ENVIRONMENTAL PATHOLOGY

1

Pathologies from physical agents

- Energy transfer:
  - Radiations
  - Electricity
  - Temperature
  - Mechanical Energy (traumas)
- Sound waves
- Atmospheric Pressure

2

Pathologies due to Transfer of electric energy

In order to assess the type of damage we consider two types of electricity:

Continue current (or direct current): constant current unidirectional and with minimal fluctuations

Alternating current: current whose polarity and intensity varies over time

In general, the direct current (DC) is less dangerous than alternating current (AC).

The biological damage varies in function of the Intensity (I) of the electrical current (measured in amps): I= (V)/(R)

Voltage (V) - measured in volts
Resistance (R) - measured in Ohms

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Effects of electrical current

•In general, the higher the voltage and amperage, the greater will be the damage determined by both types of current. The high-voltage current (> 500-1000 V) causes deep burns, while the low voltage immobilizes the subject in the electrical circuit

•DC tends to cause a convulsive contraction, which often determines the spontaneous detachment of the individual from the source of the current.

•In contrast, a 60 Hz AC (household current) causes muscle tetany, immobilizing his hands on the power source (risk of prolonged exposure).

•The maximum amperage that can cause contraction of the flexor muscles of the arm, but that still allows the person to free his hand from the power source, is defined current "let-go". For the DC value of the current "let-go" is about 75 mA, while the CA is about 15 mA

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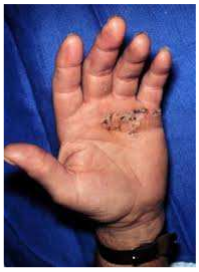
Biological damages from electric energy I

Thermical effects:

Production of heat that depends on the intensity of the current, the resistance offered by the medium and by the time required for the crossing of the tissues (burns at points of entry and exit of the current and along the route).



The resistance of the body (measured in ohm/cm2) depends on the type of tissues, and is primarily on the skin (The thickened skin has higher resistance).

At the time of the passage of current through the skin is the dispersion in the surface of a lot of energy, which produce large surface burns at points of entry and exit, (heat = ampers^2 × resistance).

Even the internal tissues are affected in relation to their resistance: nerves, blood vessels and muscles are damaged then preferentially.

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Biological damages from electric energy II

- Electrochemical effects
- Variation in the distribution of electrolytes due to the flow of electrons that constitute the electric current (necrotic lesions as from exposure to acids and bases that are formed at the poles)
- Biological effects
- Muscle contraction, nerve impulse transmission, heart rate are dependent on physiological flow of electrical current that can be altered by external source of electricity (such as ventricular fibrillation)

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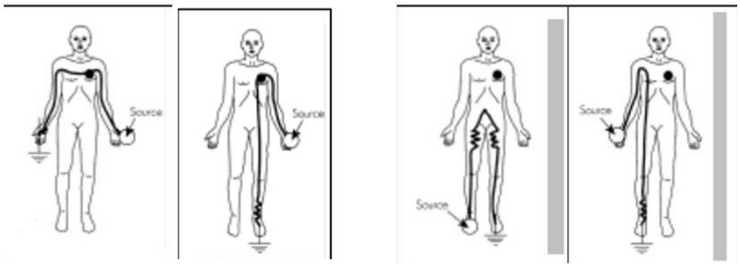
The current paths

The current path through the body determines the nature of the damage.

If the current passes through the heart, the effects are very dangerous, especially the route right arm-left arm, left-foot arm, head-feet.
A CA of 60 Hz low-voltage (110 to 220 V), which passes through the chest for a fraction of a second, can cause a ventricular fibrillation, also with amperages of just 60-100 mA;



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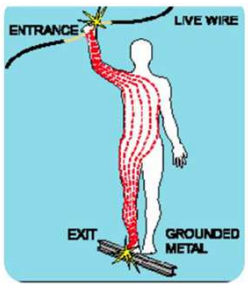
The current paths

Electrical injuries to the head can cause seizures, intraventricular hemorrhage, respiratory arrest, ventricular fibrillation or asystole and, as a delayed effect, cataracts.

Typically, the duration of the current flow through the body is directly proportional to the extent of the damage, because prolonged exposure, allowing the passage of current (and heat production) in depth, causes the destruction of internal tissues.



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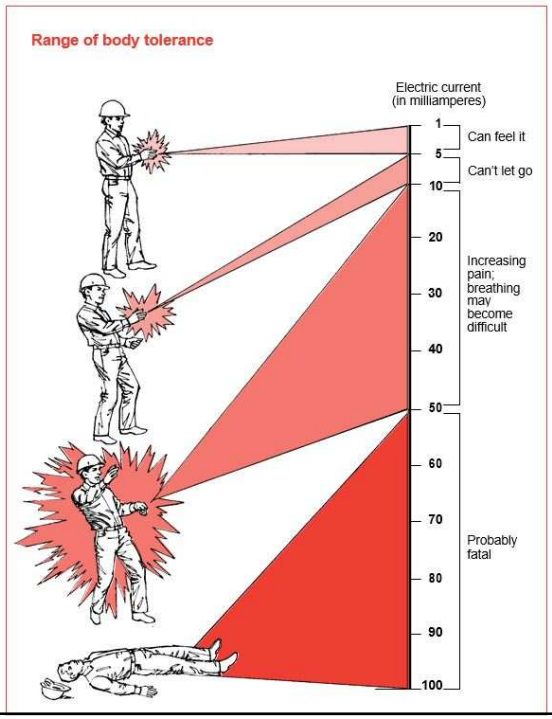

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Temperature

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Temperature

Optimal temperatures : present in the temperate zones of the planet
modest varations

Limits of tolerance to high/low temperature are quite narrow and depends on:
-Type of clothing
- heating capabilities
- Proper energy feeding
- Capacity for acclimatization

Body temperature is controlled by the "Centre for thermoregulation" present in the hypothalamus (pre-optic area)
-heat-dissipation: vasodilatation, sweating, run

-heat-production: muscle contration, cell metabolism, vasoconstriction, shivering

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Thermoregulation

The maintenance of a particular temperature in a living body.

Core temperature (T_{CO}) is in dynamic equilibrium as a result of balance between heat gain and heat loss.

Mean body temperature (T_{body}) represents an average of

skin and internal temperatures.

