Environmental Pathology I

APPROVED

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Definitions

Straight from the book

- **Environment:** Encompasses outdoor, indoor, and occupational environments shared by small and large populations, and our own environment.

"our own env" (smoking / drugs / etc that you do to yourself) is typically much more important than ambient env

- **Environmental disease:** Conditions caused by exposure to chemical or physical agents in the ambient, workplace, and personal environment, including diseases of nutritional origin

many of these in Robbins that won't go through in this lecture - these are important in developing world

Facts

- What is the single leading global cause of morbidity and premature death?

next slide

Facts

- What is the single leading global cause of morbidity and premature death?
  Undernutrition

includes lack of sufficient vitamins that may make people more susceptible to illness - so it's "complicated"

Facts

- What is the single leading global cause of morbidity and premature death?
  Undernutrition
- What is the leading cause of death in developed countries?

next slide

Facts

- What is the single leading global cause of morbidity and premature death? **Undernutrition**
- What is the leading cause of death in developed countries? **Ischemic heart disease and cerebrovascular disease**

I say overnutrition
- I agree Dr. H

Facts

- In developing countries*, infectious diseases* make *up 5 of the 10* leading causes of death
  - HIV
  - Diarrheal diseases
  - Tuberculosis
  - Malaria
  - Respiratory infections

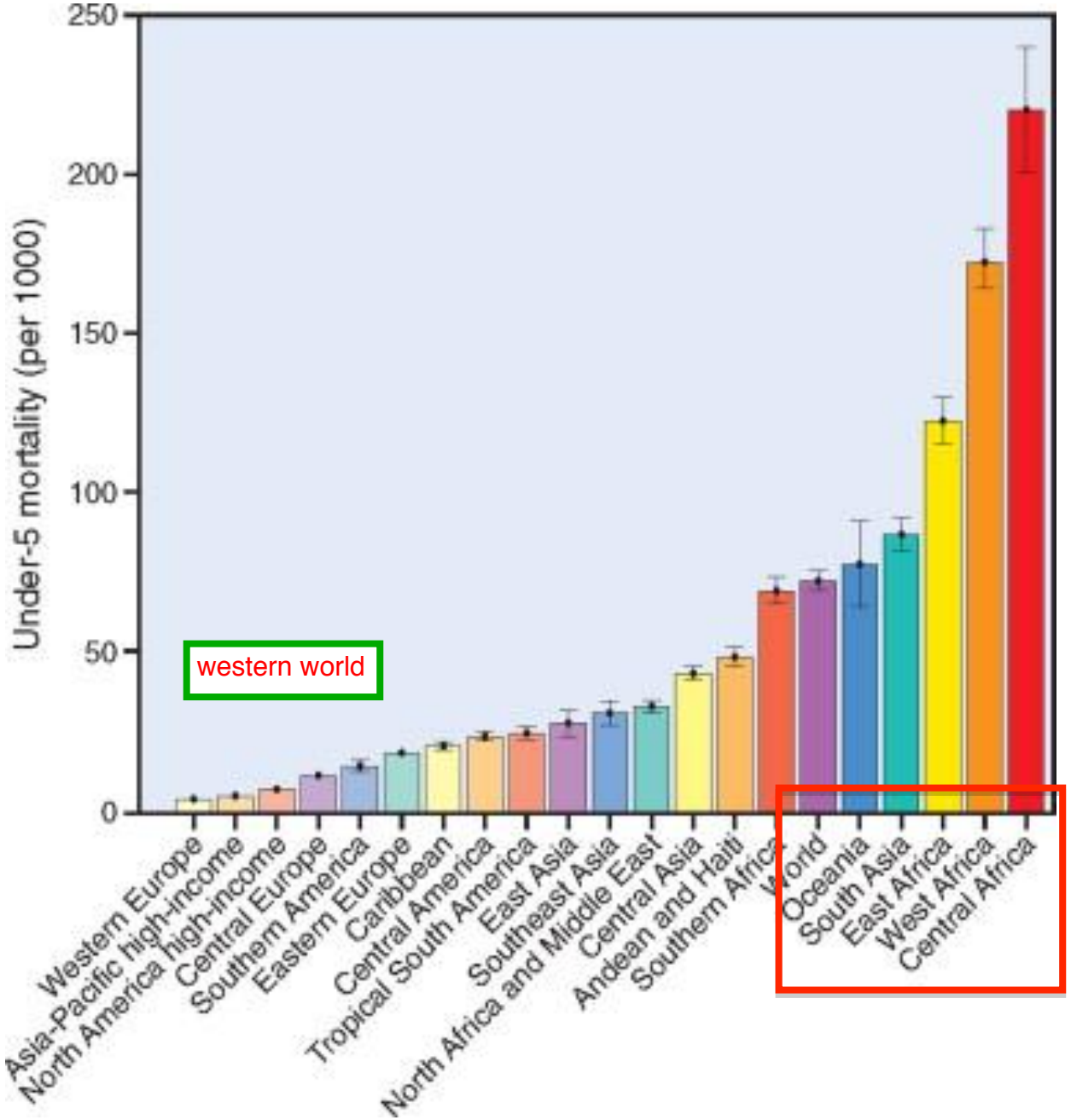
preventable

don't have sterile intravenous saline treatments available

Facts

- About 70% of all child deaths are attributable to five preventable conditions:
  - Pneumonia
  - Diarrhea
  - Malaria
  - Measles
  - Perinatal / neonatal problems (e.g. prematurity, neonatal infection)

just went down list


Under-5 mortality (per 1000)
250
200
150
100
50
0
western world
Western Europe
Asia-Pacific high-income
North America high-income
Central Europe
Southern America
Eastern Europe
Caribbean
Central America
Tropical South America
East Asia
Southeast Asia
North Africa and Middle East
Central Asia
Andean and Haiti
Southern Africa
World
Oceania
South Asia
East Africa
West Africa
Central Africa

Outline

- Pollution and poisons
- Tobacco
- Alcohol
- Occupational exposures
- Drugs
  - Therapeutic
  - Recreational
- Physical agents

Outline

- **Pollution and poisons**
- Tobacco
- Alcohol
- Occupational exposures
- Drugs
  - Therapeutic
  - Recreational
- Physical agents

What does this mean? I looked this up - the lower layer of atmosphere (the troposphere) above the United States has a mass of ~ 10^17 pounds - so this may have little value in terms of individual exposure- However, if you live near a toxic chemical plant it might.

