the levels of stuff, they'll be elevated
- many people who have epilepsy have no seizure focus, undetectable in a lab

Treatment of Epilepsy

- Four strategies: antiepileptic drugs, surgical excision of epileptic foci/other surgical measures, removal of causative/precipitating factors, regulation of physical /mental activity
- ~70 percent of pts have seizures are controlled completely/almost so by medications; additional 20 to 25 percent, attacks significantly reduced in number/severity.~20 drugs used (Notes *p* 12)
- Surgical excision of epileptic foci (when meds fail) used with increasing effectiveness. >Half benefit
- Many pts wait too long before asking for the surgical option
- Considerable effort/time/technology required to determine site of epileptic discharge and method of safe removal of cortical tissue
- Sophisticated clinical, imaging (functional imaging, magneto-encephalography), and EEG (long-term video/EEG monitoring, depth/subdural electrodes, specialized analysis) techniques
- Other surgical procedures: sectioning of corpus callosum, hemispherectomy
- Sectioning of the corpus callosum (connecting of both the hemispheres)

Other Treatments of Epilepsy

- **Vagal Nerve Stimulation**
  - Pacemaker-like device implanted in the

anterior chest wall, stimulating electrodes are connected to the vagus at left carotid bifurcation

  - 25% Reduction in seizure frequency among med-resistant pts
  - Mechanism unclear, and role still being defined

- **Ketogenic Diet**
  - Known since 1920s,use has varied, usually for children 1 -10 yo with intractable epilepsy
  - No controlled studies, agreed upon mechanism
  - Regimen initiated during hospitalization: starvation x 1-2 days ketosis, followed by a diet in which 80-90% of calories derived from fat
  - Diet unpalatable, 1/3 of children and their families abandon

Coma and Disorders of Consciousness

Definitions

- Terms consciousness, confusion, stupor, unconsciousness, and coma somewhat ambigious ; many different meanings, not strictly medical timer
- Consciousness — judged by wha individuals says and/or does, but difficult to define
- Unconsciousness — state of unawareness of self/environment; Suspension of required mental acitvities. Diminished responsiveness to environmental stimuli
- Arousal — level of consciouness. Gives appearance of being awake
- Content of consciousness — quality/coherence of thought/behaviours
- Coma — complete loss of arousal
- Normal consciousness — individuals awake, fully responsive, aware self/environment, attention to/interaction with immediate surroundings. Fluctuates during day: keen alertness/deep concentration and mild general inattentiveness

Confusion

- Clouding of the sensorium
- Inability to think customary speed/ clarity, coherence
- Inattentive to imperceptive environment, disorientation distractible
- Global brain dysfunction ; toxic, metabolic, dementia, drowsiness or stupor
- Or focal cerebral disease in various locations
- Can range from mild to severe, attention span reduces, cant stay on one topic, distractible, poor planning, inability to recall recent events, deficits in working memory
- Mild ; inconsistent responses,attention span reduces, cant stay on one topic
- Severe ; misidentify objects, oeioke, delirium, component of fear and agitation, component of hallucinations and delusions, greatly unaware,
- Worse in evening ; sundowning (late day confusion seen in Alzheimers)

Drowsiness and Stupor

- Mentation, speech physical activity reduces
- Drowsiness;
  - (1) Inability to sustain wakeful state without external stimuli
  - (2) Alterness sustained spontaneously
  - (3) Some innatentiveness, mild confusion
  - (4) Light sleep ; lids droop/ muscles/ slack / limbs are relaxed
- Stupor;
  - i) Aroused only by vigorous/repeated stimuli

ii) Responses to spoken commands absent/inadequate

iii) Deep sleep ; eyes move out/upward

Coma

- Incapable of being aroused by external stimuli or inner need
- Variations in degrees of deepest and lighter stages ;
- Deepest stages ; no meaningful/purposeful reactions
- Corneal, pupillary, pharyngeal responses diminished
- Reflexes are gone are very diminishes
- Lighter stages ; more severe than stupor, some reflexes , seminicoma/obtundation

Causes

- Discrete structural lesion in certain parts of the brain
- More widespread
- Depth of the coma/stupor assessed serially (day to day) for direction in which disease evolving

Reticular activating system

- Reticular formation in brain stem ; sends signals into the cortex ; throughout the brainstem
- Maintains alert state
- Inactivation/destruction ; un-arousal state
- Projects to medial thalamus and then cerebral hemispheres
- Maintained in tonically active state
- Widespread innervation by ascending sensory systems

Faintness and Syncope

Intro

- Medically, syncope refers to an episodic loss of consciousness and postural tone and an inability to stand because of a diminished flow of blood to brain
- Synonymous in everyday language with fainting
- Among the most common of all medical problems.
- Other typical features: relatively abrupt onset, brief duration, spontaneous and complete recovery not requiring specific resuscitative measures
- Description of symptoms often ambiguous, since a subjective state: light-headedness, dizziness, a "drunk feeling," a weak spell, or, if consciousness was lost, a “blackout.“
- Clearly different from certain types of epilepsy, the other major cause of episodic unconsciousness, and from disorders such as cataplexy, transient ischemic attacks (TIAs), "drop attacks," and vertigo, which are also characterized by episodic attacks of generalized weakness or inability to stand upright, but not by a loss of consciousne

Causes

- 4 main causes
- Ultimately: cause of a temporary reduction in blood flow, that can refrain from hypotension

1. Withdrawal of vascular sympathetic to heart and excessive vagal effect and bradycardia you need the sympathetic nervous system to speed up the heart, keep from slowing down, if that’s withdrawn from parasympathetic vagul input; (vasovagal syncope) ; usually

accompanied by severe pain ; reduced blood flow to heart, breath0holding, weight lifting, postprandial state, can happen after you eat, certain psychic stimula (fear , anxirty, sight of blood, hysterical)

2. Failure of sympathetic innervation of blood vessels and of autonomically activated compensatory responses (reflex tachycardia and vasoconstriction)
    - o Leads to pooling of blood in lower body, and *orthostatic hypotension* . Again, no underlying cardiac disease.
    - o PNS autonomic failure/peripheral neuropathy/autonomic neuropathy (*eg* diabetes, antihypertensive meds) and CNS autonomic failure (*eg* primary/idiopathic, Parkinson disease, spinal cord trauma)
    - o Blood pooling in the lower body
3. Diminished cardiac output because of disease of the heart itself or from inadequate intravascular volume (hypovolemia)
    - arrhythmias, myocardial (*eg* angina, infarction, or severe congestive heart failure, obstruction to left ventricular output, aortic outflow, or pulmonary flow, cardiac tamponade, as well as inadequate intravascular volume (*eg* hemorrhage, dehydration)
4. Other Causes of Episodic faintness and syncope
    - Hypoxia, severe anemia, diminished CO2 as a result of hyperventilation, hypoglycemia and environmental overheating
    - Not from conventional cerebrovascular disease (atherosclerosis) – notes *p* 19

Clinical Features of Syncope

The Common Faint (Vasodepressor Syncope)