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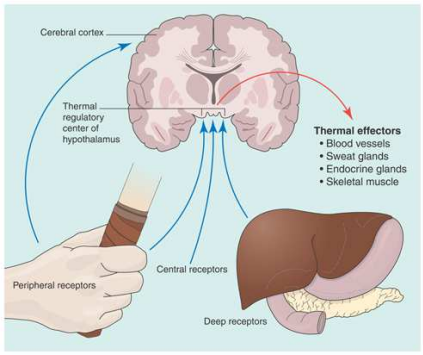
Hypothalamus: Regulation of Temperature



- Mechanisms are activated in two ways:
  - Thermal receptors in skin provide input to central command
  - Direct stimulation of hypothalamus through changes in blood temperature perfusing area

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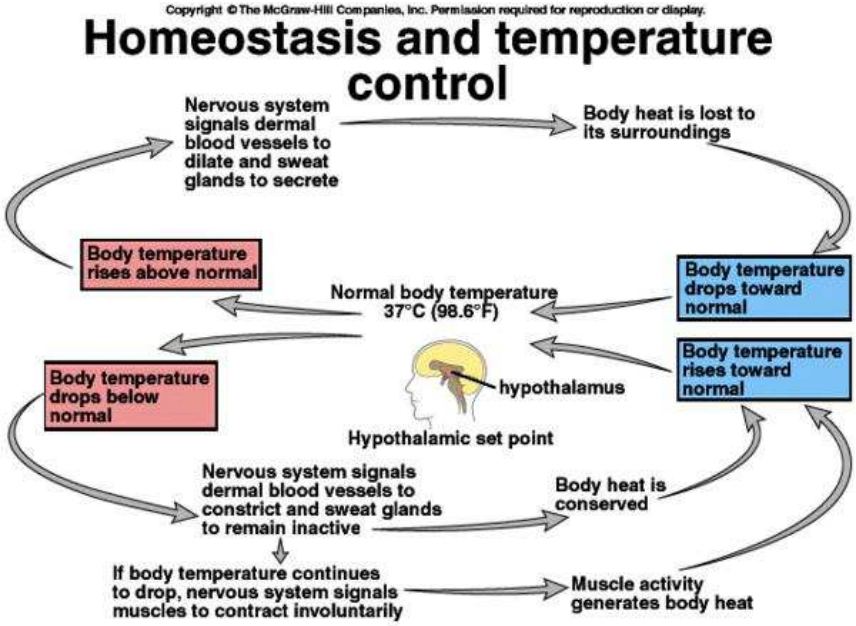

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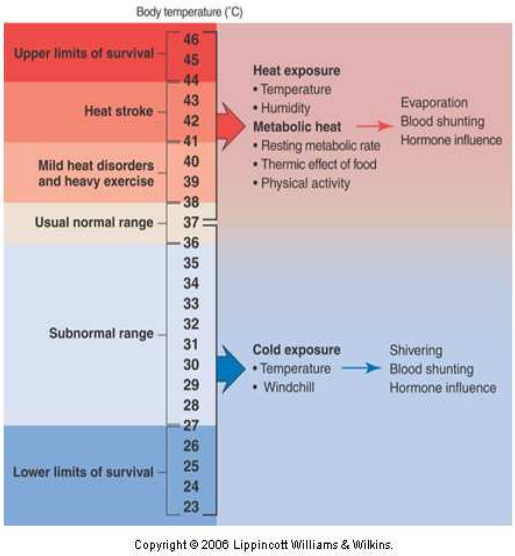
Hypothalamus: Regulation of Temperature

- Hypothalamus acts as "thermostat" that makes thermoregulatory adjustments to deviations from temperature norm in the brain (37°C ± 1° C or 98.6°±1.8° F).



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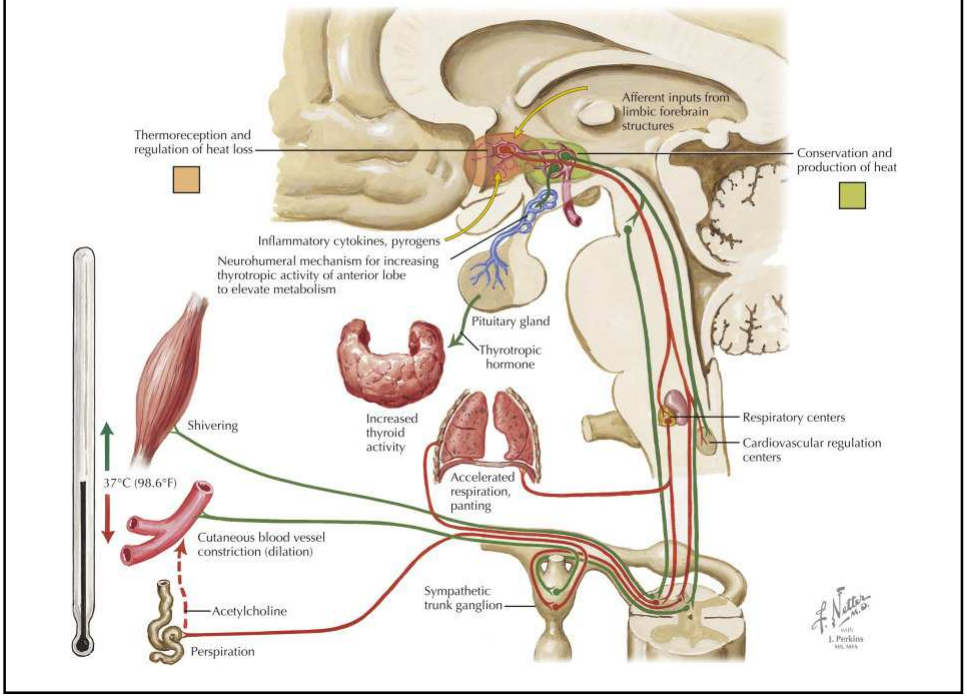

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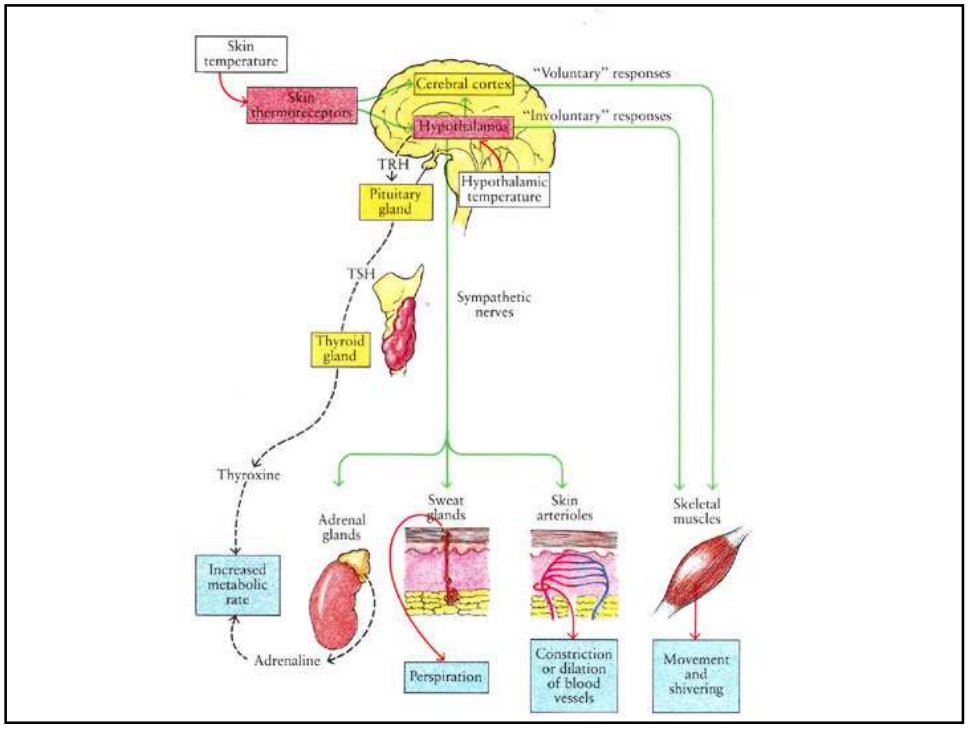