Pollution

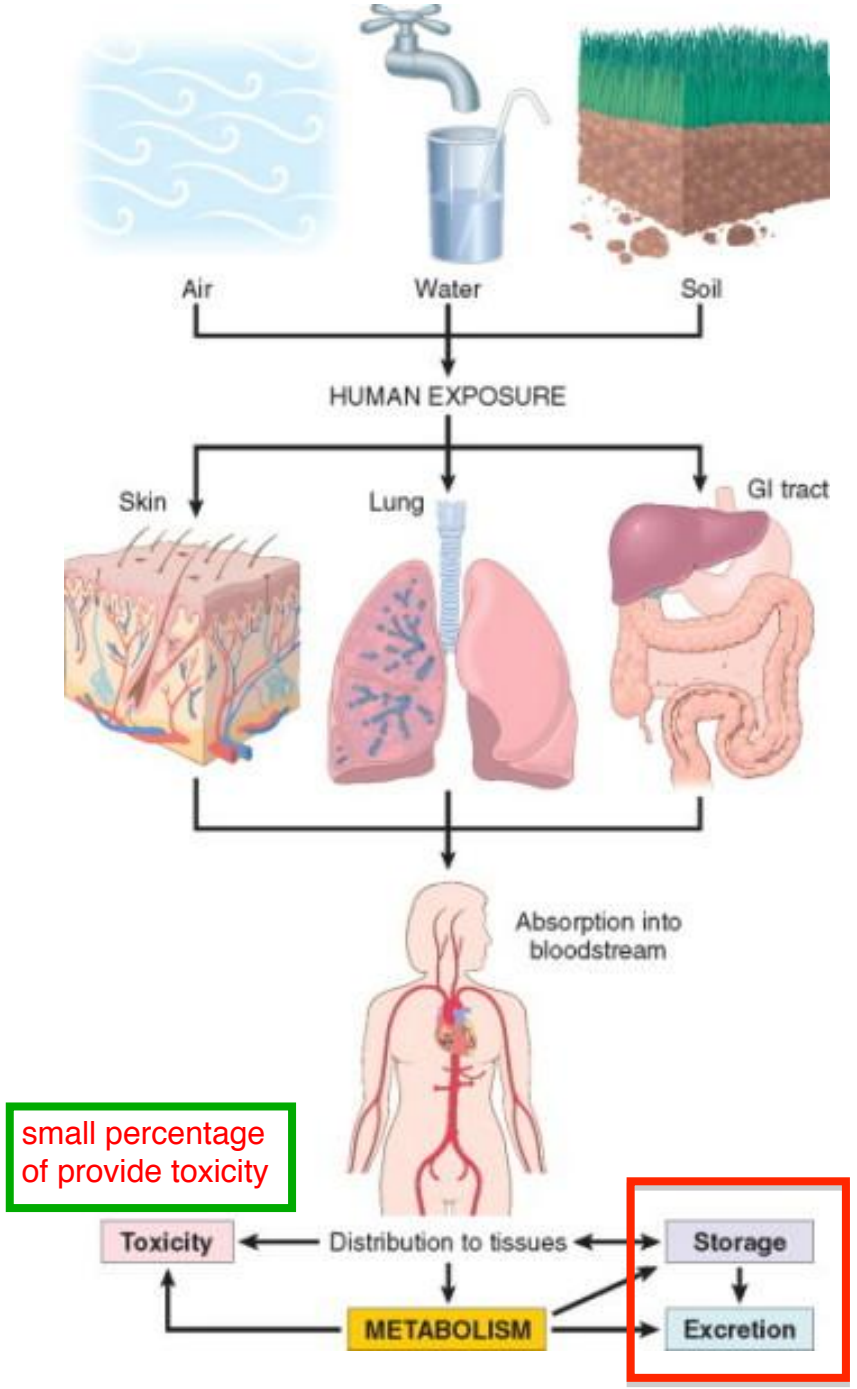
- **4 billion pounds** of toxic chemicals are released into the environment each year in the United States
  - 72 million pounds of known carcinogens
- State agencies set permissible levels for pollutants
  - **Individual susceptibilities vary greatly**
  - Most commercially used chemicals **have not been tested** for health effects