- From strong emotion, physical injury perspiration,áperistalsis, nausea, salivation, hunger, fatigue, alcohol, pain, exercise
- Usually initially upright position
  o Prodrome few sec to min. Lying down averts attack
  o Queasy, giddy, apprehensive, headache
- Pallor/ashen-gray face, body bathed in cool perspiration
- Salivation, epigastric distress, nausea, vomiting
- Patient tries to suppress by yawning, sighing, or breathing deeply
- Vision dims/closes in, ears ring, thinking unclear
- Consciousness lost, pt falls to ground
- Depth/duration of unconsciousness varies; may hear voices/see blurred outlines, usually complete lack of awareness/response
- Motionless, skeletal muscles relaxed. Sphincteric control not lost
- Pupils dilated. Pulse slow/fast, weak, systolic BP reduced (<60 mm), breathing almost imperceptible
- “Almost simulates death”

The Common Faint (continued)

- Once pt horizontal, blood flow to the brain restored. Vital signs recover
  o Eyelids flutter. Consciousness quickly regained

- If unconscious > 15-20 s, convulsive movements: brief, mild, clonic jerks limbs/trunk, face twitching, tonic extension trunk, jaw clenching
- Not a seizure - very rarely urinary incontinence/tongue biting. No confusion, H/A, drowsiness after attack
- But pt often weak and groggy. Arising too soon - another faint.
- Do feel weak and groggy, don't bite your tongue

Exercise-Induced Syncope

- Aerobic exercise -> presyncopal symptoms even when ECG WNL/no structural heart problems
- Of course, can also precipitate if underlying cardiac conditions (ecgs in notes)

Carotid Sinus Syncope

- Carotid sinus massage -> reflex cardiac slowing (sinus bradycardia, sinus arrest, or even atrioventricular block)—*vagal response*, or BP without cardiac slowing—*vasodepressor* response
- Also by turning of head to one side, tight collar, shaving!
- Occurs when pt upright. Onset sudden, often falling, Small convulsive movements occur quite frequently
- Unconsciousness x <30 s. Sensorium clear afterwards
- Cardiac slowing also from direct irritation of the vagus nerves (see notes), tumour/lymph node enlargements, post-radiation fibrosis

Micturation Syndrome

- When man arise at night to urinate. At end of micturition
- LOC abrupt/rapid and complete recovery
- Causes: bladder emptying vasoconstriction/vasodilatation, + postural hypotension?, EtOH, hunger, fatigue, upper respiratory infection. alpha-Adrenergic blockers for bladder outlet obstruction (BPH)

Tussive/Valsalva Syncope

- In heavyset males who smoke with chronic bronchitis
- Sustained hard cough/weak/brief LOC
- intra-abdominal pressure, interferes with venous return
- lots of coughing can cause a loss of consciousness
- similarly when try to exhale against closed glottis (Valsalva maneuver), breath-holding spells in infants, competitive weight lifting, unrestrained laughing, straining at stool, effortful trumpet playing

Orthostatic Hypotension

- BP drops precipitously on assuming an upright position
- Blood pools in the lower body is normally when reflex arteriolar constriction (via alpha- and beta-adrenergic mechanisms) and reflex acceleration hear (aortic/carotid reflexes) fail
- Aging progressively impairs these compensatory mechanisms
- No autonomic responses (pallor, sweating, nausea) seen- unlike

Vasodepressor syncope

- BP drops when you stand up, blood pools in body, constriction of arterioles, reflexed of the heart don't work
- Common in elderly people
- Cause autonomic nervous system is failing, you don't see these symptoms, check BP and HR and then have them stand up and do it again .. is BP drops more than drops 30 and HR increases more than 25 BPM, and patient will report dizziness, you need to recognize this orthastatic hypotension, if you fall on the bed its fine, if an elderly person does they can fall and break their hips, tell them to stand up slowly and if they feel dizzy sit or lie down immediately
- Do a thorough history physical and see if theres a reversible cause

Sleep and Abnormalities

Insomnia — Chronic inability to sleep despite adequate opportunity to do so: difficulty in falling/ remaining asleep and/or awakening too early. 20-40% of population, old > young, W > M

- Can be primary abnormality of normal sleep mechanism
- Or secondary to:
    - Drug/alcohol abuse from chronic or short-term alcohol/ barbiturate/sedative-hypnotic drugs/ineffective or 'rebound insomnia'
    - Situational anxiety/worry, clinical depression, frightening nightmares etc (see below), senility

Various Neurologic Diseases (notes, *p* 23)

- Joint/spine, peptic ulcers, cancer, multiple medications (notes *p* 22), pulmonary/ cardiovascular insufficiency, prostatism) o Circadian rhythm disturbance (jet-leg, shift work)
- Take these meds to help you sleep or they're wearing off in the middle of the night ; rebound insomnia
- Clinical depression can have nothing to do with .. its not a reaction to stress or a situation, you can be depressed for absolutely no reason or can be depressed for situational causes, in either event, if it reaches clinical depression ; sleep disturbances, guilty, loss of appetite and interest, no interests in life, suicidal. Doesn't matter if its spontaneous and situational, you need to treat it!!!!

Restless Legs Syndrome (RLS) Periodic Leg Movements of Sleep

- Aching/drawing, creeping/crawling sensations ("worms," "internal itch") in calves/thighs provoked by rest, temporarily, relieved by moving the legs (irresistible urge to do so). Persists x many years.
- Rarely: spill over into wakefulness: involuntary foot spasms/stamping, body rocking
- Idiopathic, although associated with iron deficiency, thyroid disease, pregnancy, certain drugs. "Seminal" genetic finding: nucleotide variant in short segment of chromosome 6p is associated
- Closely related disturbance is periodic leg movements of sleep ('nocturnal myoclonus'). Sleep lab needed to diagnose, whereas restless leg syndrome is identified on clinical grounds
- RX: search for and correct iron deficiency. Large number of medications have proved helpful
- temporary remove the pain by moving your legs, but only works for a bit
- just 1 nucleotide is all it takes

- cant make this diagnosis until you go to a sleep lab and get hooked up to an ECG

Treatment of Insomnia

A sedative-hypnotic drug , but only as a short-term aid. In practice used long-term

▪ Benzodiazepine receptor agonists (benzodiazepines, newer – but equally problematic – "nonbenzodiazepines"

- Avoid during pregnancy, with alcoholism, advanced renal/hepatic/ pulmonary disease, sleep apnea syndrome

▪ Alternatives drugs: melatonin (? efficacy), 'old' antidepressants (*eg* amitriptyline, trazadone). Nonprescription drugs (diphenhydramine, valerian) minimally or not at all effective

▪ Non-pharmacologic: psychotherapy for situational problems, regular daily/nighttime schedules, physically active during the day, avoid mental activity/TV? before bedtime, curb dietary excesses, avoid HS coffee/alcohol, simple behavioural modifications

- Very often people end up taking them forever, they don't ware off during the night or they don't stop working, but sometimes you can end up running into problems with it and escalating the dose and they stop working