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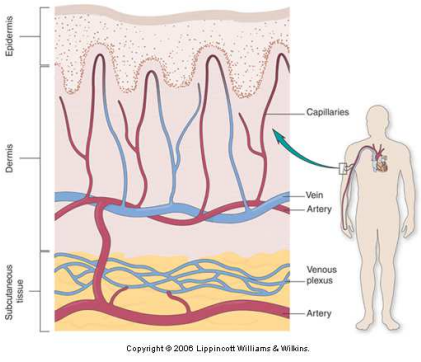
Integration of Heat-Dissipating Mechanisms



- Circulation. Superficial venous and arterial blood vessels dilate to divert warm blood to the body shell.

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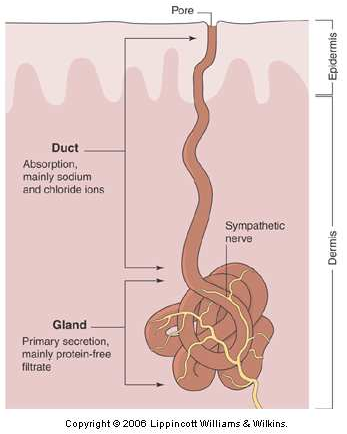
Integration of Heat-Dissipating Mechanisms

- Evaporation. Sweating begins within 1.5 s after start of vigorous exercise.
- Hormonal adjustments. Certain hormonal adjustments are initiated in heat stress as body attempts to conserve fluids and sodium.



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Hormones in Heat Stress

- Antidiuretic hormone (ADH) is released to increase water re-absorption from kidneys.
- Aldosterone is released to increase the re-absorption of sodium.

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Effects of Temperature variations

Exceeding the limits of tolerance of the optimal temperature has different effects depending on:

- The magnitude of the temperature difference
- Extension of the exposed surface
- Duration of exposure
- Type of tissue exposed
- Amount 'of moisture' in the environment

The consequences are hyperthermia or hypothermia, which may be local or systemic. They lead to alterations in cellular metabolism up to the death of cells and tissues

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Heat Illness

Table 1 Heat Illness: Causes, Signs and Symptoms, and Prevention

CONDITION	CAUSES	SIGNS AND SYMPTOMS	PREVENTION
Heat Cramps	Intense, prolonged exercise in the heat	Tightening, cramps, involuntary spasms of active muscles; low serum Na^+	Cease exercise; rehydrate
Heat Syncope	Peripheal vasodilatation and pooling of venous blood; hypotension; hypohydration	Lightheadedness; syncope, mostly in upright position during rest or exercise; pallor; high rectal temperature	Ensure acclimatization and fluid replenishment; reduce exertion on hot days; avoid standing
Heat Exhaustion	Cumulative negative water balance	Exhaustion; hypohydration, flushed skin; reduced sweating in extreme dehydration syncope, high rectal temperature	Proper hydration before exercise and adequate replenishment during exercise; ensure acclimatization
Heat Stroke	Extreme hyperthermia leads to thermoregulatory failure; aggravated by dehydration	Acute medical emergency; includes hyperpyrexia (rectal temperature >41°C, 105.8°F); lack of sweating and neurologic deficit (disorientation, twitching, seizures, coma)	Ensure acclimatization; identify and exclude individuals at risk; adapt activities to climatic constraints

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SYSTEMIC HYPERTHERMIA

Consequences: sympathetic excitations and increase:

- superficial blood flow velocity;
- Sweating and subsequent evaporation;
- Cutaneous vasodilatation.

HEAT STROKE

Heat stroke occurs when thermoregulation is overwhelmed by a combination of excessive metabolic production of heat (exertion), excessive environmental heat, and insufficient or impaired heat loss, resulting in an abnormally high body temperature. In severe cases, temperatures can exceed 40 °C. Heat stroke may be non-exertional (classic) or exertional. Significant physical exertion in hot conditions can generate heat beyond the ability to cool, because, in addition to the heat, humidity of the environment may reduce the efficiency of the body's normal cooling mechanisms.
Heat stroke presents also sun burns of the I and II levels.
Features of the Heat stroke are headache- psychic disturbances- sometime death.

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Local Hyperthermia: BURNS

They occur when the temperature of the area exceeds 40-45 ° C

The type of response of a tissue at high temperatures depends on the intensity of the heat and the time of exposure as well as the extent and depth of the lesion.
the skin lesions are divided into categories according to severity:

	depth	Main Effects	Outcome
Grade I	Epidermis	Vasodilatation	Erythema, mild swelling
Grade II	Dermis; Papillary region	Inflammation	Blisters, pain, severe swelling
Grade III	Dermis; reticular region	Necrosis	Eschar, white, leathery, relatively painless
Grade IV	Hypodermis, (subcutaneous tissues)	Combustion	Charred, tissue carbonization

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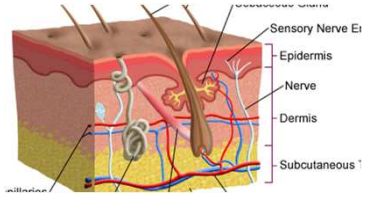
first-degree burns : Superficial, affect only the epidermis.
Mild sunburn is an example
The burn site is red (erythema), swelled (oedema), painful, dry, and with no blisters..
There is a mild inflammatory process.
Long-term tissue damage is rare and usually consists of an increase or decrease in the skin color.

Second-degree burns (also known as partial thickness burns) involve the epidermis and part of the dermis layer of skin.
The burn site appears red, blistered, and may be swollen and painful.

Increase of the vascular permeability, with plasma that accumulates between epidermis and dermis

Healing may require several days.
Complicances: secondary infection



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A third-degree burn is referred to as a full thickness burn. This type of burn destroys the outer layer of skin (epidermis) and the entire layer beneath (the dermis).
-Necrosis
-Because the epidermis and hair follicles are destroyed, new skin will not grow. Necrotic areas may be replaced by scars.