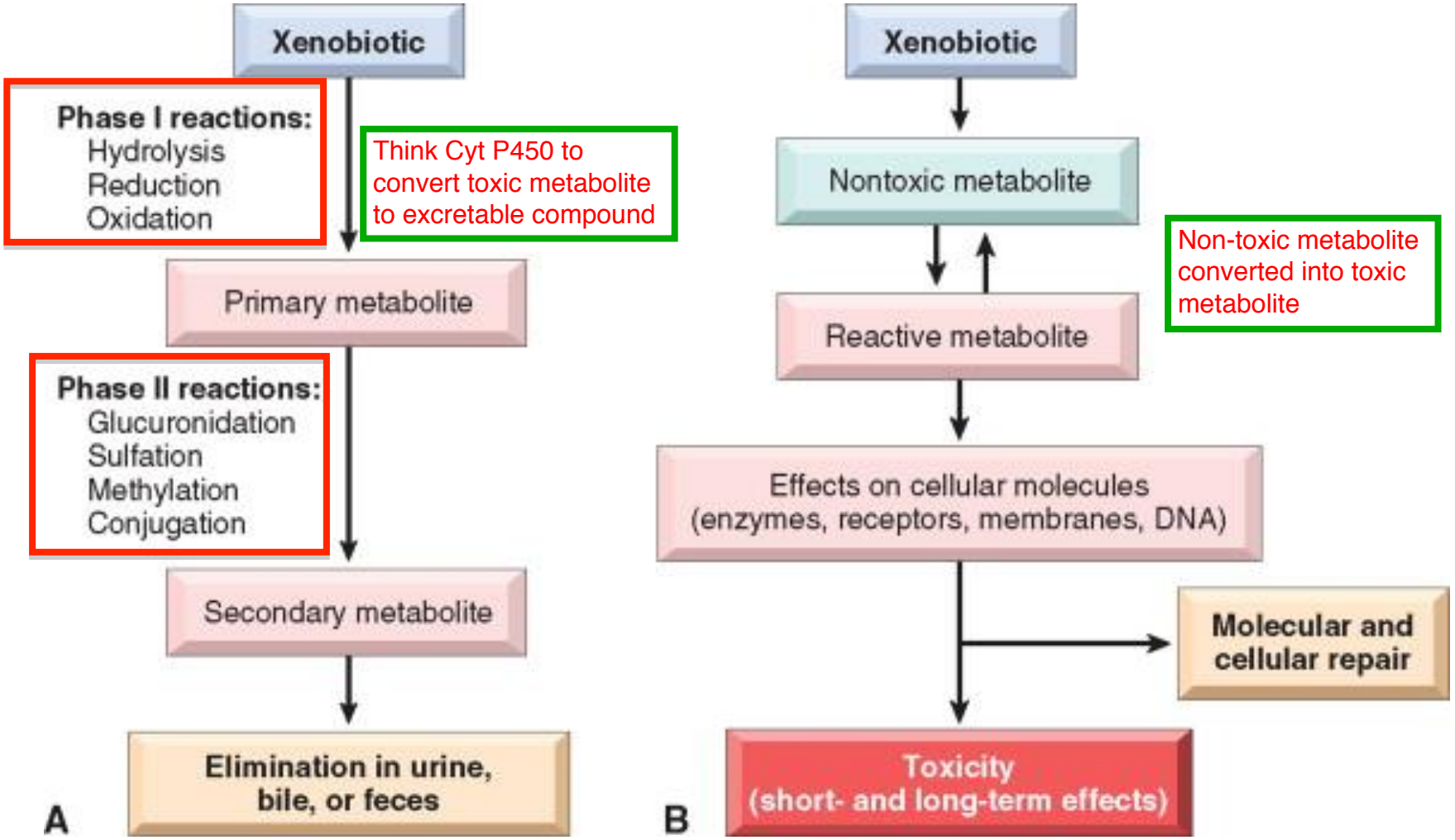
what is considered a carcinogen? some threshold defined by state agencies and will allow companies to "pop-out" into the atmosphere. Problem: different people have different thresholds

Pollution

- **Poison**: Difficult to define because it depends on dosage ("the dose makes the poison")
  - "All substances are poisons; the right dosage differentiates a poison from a remedy." – *Paracelsus, 16th century*

- **Xenobiotic**: Exogeneous chemicals in air, food, water, and soil that can be absorbed through inhalation, ingestion, and skin contact





Xenobiotic metabolism.

A) Detoxification B) Formation of reactive metabolites

Xenobiotic metabolism

- Phase I reactions
  - Hydrolysis, oxidation, or reduction
  - Usually produces easily excreted water-soluble compounds
  - Mostly occurs in the **cytochrome P450** system in the liver
    - May vary widely between individuals
  - Toxic example: Production of trichloromethyl free radicals from carbon tetrachloride

we know this - variations lead to differences in the ways people metabolize

Xenobiotic metabolism

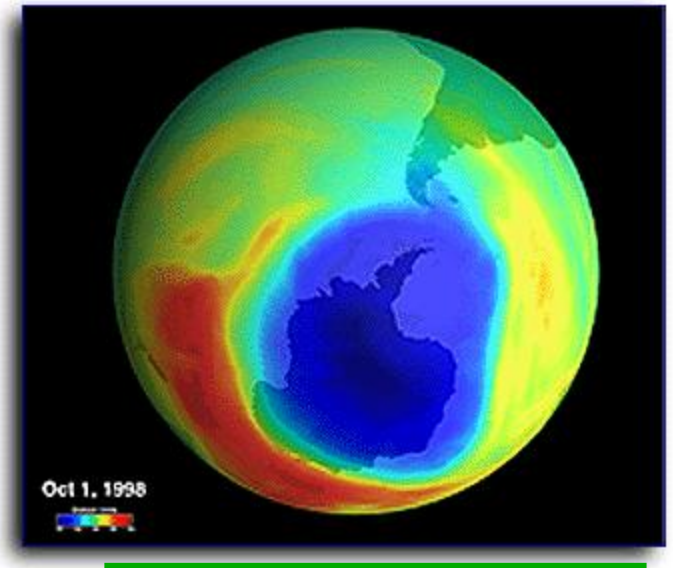
- Phase II reactions
  - Glucuronidation, sulfation, methylation, and conjugation with glutathione
  - Typically affixes polar groups to solubilize insoluble compounds

Air pollution

- Ozone
  - Good

high in the atmosphere

    - Product of UV radiation action on oxygen
    - Accumulates in the ozone layer 10-30 miles above the earth
    - Absorbs most of the dangerous UV radiation emitted by the sun



"We no longer use culprit chemicals [that contribute to ozone destruction] so I believe the ozone hole is closing"

Air pollution

- Ozone
  - Bad ← in our environment
    - Product of nitrogen oxides and volatile organics + sunlight
    - Accumulates at ground level
    - Results in production of free radicals which cause respiratory injury and inflammation
    - May be quite detrimental in people with underlying airway disease (e.g. asthma)