Parasomnic Disturbances

- Somnolescent (Sleep, Hypnic, Myoclonic) Starts
    - Sudden bodily jerk (legs/trunk/arms) - rouse incipient sleeper
    - Seen in otherwise healthy newborn, disappear within months
- Sensory Sleep Paroxysms (Nb: Not calling them "Seizures)
    - When dropping off to sleep: sudden flash of light/crashing sound/ thunderclap of head pain ("exploding head syndrome") / sensation of being lifted and dashed to ground
    - Felt to be benign
- Sleep paralysis
    - In AM (hypnopompic)/falling asleep (hypnogogic) — though awake/conscious/fully reunited — unable to activate muscles
    - Respiratory/diaphragmatic/eye movements usually unaffected. Otherwise healthy. Dissociated form of REM sleep atonia?
- Night Terrors (Pavor Nocturnus)
    - Mainly problem of childhood; soon after falling asleep during stage 3/4 sleep
    - Child awakens abruptly, intensely frightened/screaming/moaning
    - Tachycardia (15-170)/deep, rapid respirations
    - Child often sleepwalkers as well; both may be simultaneous
    - Lasts 1-2 min
    - In AM child recalls nothing or only vague unpleasant dream
    - As with somnambulism (see below), EEGs (polysomnographic recordings) suggest impaired/partial arousal from deep sleep
    - generally seen with children: no psychopathology, tend to outgrow
    - Much less common than nightmares, seen in children/adults alike
        - In normal REM sleep
        - Withdrawal of EtOH/sedative-hypnotics (surpress REM(

        - No autonomic changes
        - Can usu be recalled
- Somnambulism and Sleep Automatism
    - Far more common in young children (ave. 4-6 yo)
    - Often associated with nocturnal enuresis and night terrors
    - Motor performance/responsiveness vary considerably. Most common just sit up. When walking: familiar act (eg turn on light); no emotion or frightened (but not frenzied/ aggressive as with some adults); generally eyes open/guided by vision, but can hit obstacles[?]injury; no response when spoken to; can mutter strange phrases/perform simple repetitive acts
    - Lasts few min; no/fragmentary recall
    - Occurs during deep NREM sleep, so not acting out a dream
    - Not a form of epilepsy (eg. fugue states/ambulatory automatisms of complex partial seizures [CPS])oParental precautions – see notes
    - Children usually outgrow; not sign of psychiatric/other disease
    - Adult onset “most unusual (psychiatruc disease/drug intoxication)” but “29% US adults if nocturnal wandering included”; usually h/o childhood sleepwalking; also NREM sleep
    - Often frenzied/violent behaviour/ fear seen
    - Sometimes self-injury
    - Crimes reportedly been committed, but organized/planned sequential activity not possible
    - If EEG normal then not CPS
    - Related conditions: Sleep eating/ sexomnia (engages in sexual activity, sometimes forcefully); no memory
- REM Sleep Behaviour Disorder
    - Mainly in older men with no h/o childhood sleepwalking
    - Attacks of vigorous/agitated/often dangerous motor activity (egshouted angry speech, violent activity – injury to self/bed mate) + vivid dreams.
    - Very high arousal threshold; sometimes detailed recall of nightmare (being attacked/ fighting back/attempting to flee
    - Frequency: Q 1-2 wk[?]several X nightly
    - Out of keeping with waking personality -> EEG: augmented muscle tone but no seizure activity
    - Early manifestation of a degenerative brain disease (deposition of alpha-synuclein in certain neuronal system
- Nocturnal Epilepsy
    - Both convulsive/non-convulsive seizures enhanced by sleep (so sleep-deprived EEGs used to activate EEG study – if not a seizure!); also in 1st hr after awakening
    - Same symptoms/course as daytime seizures (see above); if alone, only indirect evidence in AM; can be fatal (smothering in bed clothes, aspirate vomitus, respiratory/ cardiac dysrhythm
- Pathologic Excessive Sleep — Hypersomnia
    - Protracted sleep (days-wks); pt kept awake constant stimulation

    - Causes: post-influenza (encephalitis lethargic", "von Economo", "epidemic encephalitis", now extinct, following WWI [1914-18] pandemic); trypanosomiasis (sleeping sickness, worm blood infection common in Africa); other diseases in mesencephalon, floor/walls 3rd ventricle.
    - Sleep Drunkenness: pt not fully alert for long period after awakening - unsteady, drowsy, disoriented, automatic behaviour
- Kleine-Levin Syndrome
    - Episodic (ds-wks) somnolence (>18 hr/d) & compulsive overeating (3X normal)
    - Mostly adolescent boys – usually disappears during adulthood oAwakening (barely) only long enough to eat /attend to toilet needs
    - At other time, can be hallucinations, social withdrawal, negativism, slow thinking, incoherence, inattentiveness, disturbances of memory
    - Basis never clarified; possibly 'psychogenic'oNot narcolepsy – no consistent change in CSF hypocretin (orexin) – see below – but stimulants used for its RX may be useful; other antidepressants don't work

Sleep Apnea

- Excessive day time sleepiness
- Must first rule out (R/O) other causes of insomnia (see above)
- Obstructive Sleep Apnea (OSA). REM/NREM. Posterior pharyngeal muscles collapse -> obstruct upper airway. Causes: obesity; acromegaly/hypothyroidism; micrognathia (small jaw); NM disease, sedatives/EtOH, xs tiredness; recent stroke; head trauma; lung disease. Sequence (several hundred X/night): snore -> airflow ceases ->apnea (10 - >30 s) -> hypoxia ->breathing resumes (snort & brief arousal) -> sleep. Total sleep time
- Central Sleep Apnea (CSA). Causes: severe and life-threatening lower brainstem lesions (egC. reutzfeldt-Jakob disease, anoxic encephalopathy; see notes), heart failure, nasal obstruction

Narcolepsy and Cataplexy

- Irresistible sleep attacks (several/d) of narcolepsy (eyes close, muscles relax, breathing deepens, 'dozing', <15 min); falls from cataplexy (sudden muscle tone loss; head/jaw drop/ knees buckle, sink to ground—all with no LOC, last few sec–min); during laughter/anger/ surprise, etc, or intense athletic activity
- May also be terrifying hypnagogic hallucinations (visual, auditory, vestibular [sense of motion], somatic [feel a body part enlarged/ transformed]) and sleep paralysis (see above)
- Once established usually continue for life
- Cause/Pathogenesis. Familial. Mutations in gene for hypocretin receptor; controls sleep, appetite?; or autoimmune attack on hypothalamic neurons?

Bruxism

- Nocturnal/diurnal grinding of teeth, all ages, affecting sleep (and teeth); may be as distressing to bystander as to pt
    - Daytime may be tar dive dyskinesia (which disappears at night)
- Unexplained: stress; EMG show jaw muscles excessively contracted

Nocturnal Enuresis

- Frequently in childhood (10%, M/F), may persist into adult (1-3%)

- Familial peculiarity of bladder physiology: much higher intravesicular pressures, smaller functional bladder capacity
- Tx: training exercises designed to increase the functional bladder capacity and sphincter tone, no pre-HS fluids, awaken pt to void 3 h after going to sleep; antidiuretic hormone analogue (desmopressin)
- R/O UTI, diabetes mellitus/insipidus, epilepsi, sleep apnea, sickle cell anemia, and spinal cord/cauda equine disease