If more than one-third of the body surface is burned (III) the general disorders which result can induce DEATH
Symptoms: Primary-Shock: acute heart failure / cardiac arrest
high-hyperthermia
-serious state of nervous excitement (delirium and anxiety)
-Hypovolemia and hemoconcentration (the skin surface is no longer protected from the epithelium, and exudes plasma)
- hemolysis, anemia
- Coma

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Systemic Hypotermia

Temperatures between 4 ° C and 10 ° C causes:
-increased peripheral vasoconstriction, cell metabolism and shivering

-Hyperventilation - decrease in arterial concentration of CO2
- secondary constriction of the cerebral vasculature
MENTAL CONFUSION

-An increased vagal stimulation leads to premature ventricular contractions - ventricular arhythmia – fibrillation;

frostbite: Suppression of thermo-regulatory activity
– reduced metabolic reactions
– reduced motor activity
– drowsiness - DEATH
- reduced body's defenses against infection
The main factor responsible for the death is cardiac arrest

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LOCALIZED HYPOTHERMIA: frostbites

Prolonged exposition to low temperatures: FREEZING, cristallizzation of water in the tissues

Local vasoconstriction: if the circulation does not compensate for the loss of heat, water tissues crystallizes

Slow freezing: inside the cells and in the interstitial spaces ice crystals are formed. Ionic changes cause damage to organelles (mitochondria, ER, microsomes).

Quick freezing: No ice crystals form but a gel-like structure. The most serious damage occurs during thawing due to mechanical failure of the membranes. Vascular endothelium: alteration of the permeability, edema and inflammation.

Cellular damage at the level of endothelial cells of capillaries and venules determines alteration of the circulation with persistent arterial spasm, ischemia and tissue necrosis due to insufficient supply of oxygen.

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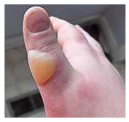
First grade frostbites: - Local ischemia (white skin due to vasoconstriction)
- vasoparalitic phenomena ⇒ redness
- EDEMA (passive hyperemia)
- conglutinate red blood cells⇒ slowing down of circulation
- CYANOSIS



II grade frostbite : - BLISTERS

III grade frostbite : - Necrosis of the cutanoues layers, going deep to muscle tissue and bones

IV grade frostbite - WET GANGRENE presence of pathogens in the necrotic area, with colliquation and loss of tissue in the area

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Injury by physical agents
Mechanical energy transfer: trauma

We recognize deep and superficial trauma

Superficial traumas:

- abrasion - scraping or rubbing - removal of superficial layer
- contusion - blunt injury, extravasations of blood into tissues - hematoma
- laceration - disruptive stretching of tissue - jagged, irregular edges
- incised wound - by sharp instrument
- puncture wound - long narrow instrument - penetrating (in) or perforating (in+out)

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Deep traumas

Involving soft tissues:

- Rupture: hollow organs, large vessels
- Volvulus: twisted organ (rotation)

Pneumo-thorax-pericardium, peritoneum-: injury with penetration of air into the cavity 'pleura, pericardium or peritoneum. (There are also the Haemopericardium and Haemoperitoneum, with collection of blood).
Concussion or visceral trauma: involvement of brain or abdominal organs without breaking

Trauma of the skeletal system:

- Contusion: compression of skeletal segment
- Dislocation: dislocation of bone from the joint
- Distortion: laceration of articulation
- Fracture: loss of bone continuity

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Pressure

Altitude sickness (mountain sickness)

Syndromes due to a deficiency of O2 at high altitudes.

Atmospheric pressure decreases with increasing altitude , while the percentage of O2 in the atmosphere remains constant , it follows that the partial pressure of O2 decreases at high altitudes and at 5500 m is about half of that which is found at sea level .

The higher the altitude, the longer it takes to get full acclimatization .

Most people acclimatize to altitudes up to 3000 m in a few days . Above 5100 mt, no one is able to live for a long time .

The acclimatization consists of a complex series of responses that gradually restore tissue oxygenation to normal. The signs of acclimatization include hyperventilation, alkalosis with persistent partially offset , initial increase in cardiac output , increased erythrocyte mass and anaerobic exercise tolerance .

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DIVE INJURY OR WORK IN COMPRESSED AIR

The deep divers may face problems arising from the high pressures they are subjected , similarly to workers who work in pressurized Local differences in pressure (" barotrauma "): with increasing external pressure on the body to greater depths, there is a parallel increase of the gas pressure in the lungs and airways.

The expansion of pulmonary gas during the emergence may result in complications that threaten the life of the sub. If a diver inhales even a single breath of air or other gas in depth and not the exhale freely during the emersion , the expanding gas can overextend the lungs.

The consequences can be pneumothorax , subcutaneous and mediastinal emphysema and air embolism to arterial level , the latter is a situation of extreme emergency and is the leading cause of death among divers.

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Chemical agents

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Chemical agents: Environmental pollution

- Air pollution
- smog (smoke+fog)
- 2 types - reducing smog - coal combustion - sulfur oxides+particulates - Europe, NE USA
- - photochemical oxidant smog - incompletely burned hydrocarbons - CO, CO_2, NO_X+sunlight - ozone, free radicals - LA, CA USA
- acute or chronic inflammation, emphysema, asthma, pneumoconiosis, tumors

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Factors:

- Dose
- Duration of the stimulus/contact
- Metabolic conversion
- Entry site, accumulation, excretion
- Individual variation
- Immunogenicity

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Tobacco smoke

- 1979 - U.S. Surgeon General: tobacco smoking is the single most common cause of preventable mortality
- PREVENTION!
- US smokers:
- | | males | females |
- 1970 | 52% | 41%
- 1992 | 29% | 27%
- 2000 | <20% estd.

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Tobacco smoke

An important risk factor for diseases of the lung, mouth, larynx, esophagus, heart, stomach, pancreas, bladder

Synergistic action with other types of environmental exposure

Corpusculate phase:	tars
Nicotine:	Causes addiction
Gas phase:	Carbon monoxide: decrease in oxygenation to the tissues

increased heart rate, blood pressure, coronary arterial flow, contractility and cardiac output

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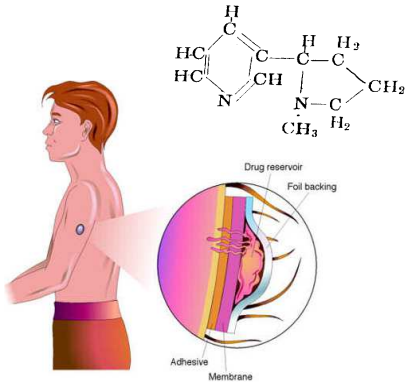
Nicotine: Pharmacocinetics



- Absorbed quickly by:
  - Lungs (smoked)
  - Mucose (cigar, chewing tobacco, gum, nasal spray)
  - Skin (patch)
  - Gastrointestinal tract (uncommon)