a very reactive molecule

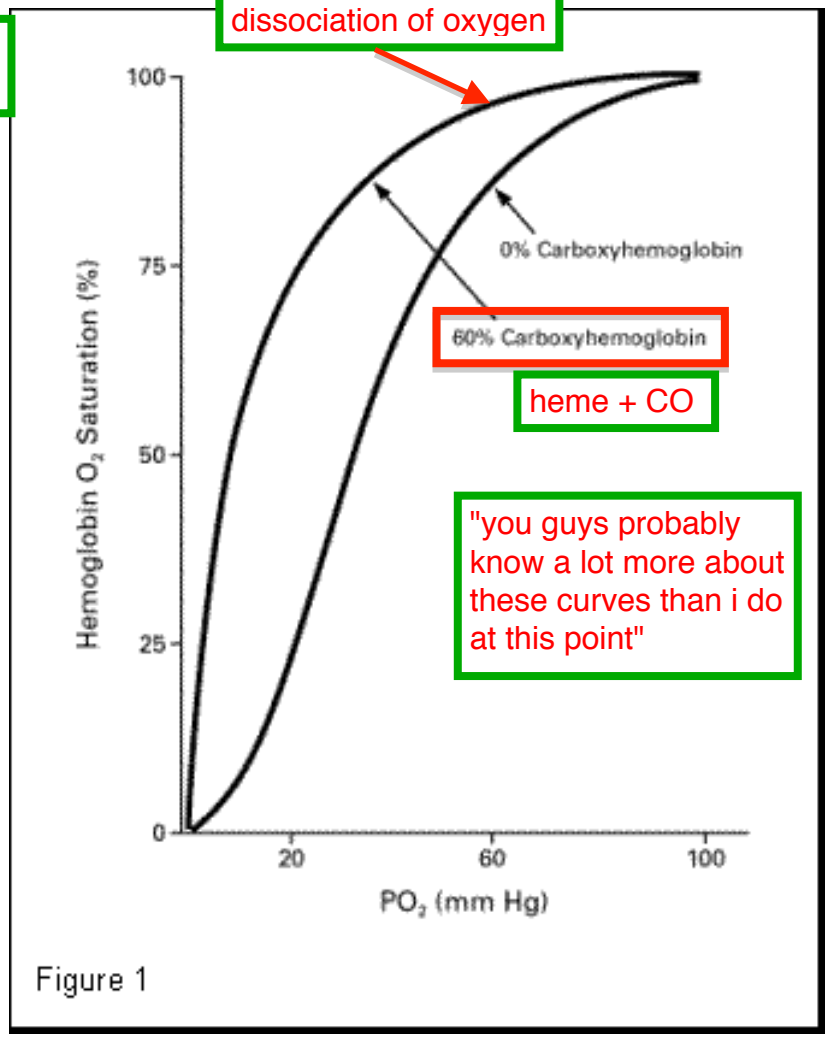
Air pollution

- Carbon monoxide
  - Colorless, tasteless, odorless
  - Produced in car exhaust and burning of wood and fossil fuels
  - Hemoglobin has a 200x higher affinity for carbon monoxide than oxygen, resulting in impaired peripheral oxygen delivery
  - May cause acute or chronic toxicity

not uncommon poisoning

incomplete oxidation

in peripheral tissues, will not be adequate dissociation of oxygen



heme + CO

"you guys probably know a lot more about these curves than i do at this point"

Figure 1

Air pollution

- Carbon monoxide
  - What is the “buzzword” clinical finding in a person with acute carbon monoxide poisioning?

next slide

Air pollution

- Carbon monoxide
  - What is the “buzzword” clinical finding in a person with acute carbon monoxide poisioning?
  - **Cherry red skin and mucous membrane coloration**

someone looks healthy as a horse but is dead - think CO poisoning

"people kill themselves with CO poisoning all the time" - intentionally or unintentionally. if you start the car in your garage and close the door, you can get poisoning in "just a few minutes"

Metal pollution

he's listing the metals that are most clinically relevant and "testable"

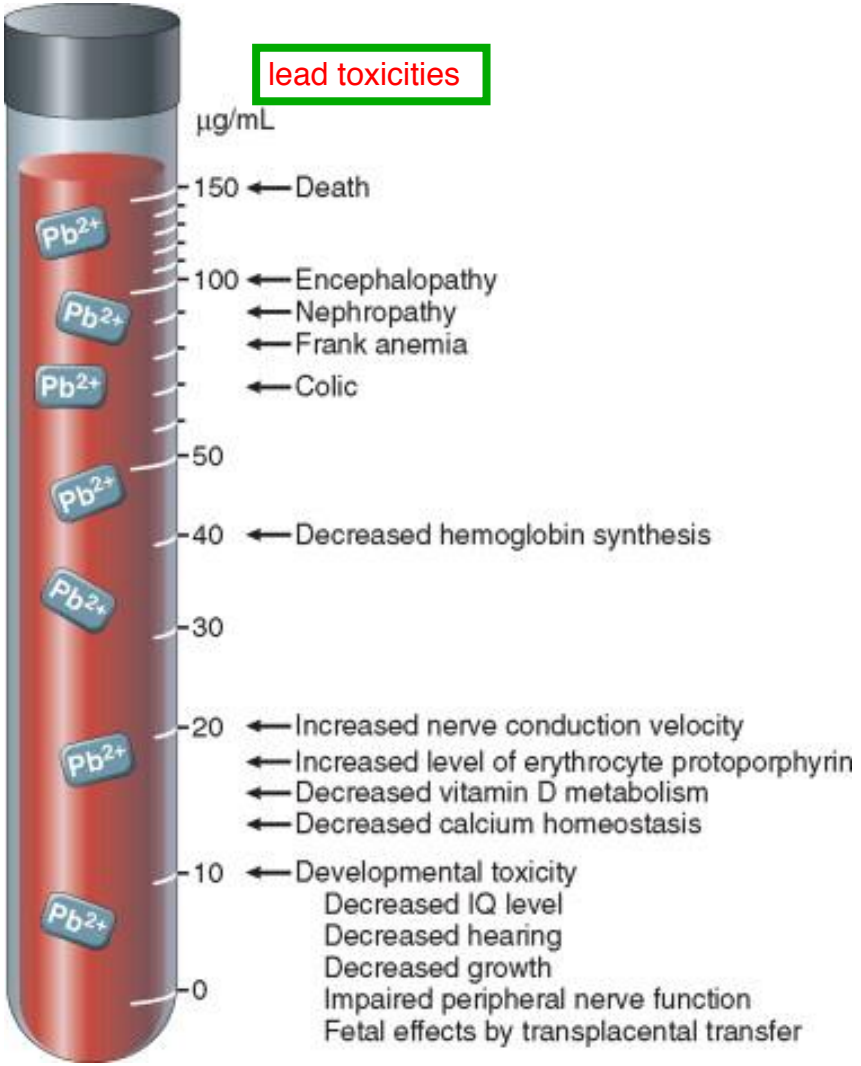
METAL #1: LEAD

Metal pollution

- Lead
  - Historically found in house paint and gasoline
  - Most current exposures in children occur due to flaking lead paint and contaminated soil
  - Interferes with calcium metabolism