Delirium and Other Acute Confusional States

Definition of Terms

- Confusion
    - Incapacity to think with customary speed, clarity, and coherence
    - Features: impaired attention/concentration, disorientation, inability to properly register events and recall them, reduction in amount/ quality of mental activity, bewilderment
    - Seen with:
        - Global brain disease:
            - If normal arousal not maintained
            - Focal lesions of association
            - Specific syndromes (eg unilateral neglect of self/ environment, inability to identify persons/objects, sensorimotor defects, aphasia (see below)
        - Local brain disease: If normal arousal not maintained ? Focal lesions of association
            - Acute: eg metabolic encephalopathies
            - Chronic: eg long-standing, progressive dementias (see below)
            - Intermediate: eg emotional disturbance of mania/depression
- Delirium — confusion (as above) plus disordered perception (hallucinations, vivid dreams, delusions); inability to sleep; twitch/tremble/convulse; intense fear or other emotional reactions; agitation
    - Extreme inattentiveness/amnesia in spite of heightened alertness
    - Overactivity of psychomotor and ANS functions
- Amnesia — loss of past memories and inability to form new ones despite alert state of mind & normal attentiveness
    - Failure of retention, recall and reproduction; unique confusion/delirium, where information/events not adequately perceived/registered to begin with
- Dementia — gradual deterioration of all intellectual/cognitive functions in a formerly normal mind

Clinically Observable Aspects

- Disturbances of Attention — selectively maintain awareness, disregard distracting stimuli; involve entire cerebrum
- Disturbances of Perception — misidentifications of stimuli (illusions), misidentifications of persons. Sensing stimuli not evident to examiner (hallucinations)
    - Inability to perceive simultaneously all elements of large complex (clouding of the sensorium) or partial losses (neglect syndromes)

- Disturbances of Memory — involves 1. registration, 2. fixation/mnemonic, 3. recognition/recall, 4. reproduction
    - Usu ability to form new memories (anterograde amnesia) and recall old ones (retrograde amnesia) disturbed in tandem, e.g.. Korsakoff amnesic syndrome
        - Exception: bensodiapines, only anterograde amnesia
        - Sever retrograde amnesia alone likely hsyteria/malingering
    - Also “confabulation”, fabrications of stories to hide memory loss
- Disturbances of Thinking:
    - Highest order of intellectual activity - see notes for description - involves whole cerebrum
    - Disorders of thinking seen in delirium/other confusional states/mania/depression/dimentia/schizophrenia. Aspects include:
        - Incoherence — disorganization of thought processes, with fragmentation/preservation (repetition)
        - Flight of ideas — moving too facilely from one idea to another, with associations unclear; seen in mania, acute schizophrenia)
        - Poverty of ideas — opposite; seen in depression/chronic schizophreniz/dementia; signifies frontal lobe damage
        - Delusions — ideas not checked against reality, maintained in spite of convincing evidence to contrary, internal logical but patently absurd (eg. belief that ideas been implanted in pt’s mind by some outside agency, such as internet, radio, t.v., or atomic energy); seen in mania/depression/schizophrenia/dementia
- Disturbances of Emotion, Mood and Affect:
    - Mood — prevailing internal emotional state
    - Affect — outward/observable aspect of emotion
    - Marked individual differences in basic temperament in mortal population. Abnormalities:
        - Excessive, prolonged, and disproportionate fear and anxiety
        - Excessively labile, poorly controlled/uninhibited affective displays
        - Disconnection between reported feeling sea outward display
        - All emotional feeling/expression lacking
        - excessive cheerfulness, pathologic euphoria in face o serious adversity
        - Emotional response inappropriate to stimulus, eg. smiling to a morbid thought
- Disturbances of Activity:
    - Abulia — delay in producing movement, speech
    - Apathy–delay in producing ideation, and emotional reaction
    - Bradyphrenia/psychomotor retardation–slow mentation/movement
    - Akinetic mutism–extreme disinclination to move/act; pt wide awake/perceptive but does not speak/move for weeks
    - Catatonia–pt sits/lies silent & motionless, staring, or repeats certain movements or phrases for hrs; no reaction to sensory impressions
    - Waxy flexibility–if limbs are moved passively, retain new position for prolonged period; no actual motor rigidity except voluntary resistance (paratonia). See NS I, Slide 31

    - Excessive motor activity seen in akathisia (constant restless movements/inability to sit still); hyperactivity-inattention disorders; manic form of bipolar disease (continuous activity/insomnia/ flight of ideas/euphoria mood); following eg encephalitis or traumatic frontal lobe lesions pt in a state of constant uncontrollable/ destructive activity (organic drivenness
- Disturbances of Social Behaviour:
    - Complete indifference/anger aggression to all. Distrust/paranoia/ disrespect towards family members
    - Public urination, soiling bed without embarrassment
    - Lewd behaviour toward opposite sex
    - Kick, scream, bite, spit, aversion to touch; impossible to approach
    - Previously upstanding, socially appropriate may lose all regard for their actions and become profligate, gamblers, or alcoholics
    - In frontal lobe damage, beyond neglect for social conventions, indifference to others and to social consequences of pt's actions
    - Or, docility/amiable socially with Down and Williams syndromes
    - Social in difference,can't interpret others' emotional state in autism
- Loss of Insight:
    - Impaired/abolished awareness of nature/degree of one's deficits and their consequences
    - Rarely seeks advice/help for illnesses, noncompliance with Rx
    - Reduced capacity for introspections re psychic function

Note: abnormalities fluctuate in severity, worse at night (sundowning); Usu no consistent pathologic change is found because the abnormalities are metabolic and sub-cellular

An approach to lab tests useful in revealing common conditions that give rise to the confusional state when the cause is not self-evident from the history and physical examination is given.

Choice of tests governed by clinical circumstances

Dementia, The Amnesic Syndrome and The Neurology of Intelligence and Memory

Intro

- Intelligence: general mental efficacy; innate cognitive ability; act purposefully/ think rationally/ deal effectively environment/creativity/ capacity to have idea and reason about them
    - Global — characterizes behaviour as a whole
    - Aggregate of independent, distinguishable cognitive abilities
    - Disturbance of >1 cerebral region / cognitive function
    - Mechanisms: genetic possible, brain structure (weight/convolutions)/ function / psychologic
- Dementia; persistent deterioration of memory and other intellectual/cognitive function; little/no disturbance of consciousness/perception
    - Chronic progressive brain diseases — eg. degenerative like Alzheimer's
    - Loss of several overlapping intellectual abilities in different combinations. Also behavioural/personality changes
    - Must rule out pseudo dementia (depression/mania/schizophrenia/hysteria) — treatable and reversible

Mild Cognitive impairment (MCI) And Early Dementia

- Mild cognitive impairment or age-associated memory /cognitive impairment: memory complaints that do not interfere with daily functioning but disproportionate for age and education
- Spectrum: mild cognitive impairment or Alzheimer disease (AD)
- Difficult to differentiate boundaries from / determine risk of progression to dementia (particularly with highly intelligent individuals). 10-20%/yr with MCI acquire AD
- Identifying persons with 'presymptomatic' Alzheimer disease allows possibility of early treatment
- Risk factors: elevated BP, changes in cerebral white matter on MRI, gait abnormality, certain biologic markers (eg beta-amyloid, tau). Also level of prior education, extent of active mental life
- Clinician must exclude treatable causes but can only counsel caution and offer reassurance