Nicotine taken in by cigarette or cigar smoking takes only 10-15 seconds to reach the brain but has a direct effect on the body for relatively short time

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Pharmacocinetics

- Nicotine in smoke peaks in brain very rapidly, despite relatively slow increase in blood concentration
- A typical cigarette contains 20 mg of nicotine
- ~2.5 mg of nicotine is absorbed
- Half-life: ~ 2 hours
- 80-90% metabolized in liver

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Pharmacocinetics

- Metabolism & Elimination
  - About 80 percent of nicotine is broken down to cotinine by enzymes in liver (e.g., CYP2A6)
  - Nicotine is also metabolized in your lungs to cotinine and nicotine-N-oxide
  - Cotinine and the remaining nicotine is filtered from the blood by kidneys and excreted in the urine

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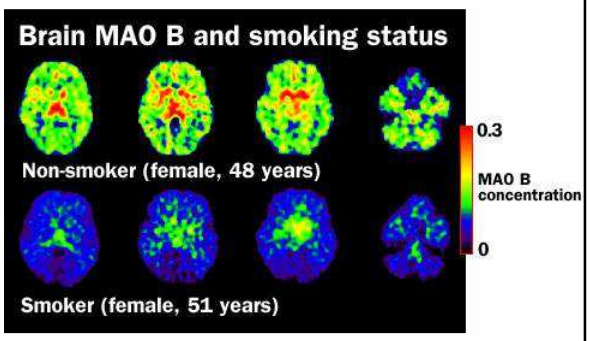
MonoAmine Oxidase levels

Components of cigarette smoke reduce the breakdown of MonoAmine Oxidase and thereby increase the level of dopamine in the brain.



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Smoke and MAOs

- MAOs are essential for the inactivation of monoamine neurotransmitters:

- Serotonin, melatonin, norepinephrine, and epinephrine are mainly broken down by MAO-A.
- Phenethylamine and benzylamine are mainly broken down by MAO-B.
- Both forms break down dopamine, tyramine, and tryptamine equally.

Monoamine oxidase inhibitors are one of the major classes of drug prescribed for the treatment of depression

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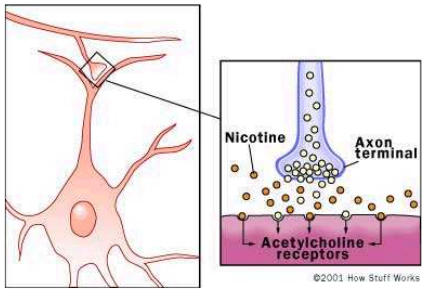
Pharmacodynamics

- Nicotine is a direct agonist for nicotinic Ach (acetylcholine) receptors

- Nicotine initially causes a rapid release of adrenaline, the "fight-or-flight" hormone



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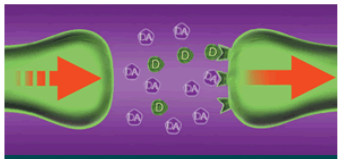
Pharmacodynamics

- nAChRs found in limbic system (e.g. striatum, hippocampus, accumbens), midbrain (e.g. VTA, substantia nigra), various cortical areas (frontal lobe)
- nAChRs both postsynaptic and presynaptic, facilitating ACh, DA, 5-HT and Glu action
- Nicotine also increases release of various neurohormones
- Has powerful effects on peripheral nervous system, heart, and other organs



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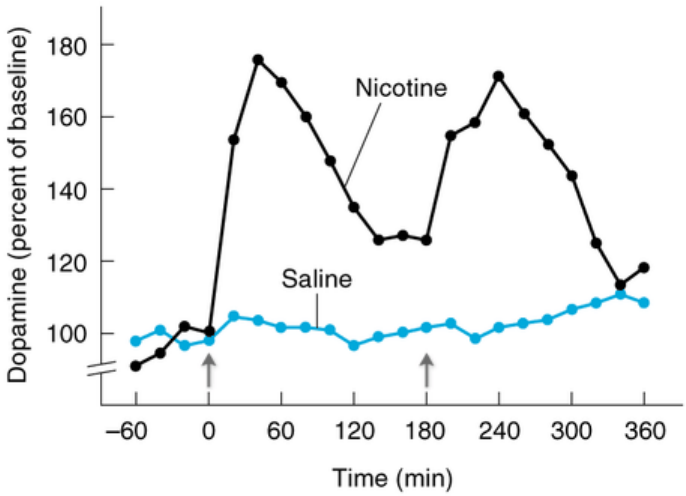
► **Changes in Dopamine Concentration in the Nucleus Accumbens**



Source: Adapted from Damsma, G., Day, J., and Fibiger, H.C. *European Journal of Pharmacology*, 1989, *168*, 363–368.

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Acute Effects of tabacco Smoke

- Classic stimulant effects of arousal (e.g. increased heart rate and blood pressure, alertness, appetite suppression)
- Carbon monoxide (in smoked form) reduces oxygen transport to heart and other organs
- Vasoconstriction
- Can have calming (anxiolytic) effects in some individuals
- Mild euphoria (relief?)
- Cognitive enhancements
- Antidepressant effects

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- morbidity and mortality in smokers is linearly related to the number of cigarettes

- passive smoking! - smoke inhaled by nonsmoking bystanders - even more dangerous (lower temp. of burning -> higher content of noxious chemicals)

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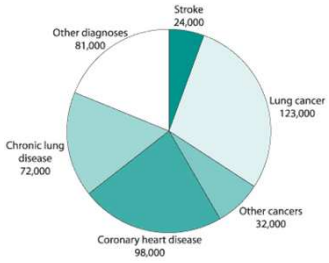
Chronic Effects: CANCER

- Tobacco use accounts for one-third of all cancers
  - **Cancers** relating to tobacco include:
    - Mouth
    - Pharynx
    - Larynx
    - Esophagus
    - Stomach
    - Lung
    - Cervix
    - Kidney
    - Bladder
    - Throat
    - Pancreas



- Cigarette smoking has been linked to about 90 percent of all lung cancer cases
- 430,000 annual deaths are attributed to cigarette smoking

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Results

- malignant tumors generally - mortality 2-4x increased in smokers
- major diseases: lung ca, chronic bronchopulmonary disease, systemic AS (namely lower extremities)
- minor diseases: laryngeal ca, esophageal ca, MI, peptic ulcer, renal ca, pancreatic ca, urinary bladder ca, lip ca, oral cavity and pharyngeal ca
- smokers have 10x higher probability of having lung ca than nonsmokers
- risk of lung ca is 3x higher in 40 cigarettes/Day than in 10 c/D