"we probably could have gotten to the moon a bit faster if it weren't for lead paint" - toxicities used to be in 15ug/mL range

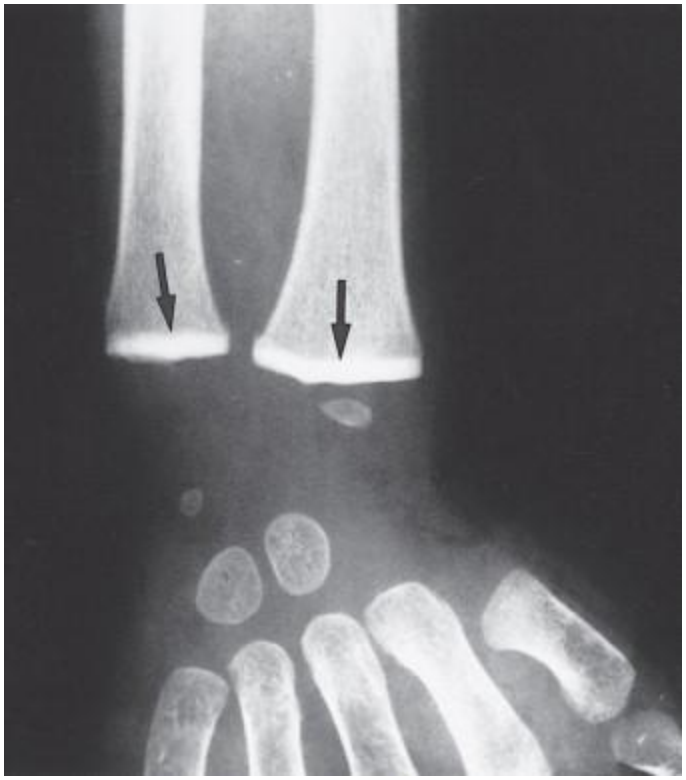
and bone remodeling



Metal pollution

- Lead
  - Absorbed into CNS, bone, and developing teeth
  - Symptoms:
    - Neurotoxicity
      - Adults: Peripheral neuropathy
      - Children: Loss of IQ, behavior problems
    - Inhibited fracture healing
      - Delayed mineralization of cartilage

Characteristic radiograph of lead poisoning: epiphyses of radius and ulna - WAY TOO RADIO-DENSE - see arrows



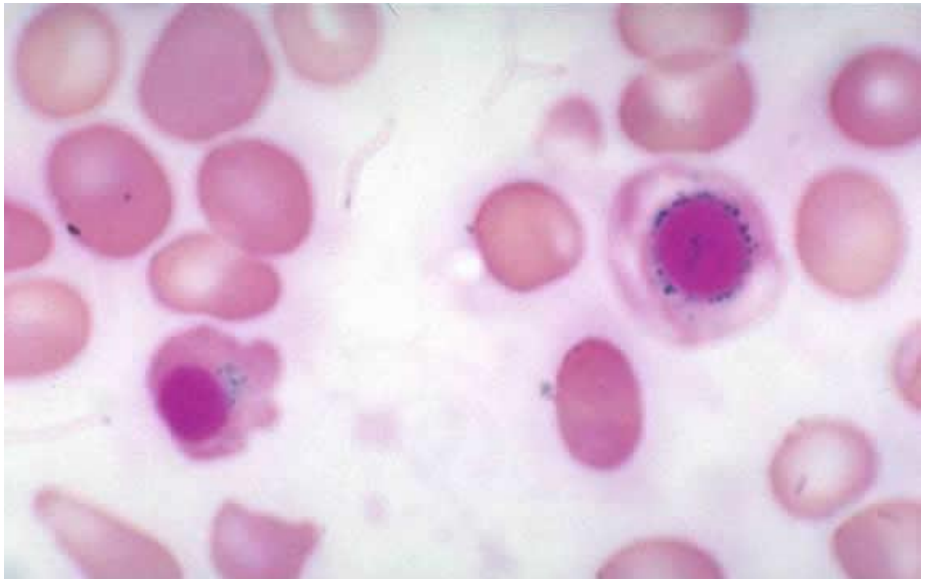
"Lead lines": Increased radiodensity of epiphyses due to impaired cartilage remodeling

IMPORTANT:

can see these lines in gums

Metal pollution

- Lead
  - Suppresses hemoglobin synthesis
    - Hypochromic, microcytic anemia



Small RBCs with less hemoglobin

"Ringed sideroblast"

iron stain - blue dots around nucleus are iron deposits: ringed sideroblast

METAL #2: MERCURY

Metal pollution

- Mercury
  - Historically used as a pigment, a cosmetic, a syphilis remedy, and a diuretic
  - Three forms:
    - Metallic (elemental)
    - Organic (methyl mercury)
    - Inorganic (mercuric chloride)

bacteria produce this

"mad as a hatter" - hatters used to get encephalopathies from exposure to Mercury

Metal pollution

- Mercury
  - Main modern sources:
    - Dental amalgam
      - Controversial
      - Not used in some countries

silver fillings

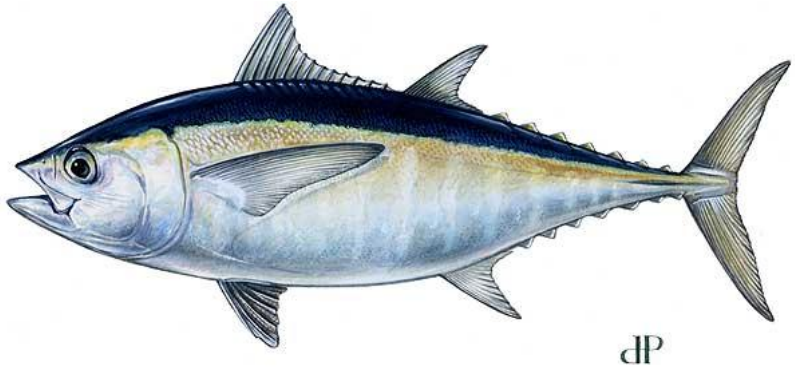
consensus is that the amount of mercury in fillings is not harmful