Dementia from Alzheimer Disease

- 5-10 yr or more from when memory defect evident
- Earliest signs:
    - Can be subtle (lack of initiative/interest in/neglect of routine tasks, abandonment of pleasurable pursuits) attributed to depression [MUST RULE OUT!!], fatigue, boredom in retirement
    - Gradual development of forgetfulness (eg proper names); difficulty in balancing chequebook/ making change; forget purpose of errand; appointments/ social events missed; repetition of same question over course of a day since answer forgotten; emotional instability (angry/tearful/aggressive/ depressed/apathetic -> cheerful/ facetious); vague physical complaints; sleep disturbance; nighttime confusion; sleep pattern inversion; increased confusion and restlessness in early evening ('sundowning'); personality changes
    - Mental failure can be brought to light dramatically by eg febrile illness/metabolic upset/ head injury/surgery/new medicine
- Symptoms that develop later:
    - Easily distracted; can't think about/discuss a problem with clarity/comprehend complex situations or accomplish/follow complex tasks/directions; get lost;
    - Ability to make deductions/ inferences; loss of social graces; impaired judgment; suspiciousness/ paranoia; little or no insight (realization; of changes occurring)
    - Gropes for proper names and common nouns, no longer formulates: ideas with well-constructed phrases/sentences, resort to clichés, stereotyped phrases, and exclamations to hide underlying defect during conversation
    - Inability to suppress impulses, tolerate frustrations/restriction
- As condition continues to progress:
    - Forget day-to-day events; perseveration/impersistence in speech/action/thought; wandering/ pacing; excessive smoking/ overeating)
    - Apraxias/agnosias (inability to perform tasks/process sensory information) develop and alter performance of simplest tasks
    - Can't understand nuances of spoken/written word; lose verbal expressiveness; conversation rambling/ repetitious

    - Paraphasias (jumbled words, meaningless sentences); dysarthria, palilalia (repetitions), and echolalia (parroting); ritualistic and repetitive behaviours; minimal word use — mutism
    - No interaction with others; pt unkempt/ unbathed; look bewildered/expression vacant
- Motor Changes (premotor areas involved):
    - Movements slow, gait altered; unable to relax muscles (paratonia), resist passive movements of limbs (gegenhalten); abnormal mouthing movements and reflexes (grasping, sucking, inability to inhibit blink on tapping glabella, snout reflex [protrude lips on perioral tapping], biting or jaw clamping [bulldog reflex], corneomandibular reflex [jaw clenching when cornea touched], palmomental reflex [retraction of one side of mouth/ chin when base of thumb stroked])
    - Occasionally, diffuse choreoathetotic movements/ random myoclonic jerking/seizures; pain/uncomfortable posture ignored
- In very later stages, physical deterioration inevitable/inexorable:
    - All intellectual faculties (especially memory, recent before distant past), greatly impaired; disagreeable behaviour (petulance/ agitation/shouting/whining), worsened with restraining pt; visual/auditory hallucinations
    - Food/drink no longer requested but swallowed if placed in mouth -> Food intake reduced - > emaciation; remain in bed; eyes open but do not look about/oblivious of surroundings; sometimes fatal infections (eg pneumonia) virtually decorticate (totally unaware, unresponsive mute, incontinent, posture of flexion (“persistent vegetative state”)

Differential Diagnosis of Dementia

- Note age of pt, mode of onset, clinical course, time span, associated neurologic signs; accessory laboratory data (CT, MRI, EEG, LP, blood urea nitrogen, calcium, electrolytes, liver function tests); pathologic exam (biopsy); genetic testing
- Treatable forms of dementia must be ruled out via ancillary labs: subdural hematoma, certain brain tumors, chronic drug intoxication, normal-pressure hydrocephalus, infection (eg HIV/ neurosyphilis/cryptococcosis), vitamin B3(pellagra)/B12/thiamine deficiency, endocrine (hypothyroidism, hypercalcemia, Cushing syndrome) uremia, other metabolic disorders, chronic intoxication with drugs/chemical agents.
- Also R/O depression/anxiety

Patient Management

Neurologic Disorders Caused By Lesions in Specific Parts of the Cerebrum

Cerebral Lesions

- Physiologic studies(eg functional imaging [PET and fMRI] /electromagnetic stimulation) now suggest that cerebral functions are diffusely represented, not localized to certain regions
- Although, via broad correlations, particular functions assignable to certain regions, no cortical localization of behavioural/mental operations lost with delirium/dementia (attention/vigilance/ apperception/analytic & synthetic thinking) possible
- Neural afferent/efferent systems, closely interconnected but widely distributed: discrete, complex networks, regional and widespread
- Nonetheless, many basic functions can be anchored in one cortical region: lesion there can cause loss of a particular intellectual ability

- Frontal/temporal/parietal/occipital subdivisions – neatly bounded by sulci and fissures but made long ago – now largely provide clinician with familiar/ manageable anatomic landmark

Derangements of Speech and Language

Speech and Language Disorders

- Functional loss exceeds all others (blindless/deafness/paralysis) in gravity
- Language involves ; production and comprehension of words
    - Derangement always means dominant cerebral hemisphere abnormality
- Speech ; articulation; genetics and phonetics of verbal expression
    - Disorder may have similar origin or abnormalities elsewhere
- 4 Categories (only 1st covered in detail in our notes):
    (1) loss/impairment of production, comprehension of spoken language (aphasia or dysphasia)
    (2) diseases of higher-order mental functions (autism, mental retardation, dementia, autism
    (3) defect in articulation; pure motor disorder of muscles of articulation (dysarthia or anarthria)
    (4) Alteration or loss of voice from disorder of larynx or its innervation (aphonia or dysphonia)

Anatomy of Language Functions

- Note that this organizational scheme is controversial – some experts feel that's theres a single central language zone – not fully supported either by conventional brain imaging techniques or by clinical observation
- How regions of brain are organized into separable but interactive modules, resulting in the complex behaviour of which we make daily use in interpersonal communication, is still being studied by linguists and cognitive neuropsychologists

Aphasia — impairment in language function — categorized into types by observing:

- Natural sounding fluency, including normal cadence, prepositions, and correct grammar
- Comprehension of language
- Proper selection, use and relationships between words
- Naming of displayed objects
- Ability to repeat in comparison to spontaneous speech
- Reading and writing

Disorders of Energy and Mood from Limbic Diseases

The Limbic Lobes

- The Numerology of Emotion
    - Emotion — any feeling state associated with certain types of bodily changes (mainly visceral and under ANS control) and leading usually to an impulse to action/certain type of behaviour
    - Components:
        1. Perceptions of stimulus (internal (an idea)/ external)
        2. The feeling

3. Autonomic-visceral changes
4. Outward display (affect)
5. Impulse to a certain type of activity

- Often not possible to separate components from one another
- Neural networks of both affective response/cognition involved
- Anatomy of limbic lobes complex, least understood in CNS

Limbic System Physiology

- Contains hypothalamus: regulates sympathetic/parasympathetic ANS, pituitary hormone secretion, hunger/thirst/body temperature/ electrolyte levels. Essential to basic homeostatic and emergency ('fight-or-flight') reactions, control of visceral activities
- Involved in elaboration of emotion and memory
- Perception of visceral activities can greatly alter emotional state (eg perception of rapid HR heightened anxiety
- Hypothalamus/amygdala/cingulate gyrus involved in production/ inhibition intense emotions
- Greatest concentrations of neurotransmitters norepinephrine, serotonin and dopamine – implicated in mood disorder/ schizophrenia found in hypothalamus/other parts of limbic system
- Although function/interconnections highly complex/only partially understood, lesions in limbic system most consistently/specifically alter emotionality

Emotional Disturbances Due to Diseases Involving Limbic Structures

- Researchers/clinicians can relate emotional disturbances in its with disease of limbic structures using knowledge from animal studies and now direct imagine
- Most readily recognized disturbances of emotion—>
    - Tentative, as our understanding of their pathologic basis incomplete: association with lesions and diseases in particular parts of human brain only just beginning to be possible.