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More Chronic Effects

- Emphysema
- Chronic bronchitis
- Stroke
- Vascular disease
- Aneurysm
- Esophageal reflux
- Heart Disease
  - It is estimated that nearly one-fifth of deaths from heart disease are attributable to smoking

* Many of these are actually caused by other chemicals in cigarette smoke or in smokeless tobacco products

- **Secondary smoke** also increases the risk for many diseases
  - Secondhand smoke is estimated to cause approximately 3,000 lung cancer deaths per year among nonsmokers and contributes to as many as 40,000 deaths related to cardiovascular disease
  - Exposure to tobacco smoke in the home increases the severity of asthma for children and is a risk factor for new cases of childhood asthma
  - Environmental tobacco smoke (ETS) exposure has been linked also with sudden infant death syndrome

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- smoking in pregnancy - impact on fetus - lower weight at birth, higher perinatal mortality
- cessation of smoking - during 1Y - decrease of frequency of MI, after 2Y - same frequency as nonsmokers! - it is never too late
- "cigarettes = coffin nails"

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Addiction

- Nicotine meets both the psychological and physiological measures of addiction
  - **Psychological** - People who are addicted to something will use it compulsively, without regard for its negative effects on their health or their life
  - **Physiological** - anything that turns on the reward pathway in the brain is addictive. Because stimulating this neural circuitry makes you feel so good, you will continue to do it again and again to get those feelings back

Recent studies suggest those excitatory amino acid systems and, in particular, *N-methyl-D-aspartate (NMDA) receptors, may have an important role in this phenomenon.*

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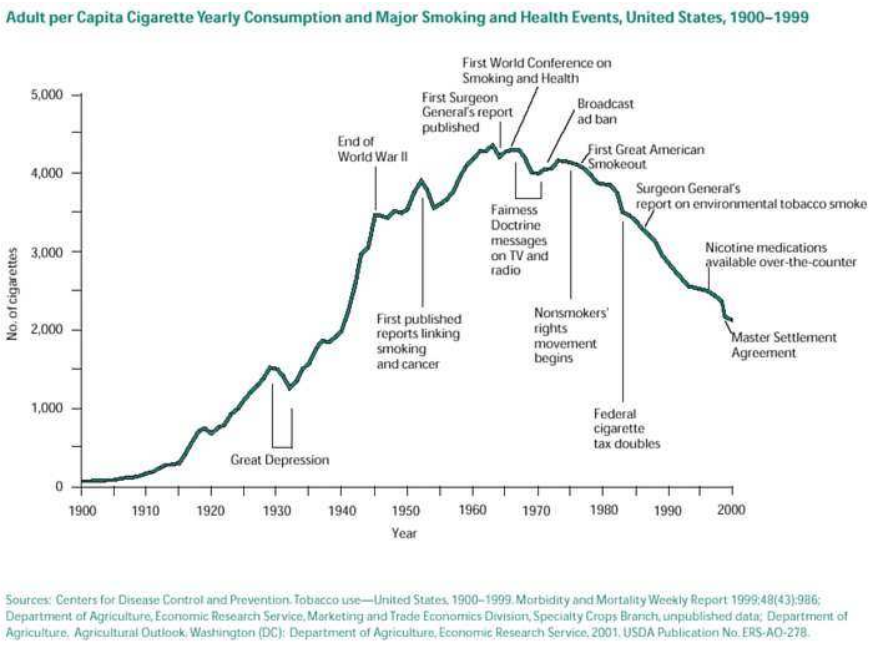

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Pneumoconioses

- non-neoplastic lung reaction to inhalation of mineral, other inorganic and organic dusts
- 4 major - coal dust, silica, asbestos, beryllium - nearly always professional

Factors:

- concentration
- size and shape of particles (1-5µm)
- chemical character of dust
- concurrent smoking

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Coal workers' pneumoconiosis

- spectrum of findings in coal workers
- - asymptomatic anthracosis
- - simple coal workers' pneumoconiosis (little pulmonary dysfunction) - slight fibrosis, non-progressive
- - progressive massive fibrosis (lung function compromised) - fibrous nodules (up to 2 cm) - sometimes coalesce - "black lung", central necrosis
- clinically - breathlessness, cough
- <10% of CWP progress to PMF
- sometimes associated with rheumatoid arthritis - Caplan's syndrome (rapidly developing nodular pulmonary lesions)

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Silicosis

- inhalation of crystalline silica
- crystalline forms (quartz, crystobalite, tridymite)
- most prevalent chronic occupational disease in the world
- very heavy exposure - acute silicosis (generalized accumulation of lipoproteinaceous material within alveoli)
- decades of exposure - coal mining, stone cutting, foundry work, ceramics, sandblasting
- in high risk professions - after 30Y - 10-15% are afflicted
- complicated by TBC, Caplan's syndrome
- pulmonary hypertension, cor pulmonale chronicum
- not increased risk of malignancy (x asbestosis!)

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Silicosis - Morphology

- parenchymal nodules (several mm) - white to black
- central fibrosis with hyalinization, periphery - fibroblasts and macrophages
- polarized light - birefringent silica particles
- coalescence - large fibrous nodes
- emphysema of remaining parenchyma - honeycomb pattern
- similar lesions also in regional LN
- eggshell calcifications in LN

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Asbestosis

asbestos=family of crystalline hydrated silicates with a fibrous geometry

long term inhalation of asbestos dust

- 1. chronic fibrosing interstitial pneumoconiosis
- 2. bronchogenic cancer
- 3. pleural effusions
- 4. fibrous plaques or diffuse pleural fibrosis
- 5. mesothelioma
- 6. other non-pulmonary neoplasms (laryngeal ca, colon ca)

slow development - decades after termination of exposition

dependent on dose and duration of exposure (10-20Y - 10%; >40Y - >50%)

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two types of asbestos

- 1. serpentine (curly fibers) - chrysotile - more frequent
- 2. amphibole (straight, stiff fibers) - more pathogenic
- asbestos fibers are coated (impregnated) by organic material containing hemosiderin (Fe+) - asbestos bodies - golden brown fusiform rods with a translucent center
- in smokers - adsorption of carcinogens from tobacco smoke on the surface

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features

- chronic interstitial lung fibrosis, namely in lower lobes - chronic cor pulmonale
- pleural fibrous plaques - hyalinized collagen - frequently on the diaphragm
- tumors - bronchogenic ca - 5x higher incidence (in smokers 50x) - more often adenoca
- - malignant mesothelioma - in 2-3% of persons with long-term exposure (20-50Y)
- Clinically - dyspnea, cough

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Berylliosis

- inhalation of dusts or vapors of Be or its oxides (electronics, nuclear industry)
- massive dose - acute pneumonitis
- protracted exposure - pulmonary and systemic granulomatous disease closely mimicking sarcoidosis
- progressive course with fatal outcome; in some patients remission and spontaneous disappearance