    - Fish

bioaccumulation in predatory fish

      - Minamata episode

pollution of Minamata Bay in Japan lead to many symptoms characteristic of Mercury poisoning



Metal pollution

- Mercury
  - Toxic effects
    - Neurotoxicity
    - "Minamata disease"
      - Cerebral palsy
      - Deafness
      - Blindness
      - Mental retardation

Metal pollution

- Mercury
  - The developing brain is extremely sensitive to mercury
    - Minimize top-of-the-food-chain fish consumption for pregnant women.
  - Thimerosal (outdated vaccine preservative)
    - Repeated studies show no proven link to autism

the same story we've heard before

this is nonsense - children should be vaccinated

METAL #3: ARSENIC

Metal pollution

- Arsenic
  - The “poison of choice” in Renaissance Italy, as symptoms mimicked those of cholera
  - Remains an important environmental health problem
  - Sources:

huge environmental reservoir in Bangladesh - lots of poisoning

    - Natural (soil and water)
    - Herbicides
    - Some traditional Chinese and Indian herbal medicines

Metal pollution

- Arsenic
  - Acute poisoning
    - Gastrointestinal, cardiovascular, and CNS disturbances that are often fatal
  - Chronic poisoning:
    - Greatly increased risk of lung and skin cancers

Skin changes in chronic arsenic poisoning. Hyperpigmentation and hyperkeratosis.

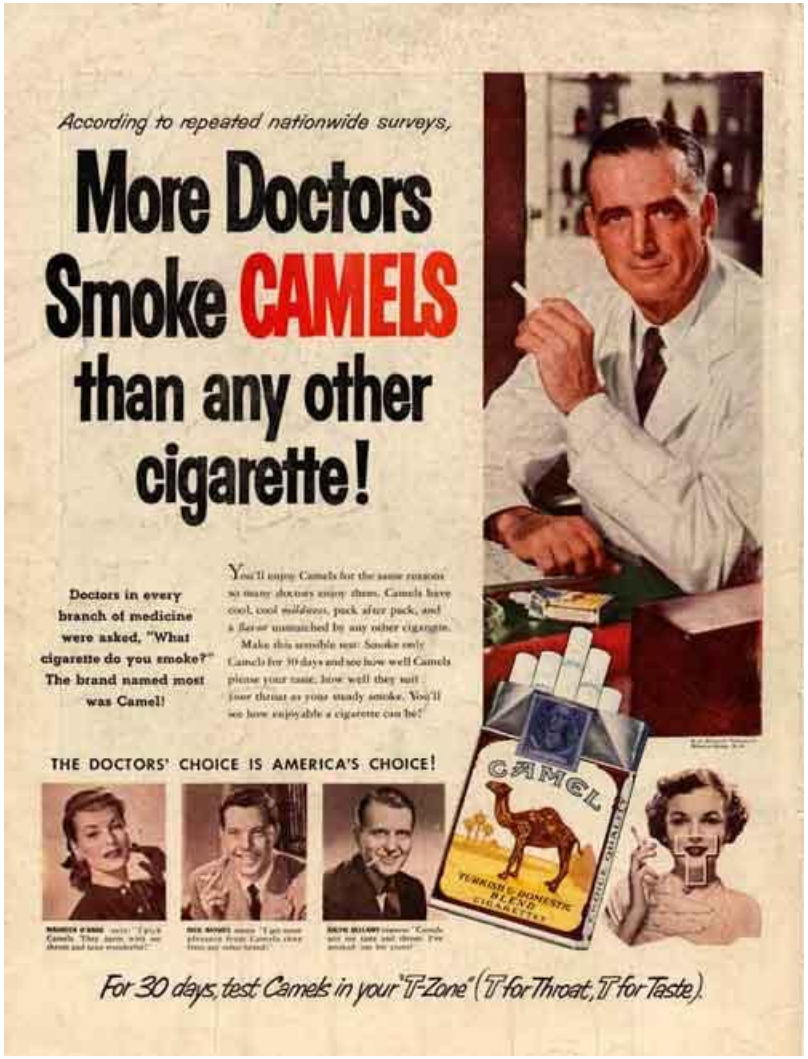
develop into squamous cell and basal cell carcinomas

Outline

- Pollution and poisons
- **Tobacco**
- Alcohol
- Occupational exposures
- Drugs
  - Therapeutic
  - Recreational
- Physical agents

Tobacco

Tobacco


According to repeated nationwide surveys,
More Doctors Smoke CAMELS than any other cigarette!
Doctors in every branch of medicine were asked, "What cigarette do you smoke?" The brand named most was Camel!
You'll enjoy Camels for the same reasons so many doctors enjoy them. Camels have cool, cool mildness, puff after puff, and a flavor unmatched by any other cigarette.
Make this sensible test: Smoke only Camels for 30 days and see how well Camels please your taste, how well they suit your throat as your steady smoke. You'll see how enjoyable a cigarette can be!
THE DOCTORS' CHOICE IS AMERICA'S CHOICE!
CAMEL
TURKISH & DOMESTIC BLEND CIGARETTES
For 30 days, test Camels in your "T-Zone" (T for Throat, T for Taste).