I.	Disturbances of emotionality because of:
	A. Perceptual abnormalities (illusions and hallucinations)
	B. Cognitive derangements (delusions)
II.	Disinhibition of emotional expression
	A. Emotional lability
	B. Pathologic laughing and crying (pseudobulbar state)
III.	Rage reactions and aggressivity
IV.	Apathy and placidity
	A. Klüver-Bucy syndrome
	B. Other syndromes (frontal and thalamic)
V.	Altered sexuality
VI.	Endogenous fear, anxiety, depression, and euphoria

TABLE 25-1. NEUROLOGY OF EMOTIONAL DISTURBANCES

- Emotional Lability:
    - Eg. Meet old friend -> cry in public, mildly amusing remark -> uncontrollable laughter, easy vacillation from one state to another
    - From many cerebral in many locations; anatomy obscure. From vascular/diffuse cerebral derangements, frontal love disease, etc.
- Pseudo bulbar Laughing and Crying:
    - Forced/involuntary, stereotyped spasms; emotional incontinence / pseudo bulbar palsy / pseudo bulbar affective state
    - Related to affect/feeling? Normal smiling/frowning lost
    - Can be from diffuse pathology (eg. multiple lacunae, ALS, MS) or localized (eg. loss of control in supra-nuclear motor pathways between thalamus and medulla in brainstem, 'gelastic epilepsy
        - 'mirthless laughter', frontotemporal dementia (FTD)

- Aggressiveness, Anger, Rage, and Violence
    - Although aggressiveness integral to social behaviour, in civilized society tantrums/rage/violence/destructiveness not condoned
    - Groundless unbridled/disorganized/blind rage, out of contact with reality/impervious to all pleading, may represent CNS disease, likely in temporal lobes, particularly medial amygdala. Testosterone promotes/ estradiol suppresses (suggests why men more disposed to anger)
    - Rage reactions seen in following medical settings:
        - temporal lobe seizure; brief, poorly directed automatism
        - acute neurologic disease; see text for examples
        - metabolic/toxic encephalopathy with clouding of consciousness
        - reaction to psychogenic drugs (eg angel dust [PCP, phencyclidine], cocaine, spice) or alcohol intoxication
        - sociopaths, no recognizable seizure (depth electrodes?)/other neurologic abnormalities
- Placidity and Apathy
    - Fewer thought/words/movements, from stimulation threshold/inattentiveness/impaired thinking/apathy/lack of impulse (abulia). Mood is neutral, unlike with depression
    - Due to impaired activation of certain areas (see text)
- Altered Sexuality in Men or Women
    - Hypersexuality – no moral-ethical restraints/disinhibited sexual behavior – can be from neurologic lesions (see text)
    - Causes: head injury, cerebral hemorrhage, dopaminergic drugs (eg in Parkinson disease), mania
    - Hyposexuality – loss of libido – usually from depressive illness. However, certain medications, or neurologic diseases (see text) may be responsible. Also possible to lose sexual performance (eg. following prostatectomy) without altering libido/orgasm
    - Note that temporal lobe epilepsy can cause either

Major Categories of Neurologic Disease

Cerebrovascular Disease and Cranial Trauma

Cerebrovascular Diseases

- Stroke most important frequent adult neurological diseases
- Very dramatic ; apoplexy, shock, CVA, cerebrovascular accident
- Definition ; relatively sudden occurrence of a focal neurological deficit
- 2 types ; ischemic (due to occlusion of cerebral BV) or hemorrhagic (from rupture of a blood vessel or an abnormal vascular structure
    - o Polar opposites but both cause cerebral infarction (neural death)

Clinical Stroke Syndrome

- All gradations of severity, but essential feature is abruptness with which deficit develops
    - Range from mild (trivial/transient) l patient doesn't seek medical attention to severe (full hemipraresis/coma) (left stroke, lose function of part of all of right side of body)

- Embolic strokes ; sudden onstet, reaches peak at once, blood clot goies into an artery (ischemic)
- Thrombotic stroke ; slower ; minutes to days, coronary thrombosis, the clot ruptures and somewhat more gradual, but local still (ischemic)
- Cerebral hemorrhage ; minutes to hours, deficit static. Progressive
- TIA ; transient ischemic attack ; rapid complete reversal of a focal stroke syndrome in <1hr

Want patient to be in if he had a TIA, they may well admit him for observation

- Second essential feature of stroke is its focal signature
  - Deficit reflect location/size of its focal signature
    - Multiple manifestation; hemiplegia, numbness, sensory deficits, aphasia, deficits, visual field deficits dizziness dysarthia, visual fields defects, diplopia

Ischemic Strome

- Caused by one of following:
  - a) atherosclerosis superimposed thrombosis (clotting) affecting large cerebral or extracerebral BV
  - b) cerebral embolism or
  - c) occlusion of small cerebral vessels within the parenchyma of the brain
- TIAs may present as transient spells of hemiparesis, aphasia, numbness or tinging on ones side of the body, dysarthia, diplopia, ataxia, obscuration of visual field or combination of these
- Risk of ischemic stroke is slightly higher

Hemorrhagic Stroke

- Aka Intracerebral hemorrhage: most from hypertension, ruptured aneurysm, hemorrhage from anticoagulants and thrombolytic agents
- Extravasation of blood into brain forms a mass that grows in volume in bleeding continues
- Adjacent brain tissues is distorted and compressed. Midline may be displaced to opposite side of cranium, reticular and respiratory centres compromised; to come and death
- CT scanning and MRI used to diagnose
- First have to suck out the blood as it builds up
- If someone has had a stroke they ABSOLUTELY need to be imaged

What Kind of Stroke?

- Ischemic *vs* hemorrhagic stroke *may be fairly reliably made* by s*killed* neurologist on basis of:
  - **Immediate past history**
    - Activity at onset of stroke, *eg* physical effort
    - Accompanying symptoms, *eg* headache, vomiting, seizures, level of consciousness
    - Temporal course/progression:
      ✓ Was onset sudden with deficit maximal at onset?
      ✓ Did deficit improve, worsen, or remain the same?

✓ If worsened – stepwise/remitting/gradually progressive? ✓ Fluctuations between normal and abnormal?