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Injury by chemical agents

- endless list..
- therapeutic agents, nontherapeutic agents
- inhalation, ingestion, injection, skin absorption
- accident or intention
- dose
- requirement for metabolic conversion (directly toxic vs. converted compounds)
- site of absorption, accumulation or excretion
- individual variation (tolerance, enzymatic defects)
- capacity to induce immune reaction (penicillin)

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Injury by therapeutic agents

- adverse drug reactions - extremely common in practice of medicine
- most frequently antibiotics, antineoplastic agents, immunosuppressive drugs
- adverse reaction
- - predictable (dose-dependent) – e.g. digitalis, streptomycin, cytostatics, sedatives
- - unpredictable - idiosyncrasy – e.g. massive necrosis of the liver after paracetamol

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Examples

- agranulocytosis, pancytopenia (chloramphenicol, quinine, antituberculotics)
- urticaria, expholiative dermatitis (ATB, barbiturates)
- acute tubular necrosis, necrosis of papillae, renal vasculitis (phenacetine, sulphonamides, analgetics)
- lung edema, fibrosis (bleomycine, busulphan)
- liver steatosis, cholestasis, necrosis of hepatocytes (tetracycline, estrogens, halothan, chlorpromazine)
- cardiomyopathy (anthracyclines - adriamycin)

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Analgetics

- aspirin (acetylsalicylic acid)
- - overdose - intoxication - respiratory alkalosis, metabolic acidosis, Reye syndrome (?)
- - chronic toxicity - erosive gastritis, ulcers
- phenacetine - kidney damage (necrotizing papillitis, chronic interstitial nonbacterial nephritis) - phenacetine kidney
- acetaminophen - very large doses - hepatotoxicity

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Hypnotics (barbiturates)

- 70% of drug suicides, often accidents (M.Monroe, E. Presley)
- (USA - 3 major causes of unnatural death - car accidents, alcohol, barbiturates)
- combination with alcohol - decreased self-control -> increased consummation ->intoxication (depression of stem centers, respiratory arrest) - the toxic dose is highly individual
- chronic abuse in combination with alcohol - impairment of liver functions - decreased degradation

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Injury by nontherapeutic toxic agents

Lead

- acute poisoning - colicky abdominal pain, fatigue, headache, encephalopathic crisis
- chronic (professional) exposure - defect of Hb synthesis - anemia, neurological disorders

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Carbon monoxide (CO)

- nonirritating, colorless, tasteless, odorless gas
- product of imperfect oxidation
- affinity of CO to Hb is 200x higher, than that of O_2 - carboxyhemoglobin - systemic hypoxia
- acute intoxication - cherry red skin, liquid blood (no post-mortal coagulation)

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Nutritional diseases

- 1/4 of world population suffers from undernourishment, 1/4 eats too much
- western countries - high energy diet, too much fat and sugar, few fibers - related to diseases
- developed countries - pediatric mortality - 10/1000 live newborns
- underdeveloped c. - >200/1000

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Malnutrition

- not only in 3rd world countries! - even developed ones - poor social classes (namely children), homeless persons, lonely aged people, chronic alcoholics, patients with psychiatric disorders (anorexia nervosa, bulimia nervosa)
- primary (shortage of nutrition)
- secondary (metabolic disorders, increased requirements - growth, pregnancy, increased losses (chronic diseases)

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Protein-energy malnutrition

- most frequent and most important
- dimension of epidemy (Africa - Ethiopia - up to 25% of children; 50% of all deaths are children <5Y)
- range of clinical syndromes, 2 main forms - marasmus & kwashiorkor

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Marasmus

- deficiency of energy (calories) - due to starving – growth retardation - arrest, loss of muscle mass, serum albumin is normal, subcutaneous fat is used as a fuel - extremities are emaciated
- anemia, immune deficiency (namely cellular immunity)

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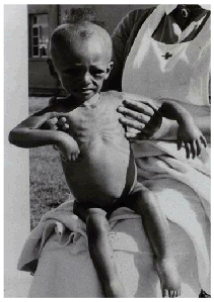
Kwashiorkor (1st son-2nd son)



- deficiency of proteins, mainly animal
- most common in Africa - children, who have been weaned too early (arrival of another child) and fed by exclusively carbohydrate diet
- kwashiorkor is more severe than marasmus - loss of visceral proteins - hypoalbuminemia - generalized edema, ascites
- skin lesions, hair changes, fatty liver, defects of immunity, secondary infections, anemia

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Vitamin deficiencies

- Healthy individuals need 45-50 compounds (9 aminoacids, 2 fatty acids, several trace elements and 13 vitamins)
- vitamin deficiency - primary (diet) or secondary (malabsorption, metabolic disorders, liver diseases)
- oversupply can be harmful as well !!!

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VITAMINS DEFICIT/EXCESS

Causes:
Deficit/excess in the diet
Defects in intestinal absorption caused by enteric diseases
Synthesis Defects

Vitamins can be subdivided in fat soluble (A, D, E e K), that can be accumulated in the adipous tissues of the organism

or water soluble (gruppo B e la vitamina C), which cannot be stored and need to be replaced frequently trough food intake

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Vitamin Deficiency

Vitamin	Function	Deficiency State
A	Vision Immune system Epithelium	Diet, malabsorption Night blindness, xerophthalmia, keratomalacia, immune deficiency
D	Blood calcium and phosphate	Diet, malabsorption, inadequate sun, liver and renal disease Rickets, osteomalacia

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Vitamin Deficiency

Vitamin	Function	Deficiency State
E tocopherols	Antioxidant Free radical scavenger	Diet, malabsorption Neuromuscular deficits
K	Clotting factors II, VII, IX, X	Malabsorption, loss of gut flora, Coumadin therapy bleeding

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Vitamin Deficiency

Vitamin	Function	Deficiency State
Thiamine (B1) TPP	Enzyme co-factor, nerve conduction	Diet, EtOH Polyneuropathy, cardiomyopathy, Wernicke-Korsakoff
Riboflavine (B2) FMN, FAD	Enzyme co-factor	Diet, EtOH Cheilosis, glossitis, dermatitis (atrophy)
Niacin NAD, NADP	Enzyme co-factor	Diet, EtOH Pellagra, dermitis, diarrhaea, dementia

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Vitamin Deficiency

Vitamin	Function	Deficiency State
Pyridoxine (B6)	Enzyme co-factor	Drugs (INH), EtOH Similar to riboflavin and niacin deficiency
C	Hydroxyl-ation of proteins Antioxidant	Diet, EtOH Scurvey, weak connective tissue Bleeding, fractures, gingival swelling, peridontal disease, poor wound healing

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Vitamin A

- retinol and related substances
- important for vision (visual pigment) and differentiation of some types of epithelial cells (mucus-secreting)
- main sources: liver, fish, milk, eggs, butter
- provitamins - carotenoids - vegetable sources (carrots, spinach)
- in 3rd world is hypovit. A frequent cause of blindness

changes:

- impaired vision in reduced light
- squamous metaplasia
- decreased resistance to infections

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Deficiency state

- Eyes - xerophtalmia, small corneal opaque (squamous keratinizing) plaques (*Bitot's spots*), keratomalacia -> total blindness
- Respiratory tract - squamous metaplasia, pulmonary infections
- Urinary tract - pelvic keratinization -> stones
- Skin - hyperkeratosis

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Vitamin D

- maintenance of normal plasma Ca+ and P levels, important for normal development and mineralization of bones

two sources:

- endogenous synthesis in the skin (UV light) from 7-dehydrocholesterol - 80% of needed amount
- exogenous - dietary sources (deep-sea fish, plants, grains)

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Causes of Vit D hypovitaminosis

- decreased endogenous synthesis (inadequate exposure to sunlight)
- decreased absorption (dietary lack, malabsorption syndrome)
- enhanced degradation (drugs)
- impaired synthesis of metabolites (liver diseases, renal disorders)
- target resistance (congenital lack of receptors)
- phosphate depletion (renal tubular disorders, long-term use of antacids)

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Vitamin A Deficiency state

- children - before closing of epiphyses - rickets (rachitic rosary, pigeon breast deformity, lumbar lordosis, bowing of the legs)
- adults - after closing of epiphyses - osteomalacia (impaired remodelation of bone mass, no mineralization of osteoid - microfractures (vertebral bodies, femoral necks)
- Hypervitaminosis D - hypercalcaemia - metastatic calcification, urolithiasis

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Vitamin K

- required cofactor for synthesis of clotting factors VII, IX, X

Causes of hypovitaminosis:

- fat malabsorption syndromes
- destruction of endogenous vit. K synthesizing flora (broad spectrum ATB)
- neonatal period (low reserve, no bacterial flora)
- diffuse liver disease
- iatrogenic decrease (warfarin)

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Vitamin K Deficiency state

- bleeding diathesis (e.g. hemorrhagic disease of the newborn - intracranial bleeding, any site - skin, umbilicus, viscera)
- adults - hematomas, hematuria, melena, ecchymoses, bleeding from the gums

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Vitamins B

- coenzymes
- major source - grains, rice, vegetables, fish, meat, yeast, seed oils
- in deficiency - involved mainly highly metabolic active tissues with short cell-turnover period (skin, oral mucosa, stomach, bone marrow, neural system)

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Vitamin B1 (thiamine)

- widely available in the diet - nonpolished rice, grains
- avitaminosis in 3rd world - in severe malnutrition
- avitaminosis in developed countries - in chronic alcoholics (25%!) (malnutrition, decreased absorption from the gut)
- affected peripheral nerves, heart, brain
- dry beri-beri (polyneuropathy) - degeneration of myelin sheaths and axons (motoric, sensoric and vegetative)
- wet beri-beri (cardiovascular syndrome) - dilatation, right heart failure, peripheral edema
- Wernicke-Korsakoff syndrome - ophthalmoplegia, nystagmus, ataxia of gait and stance, confusion, apathy, amnesia, psychosis

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Vitamin B2 (riboflavin)

- avitaminosis associated with changes at the angles of the mouth (cheilosis or cheilitis), glossitis, ocular (keratitis) and skin changes (nasolabial dermatitis), bone marrow (erythroid hypoplasia - anemia)

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Niacin (nicotinic acid)

Deficiency state:

- pellagra (rough skin) - 3 Ds
- dermatitis - neck - chronic inflamm., fissures, depigmentation, hyperpigmentation
- diarrhea - atrophy of columnar epithelium of GIT mucosa, inflammation and subsequent ulceration
- dementia - degeneration of the neurons of the brain

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Vitamin B12 (cyanocobalamine)

- deficiency in strict vegetarians or in chronic atrophic gastritis - pernicious anemia (lack of synthesis of intrinsic factor in gastric mucosa due to autoimmune inflammation with severe destruction of corporal glands)
- in deficiency - megaloblastic anemia (decreased number of RBC, increased size; hypersegmentation of neutrophilic leucocytes) and demyelinization of spinal cord and peripheral nerves = neuroanemic syndrome

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Vitamin C (ascorbic acid)

- fruits and vegetables - not synthesized endogenously
- involved in metabolism of collagen and basic intercellular matrix - involvement of vessel walls - increased fragility - bleeding
- deficiency in adults - scurvy
- deficiency in children - Möller-Barlow disease - subperiostal hematomas

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Scurvy

- sailors, travelers, today elderly persons, homeless people, etc.
- petechial skin bleeding, ecchymoses, epistaxis, melena, intraarticular bleeding
- gingival swelling, hemorrhages, secondary bacterial infection - periodontitis
- hyperkeratotic papular rash
- impaired wound healing, defective osteoid - pathologic fractures
- anemia

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Hypervitaminosis C

- mega doses of vit. C (several grams/day) - no effect in prevention or in treatment
- excretion into urine - urolithiasis
- hyperacidity in stomach - mucosal erosions

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Trace elements

- 14 anorganic elements - Fe, Cu, Co, I, Zn, Se, Mn, Mo, Cr, F, Si, Ni, Sn (tin), Va
- activity in enzymes
- primary deficiency - only I (thyroid gland - goiter)
- secondary deficiency:
- Zn - skin lesions, neurological and psychiatric syndromes, growth retardation, hypogonadism in males
- Cu - anemia, impaired synthesis of connective tissue matrix
- Se - China - Keshan disease - dilated cardiomyopathy

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Obesity

- epidemy in the USA, frequent in many western countries
- 20% of world population
- disorder of energetic balance - food derived energy chronically exceeds energy expenditure, excess calories are stored as fat
- some genetic predispositions (multifactorial disease)

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Obesity: consequences

- hypertension - 3x more frequent (in young adults 20-44Y - 6x!!!)
- DM type II. - 3x more frequent
- hypercholesterolemia - AS - MI
- more frequent malignant tumors - colon ca, breast ca, gallbladder ca, endometrial ca
- respiratory insuficiency in chronic bronchitis - *Pickwick syndrome* - pulmonary hypertension - cor pulmonale
- cholelithiasis (gallstones) - 6x more frequent + ca

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Diet and cancer

- no clear evidence yet, that diet can cause cancer
- most frequently accused:
- red meat, animal fat, cholesterol, refined sugar, chemical additives
- assumption of WHO - 1/3 of all ca - nutrition
- oral cavity, pharynx, esophagus - alcohol, smoking of cigarettes
- colorectal ca - increased intake of fat, reduced intake of fibers
- liver ca - aphlatoxin (nuts, grains) - cirrhosis - hepatocellular ca
- breast ca - fat intake (in USA - 10% of females - increasing incidence)

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