LUCKY STRIKE
20,679* Physicians say "LUCKIES are less irritating"
"It's toasted"
Your Throat Protection against irritation against cough

Tobacco

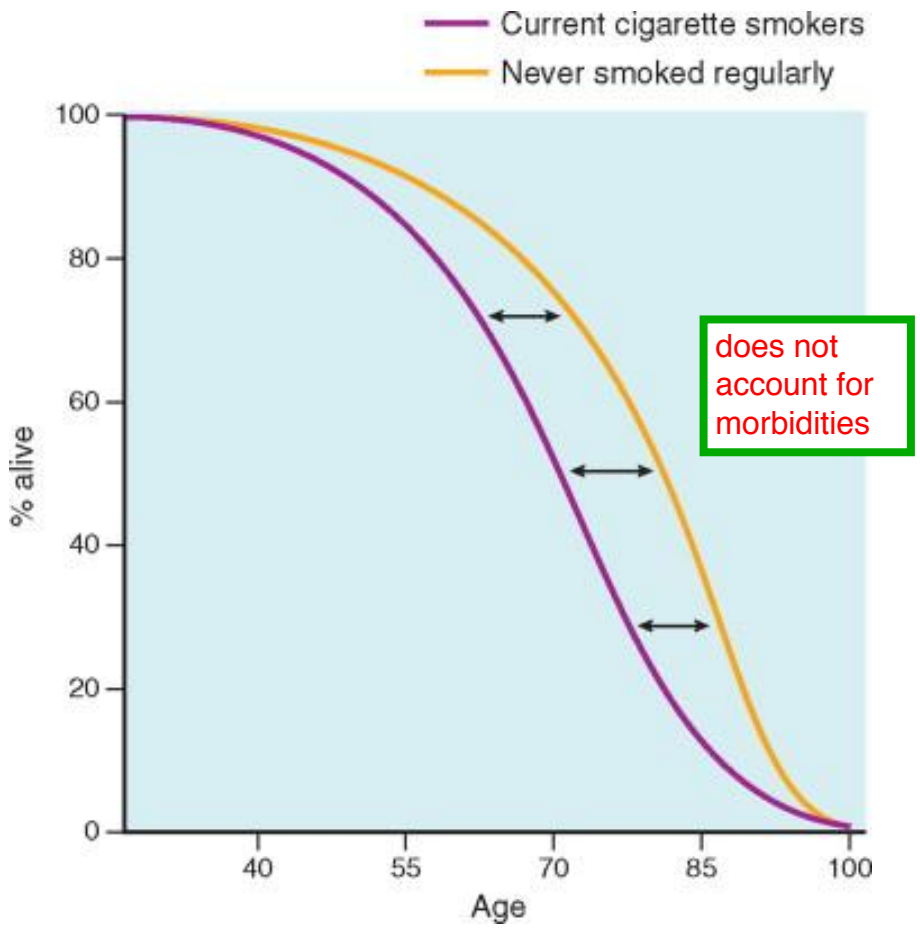
- Cigarette smoking facts
  - Causes 90% of lung cancers
  - Can cause lung cancer in non-smokers as “second-hand smoke”
  - Causes more than 5 million deaths annually from:
    - Cardiovascular disease
    - Cancer
    - Chronic respiratory problems
  - Of people alive today, 500 million will likely die of smoking-related causes

a lot of physicians forget the other 10%

Tobacco

- At age 75, the difference in survival between smokers and non-smokers is 7.5 years

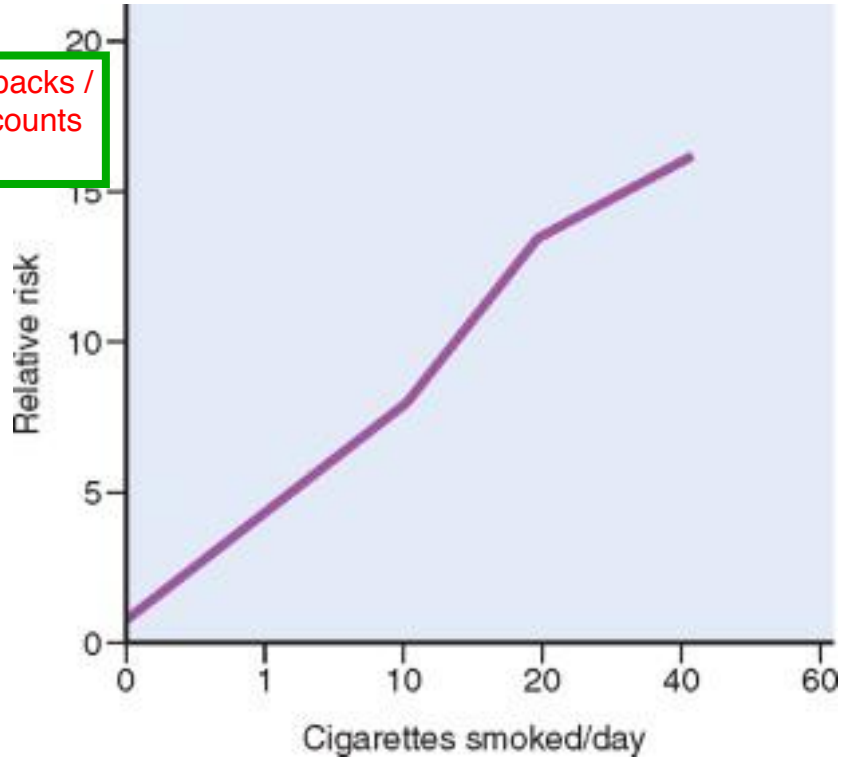
- At age 70:
  - 80% of non-smokers are alive
  - 50% of smokers are alive



Tobacco

- Smoking reduces survival in a **dose-dependent** manner
- The amount smoked is usually expressed in "**pack-years**"
- Smoking **multiplies the risk** of other carcinogens (e.g. asbestos)
- Within five years of quitting smoking:
  - The risk of cardiovascular death is greatly reduced
  - The risk of lung cancer is decreased by 21%