- **Past and present personal and family illnesses**
- **Physical/neurological examination**

▪ Ultimately, causality of whether stroke is ischemic or hemorrhagic can *only* be established with radiologic imaging modalities, *eg* CT/MRI

Craniocerebral Trauma

- Common and serious neuro disease
- At once both simple and complex
- Simple ; no difficulty determining cause (head trauma)
- Complex ; multiple delayed effects possible
- Mechanisms of injury ;
    - Cranium distorted by forceps (birth injury)
    - Gunshot wound of the brain
    - Falls (also traffic accidents)
    - Blows to the chin
    - Injury to skull and brain from falling objects
    - Concussion injuries

Lecture 11 — Blood Disorders Part 2

Malignant Disorders of White Blood Cells

Palma Cell Myeloma (Multiple Myeloma)

- Pathogenesis & Clinical Manifestations
    - Malignant disorder of mature, antibody-secreting B lymphocytes (plasma cells)
    - Occurs exclusively in adults; usually >40 years; median age 65 years; Men > women
    - Malignant plasma cells produce excessive identical monoclonal antibodies; invade bone and form multiple tumour sites
    - May also target other tissues, including lymph nodes, liver, spleen, and kidneys
    - Abnormalities in chromosome structure/number commonly found
- Diagnosis based on:
    - Monoclonal antibody peak
    - Presence of Bence Jones protein
    - Hypercalcemia (due to bone destruction)
    - Evidence of bone lesions
    - Protein in urine
- Bone marrow biopsy confirms diagnosis
    - Plasma cells occupy 30% to 95% of bone marrow; minimum of 10% to 15% for diagnosis
- Most clinical manifestation caused by bone/renal damage

- Prognosis and Treatment
    - Atineoplastic agents: induce/maintain remission in plasma cell proliferation
    - Best chemotherapy regimen not yet determined
    - High-dose chemo followed by allogenic BMT becoming more common
    - Autologous stem cell transplant optimal initial therapy
    - Pharmacologic management for renal dysfunction
    - Chronic bone pain—common problem
        - Narcotic/non-narcotic pain relievers
        - Localized application of radiation to bone lesions

Lymphomas

- A diverse group of neoplasms that develop from the proliferation of malignant lymphocytes in the lymphoid system
- Result from genetic mutations or viral infection.
- Malignant transformation produces a cell with uncontrolled & excessive growth; accumulates in the lymph nodes & other sites —> tumour masses.
- Classification is based on the cell type of origin
- Incidence rates differ with respect to age, gender, geographic location & socioeconomic class.

Hodgkin Disease

- Represents about 30% of malignant lymphoma (M>F)
- Occurs across life span; half of cases between ages 20 and 40 years
- Clinical Manifestations:
    - depend on origin site and dissemination stage
    - progression from one group of lymph nodes to another
    - the development of systemic symptoms
    - the presence of Reed-Sternberg (RS) cells (malignant lymphocyte usually a B cell) that secrete & release cytokines ?
        - accumulation of inflammatory cells ? in an enlarged, painless lymph node in the neck
    - Cytokines ? systemic effects (fever, drenching night sweats, itchy skin (pruritus) & fatigue)
- Prognosis and Tx:
    - Stage dictates treatment
    - Localized tumors:
      radiation therapy (most common)
    - Disseminated disease:
      chemotherapy
    - Overall 5 yr survival rate for all stages treated Hodgkin disease: 85%

Non-Hodgkin Disease

- Lymphomas that originate from B cells at various stages of differentiation
- Lymphomas that originate from T and NK cells

- Majority arise from lymph nodes, but can originate in any lymphoid tissue
- **Do not have Reed-Sternberg cells**
- 95% occur in older adults; M > F
- As a group: spread early and unpredictably when compared to Hodgkin's
- Signs & Symptoms — similar to Hodgkins
- Prognosis
    - Varies according to type, stage, patient age & integrity of BM
    - Common therapies:
        - Radiation; chemotherapy
        - Tissue specific therapies: monoclonal antibodies & BMT
    - Therapy effectiveness varies
        - Stages I and II: favorable outcomes
        - Stages III and IV: less favorable

Alterations in Homostasis

- Hemostasis: stepwise process for stopping of bleeding and prevention of blood loss after vessel injury

Mechanism of Hemostasis

- Primary hemostasis — platelet plus formation
- Secondary hemostasis — involves the formation of a fibrin clot through -> coagulation
    - 2 pathways
    - Intrinsic pathway
    - Extrinsic pathway
    - Both lead to the common final pathway
    - Fibrinolysis (clot dissolution) — occurs as fibrin clot is forming
- Clotting factors
    - Synthesized by the liver
    - Most are plasma proteins in an inactive state
    - Some (factors II, VII, IX, X, protein C and S) are dependent on vitamin K for synthesis

Anticoagulants	Mechanism
Antithrombin III and heparin	Inactivate factors IXa, Xa, XIa, XIIa & thrombin
Protein C	Inactivate factors Va and VIIIa
Protein S	Accelerates action of protein C
Plasmin	Breaks down fibrin into fibrin degradation products
Vitamin K antagonists (deplete the active form of vitamin K)	Inactivate factors VII, IX, X and prothrombin
Antiplatelets	ASA, NSAIDs

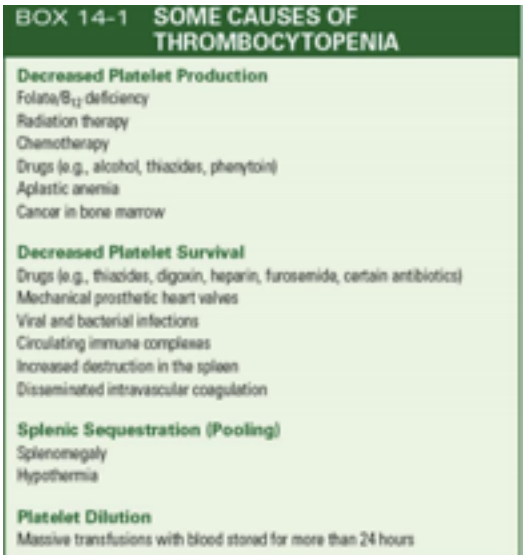
Disorders of Hemostasis

- Evaluation of hemostasis and coagulation
    - Included in patient history, physical exam, clinical assessment, lab tests
    - Especially indicated for:
        - Personal/family history of bleeding
        - Active bleeding that is unresponsive to standard interventions

    - Screening before surgery
    - Ongoing evaluation of anticoagulation therapy
- Clinical Assessment
    - Medication history
    - Aspirin and aspirin-containing preparations, non-steroidal anti-inflammatory agents, some antibiotics, anticoagulants, alcohol, chemotherapeutic and thrombolytic agents
    - Pallor
    - Jaundice
    - Hemarthrosis
    - Petechiae, purpura, ecchymosis, hematoma
- Evaluation of Primary and Secondary hemostasis
- Lab tests:
    - CBC (anemia) / platelet count / peripheral smear indicates the number and gross morphologic characteristics of platelet function
    - Bleeding time evaluates vascular status and platelet function
        - Prothrombin Time (PT/INR) assesses the extrinsic pathway of coagulation - time it takes for a sample of patient's plasma to clot after addition of tissue extract that mimics contact of blood with tissue; if abnormal -> shows coagulation defect in extrinsic pathway
        - Activated partial thromboplastin time (aPTT) assesses the intrinsic pathway - time it takes for a sample of plasma to clot after addition of compounds that mimic contact of blood with an artificial surface
    - Platelet Disorders — primary cause of bleeding is an abnormality in the quantity or quality of platelets; may be acquired (more common) or inherited in women
        - Petechia (small purple spot on skin caused by minor bleed)
        - Purpura — purple spots caused by bleeding under the skin
        - Mucosal bleeding
    - Coagulation Disorders — more common in men; delayed deep muscle bleeding, hemarthrosis, hematuria; more commonly congenital

Quantitative Platelet Disorders

1. Thrombocytopenia — Decreased platelet count (below 140 x 10^9/L)
    - Idiopathic thrombocytopenia purpura (ITP):
        - immune-mediated thrombocytopenia usually following an acute viral infection: occurs in the absence of toxins or drug exposure
    - Clinical Signs
        - Generally absent until platelets < 100,000/mL
        - Petechiae / purpura when platelets 50,000/mL
        - Spontaneous mucosal, deep tissue and intracranial bleeding
        - When thrombocytopenia is severe, there is



BOX 14-1 SOME CAUSES OF THROMBOCYTOPENIA

Decreased Platelet Production
Folate/B_{12} deficiency
Radiation therapy
Chemotherapy
Drugs (e.g., alcohol, thiazides, phenytoin)
Aplastic anemia
Cancer in bone marrow

Decreased Platelet Survival
Drugs (e.g., thiazides, digoxin, heparin, furosemide, certain antibiotics)
Mechanical prosthetic heart valves
Viral and bacterial infections
Circulating immune complexes
Increased destruction in the spleen
Disseminated intravascular coagulation

Splenic Sequestration (Pooling)
Splenomegaly
Hypothermia

Platelet Dilution
Massive transfusions with blood stored for more than 24 hours

considerable risk of visceral hemorrhages
        - Intracranial hemorrhage constitutes the main danger of severe platelet deficits; when it happens it is fatal
    - Diagnosis
        - Low platelet count
        - Prolonged bleeding time
        - Poor clot retraction
        - PT/INR, partial thromblastin time & other coagulation studies are normal
        - CBC will indicated if its isolated or not
        - Careful review of all meds being taken
    - Treatment
        - Based on the identified cause; may include: discontinuation of drugs, avoidance of aspirin or similar drugs
        - Splenectomy may be helpful: it removes major site of platelet destruction & eliminates the source of antiplatelets antibodies

2. Thrombocytosis — presence of high platelet counts in the mood (>400,000/uL)

- Transitory—due to stress/physical exercise
- Primary (essential) due to [?] megakaryocytes proliferation; can be caused by:
    - myeloproliferative diseases such as polycythemia vera , CML
- Secondary (reactive) due to [?] platelet production; can be caused by:
    - Inflammation; surgery (which leads to an inflammatory state)
    - Hypo-splenism (decreased breakdown due to [?] function of the spleen)
    - Hemorrhage and/or iron deficiency
- Often symptomless, may lead to thrombosis in some patients
- Primary thrombosis may lead to hemorrhaging into the skin & GI bleeding
- Thrombosis leading to vascular ischemia & pulmonary embolism is a possible complication
- Quantitative platelet disorders
- Treatment
    - None necessary for transitory & secondary forms
    - For primary aetiologies — Cytotoxic agents; antiplatelet or interferon therapy

Coagulation Disorders

- Coagulopathies are defects of the normal clotting mechanism
- Problems can include:
    - Bleeding from a problem with the formation, stabilization or lysis of the fibrin clot
    - Excessive clot formation due to inappropriate activation of the coagulation cascade

1. Hemophilia

- A group of hereditary disorders that affect blood clotting (coagulation)
- Most common inherited coagulation disorder resulting in excessive bleeding
- Associated with sex chromosome X; transmitted in a recessive fashion ;

- Affects boys (hemophilia C exception)
- Hemophilia A (85% of cases) — factor VIII deficiency
- Hemophilia B (Christmas disease)—factor IX deficiency
- Signs and symptoms: vary with severity
    - Easy bruising, serious bleeding episodes (prolonged bleeding and rebleeding) are the diagnostic symptoms of haemophilia, in particular hemarthroses (joint hemorrhage) in the case of severe hemophilia
- Characteristics of the hemorrhages
    - They are induced by a minor cause and are exaggerated
    - They have no tendency for spontaneous arrest
    - They start over at the time of the loss of the blood clot
- Bleeding
    - Hemorrhages from skin lesions are interminable; hemorrhages in the natural cavities are frequent -> Intracranial hemorrhage -> can cause disorientation, nausea, loss of consciousness, brain damage, and death
- Interstitial bleeding
    - Hematomas and hemarthroses are common (can be absent with the mild forms) can occur in all the major joints (knees, elbows, ankles) causing an intense pain -> lead to progressive destruction of the cartilages and joints -> arthritis
- Treatment
    - Administration of concentrates of the coagulation factors
    - Transfusion —> from blood transfusions that are given as treatment
    - Patient/family education

2. <u>von Willebrand Disease</u>

- vWF & Factor VIIII circulate as a complex
- vWF necessary for stabilization of factor VIII
- Due to a decrease/absence of the von Willebrand factor & dec of factor VIII
    - The most common hereditary coagulation abnormality in human (present in 1 in 100 ppl; 1 in 10,000 have symptoms)
- Signs & Symptoms
    - Most frequent - hemorrhages on the mucous membranes, nose & GI bleeding, ecchymosis and menorrhagia
- Diagnosis
    - ↑ bleeding time, aPTT ; normal platelet count; normal PT/INR
- Treatment
    - Desmopressin, which releases vWF & factor VIII from vascular endothelial cells
    - Cryoprecipitate and humate-P used to manage severe bleeding
    - Avoid anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen (Why?)
    - Prophylactic (e.g., before surgery) ? factor VIII concentrates complexed to vWF (antihemophilic factor)

3. <u>Vitamin K deficiency</u>

- Bleeding in infancy:
    - due to deficiency of vit K–dependent coagulation factors (II, VII, IX, and X)
    - occurs in approx. 1 in 10.000 babies (melena-black feces, hematuria, umbilical bleeding etc. Serious complication: intracranial hemorrhage, hypovolemic shock)
      In NA newborns are administered vitamin K injections within 6 hours of delivery!!!
- Acquired vitamin K deficiency
    - May occur with malnutrition, malabsorption, chronic hepatic disease, antibiotic therapy, oral anticoagulation therapy, older people eating little green vegetables
- Signs and symptoms
  Bleeding: mucosal, gastrointestinal, menorrhagia, hematuria, etc., fractures
- Treatment:
    - administration of Vit. K restores level in the kidney
    - with severe hemorrhage: plasma transfusion -> immediate supply of clotting factors

4. Disseminated Intravascular Coagulation (DIC) —complex; acquired thrombo-hemmorhagic disorder

- Paradox: widespread coagulation & bleeding in vascular compartments
    - Chronic form: cancer patients with malignancy
    - Acute: secondary to malignancy, sepsis, snake bite, trauma, crush injuries
- Signs & Symptoms
    - Initially bleeding predominates -> petechiae, ecchymoses on skin & mucous membrane, bleeding into orifices
    - Cold, mottled fingers and toes (due to microthrombi in toes & fingers)
    - Dyspnea, crackles, etc. (pulmonary microcirculation occlusions)
    - Possibility of acute renal failure (thrombi in renal microvasculature)
- Lab Findings
    - Dec Platelet count
    - Dec Fibrinogen concentration
    - Inc PT/INR (extrinsic pathway) and Inc aPTT(intrinsic pathway) -> prolonged
- Treatment
    - Removal/correction of underlying cause
    - Support major organs
    - Fresh frozen plasma, packed red blood cells, platelets, or cryoprecipitate
    - Heparin used to minimize further consumption of clotting factors (controversial)