if you smoked 2 packs / day for 5 years, counts as 10 pack years



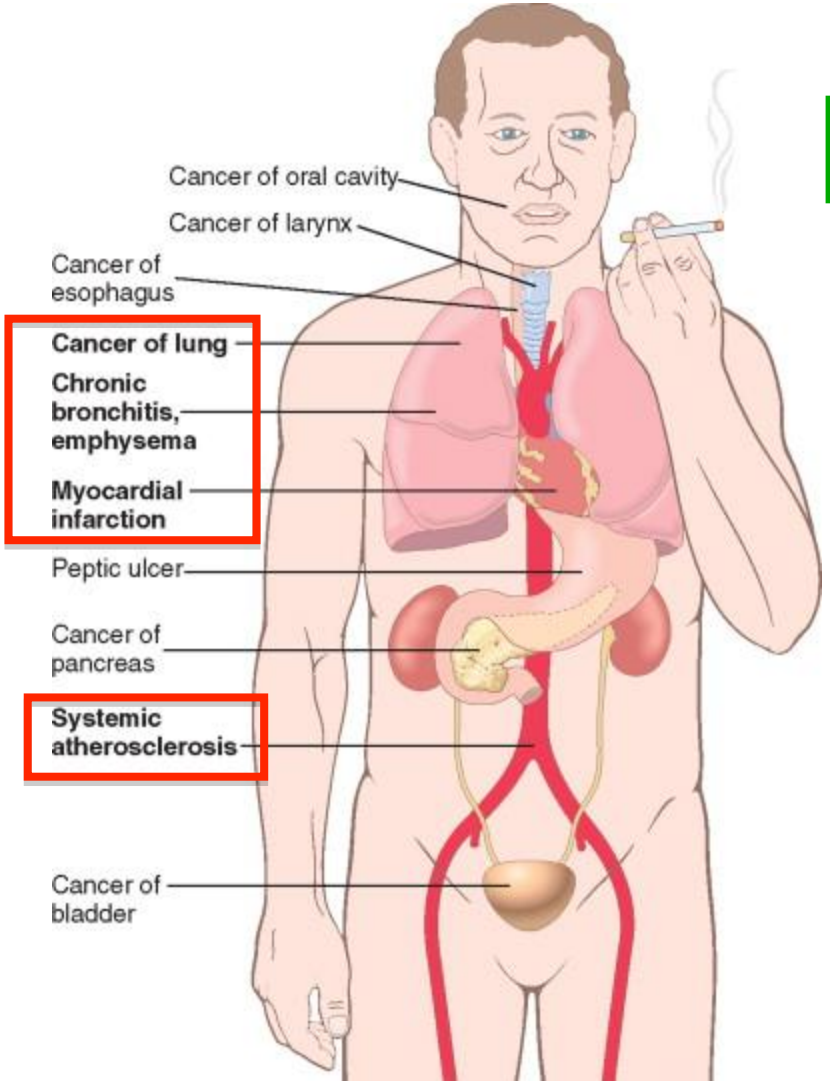
Relative risk of lung cancer

Tobacco

Substance	Effect
Tar	Carcinogenesis
Polycyclic aromatic hydrocarbons	Carcinogenesis
Nicotine	Ganglionic stimulation and depression; tumor promotion
Phenol	Tumor promotion; mucosal irritation
Benzopyrene	Carcinogenesis
Carbon monoxide	Impaired oxygen transport and utilization
Formaldehyde	Toxicity to cilia; mucosal irritation
Oxides of nitrogen	Toxicity to cilia; mucosal irritation
Nitrosamine	Carcinogenesis

Organ	Carcinogen
Lung, larynx	Polycyclic aromatic hydrocarbons 4-(Methylnitrosoamino)-1-(3-pyridyl)-1-buta-none (NNK), polonium 210
Esophagus	N'-Nitrosonornicotine (NNN)
Pancreas	NNK (?)
Bladder	4-Aminobiphenyl, 2-naphthylamine
Oral cavity (smoking)	Polycyclic aromatic hydrocarbons, NNK, NNN
Oral cavity (snuff)	NNK, NNN, polonium 210

Tobacco



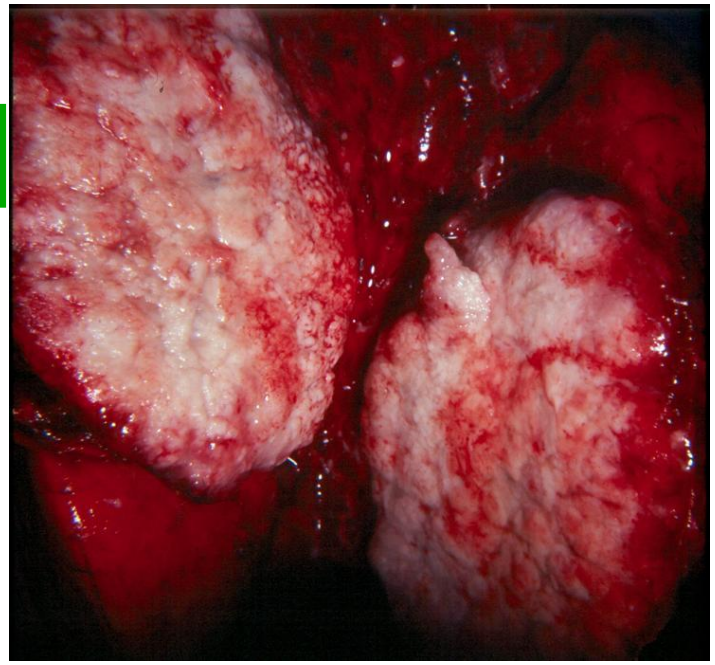
"I put this in because this picture is funny"

Tobacco

- Lung cancer
  - Polycyclic hydrocarbon and nitrosamine metabolites cause mutations in oncogenes and tumor suppressor genes

more details in book for mechanism of action

- Emphysema and bronchitis
  - Leukocyte recruitment to lung
  - Increased elastase production
  - Chronic tissue damage



Lung cancer

Tobacco

- Myocardial infarction and stroke
  - Increased platelet aggregation
  - Decreased myocardial oxygen supply due to lung disease
    - Lung disease
    - Carbon monoxide
  - Increased oxygen demand
  - Decreased threshold for ventricular fibrillation

Tobacco

- Smoking while pregnant increases the risk of:
  - Preterm birth
  - Intrauterine growth restriction
  - Spontaneous abortion

Outline

- Pollution and poisons
- Tobacco
- **Alcohol**
- Occupational exposures
- Drugs
  - Therapeutic
  - Recreational
- Physical agents

Alcohol

"let's just look at these for a minute"

Alcohol

- Facts:
  - 50% of adults in the Western world drink alcohol
  - 5 – 10% are alcoholics
  - Alcohol causes more than 100,000 deaths in the U.S. annually
    - Half due to accidents, homicides, and suicides
    - About 10% due to cirrhosis of the liver

"in my experience it's greater than that"

most due to behavioral changes

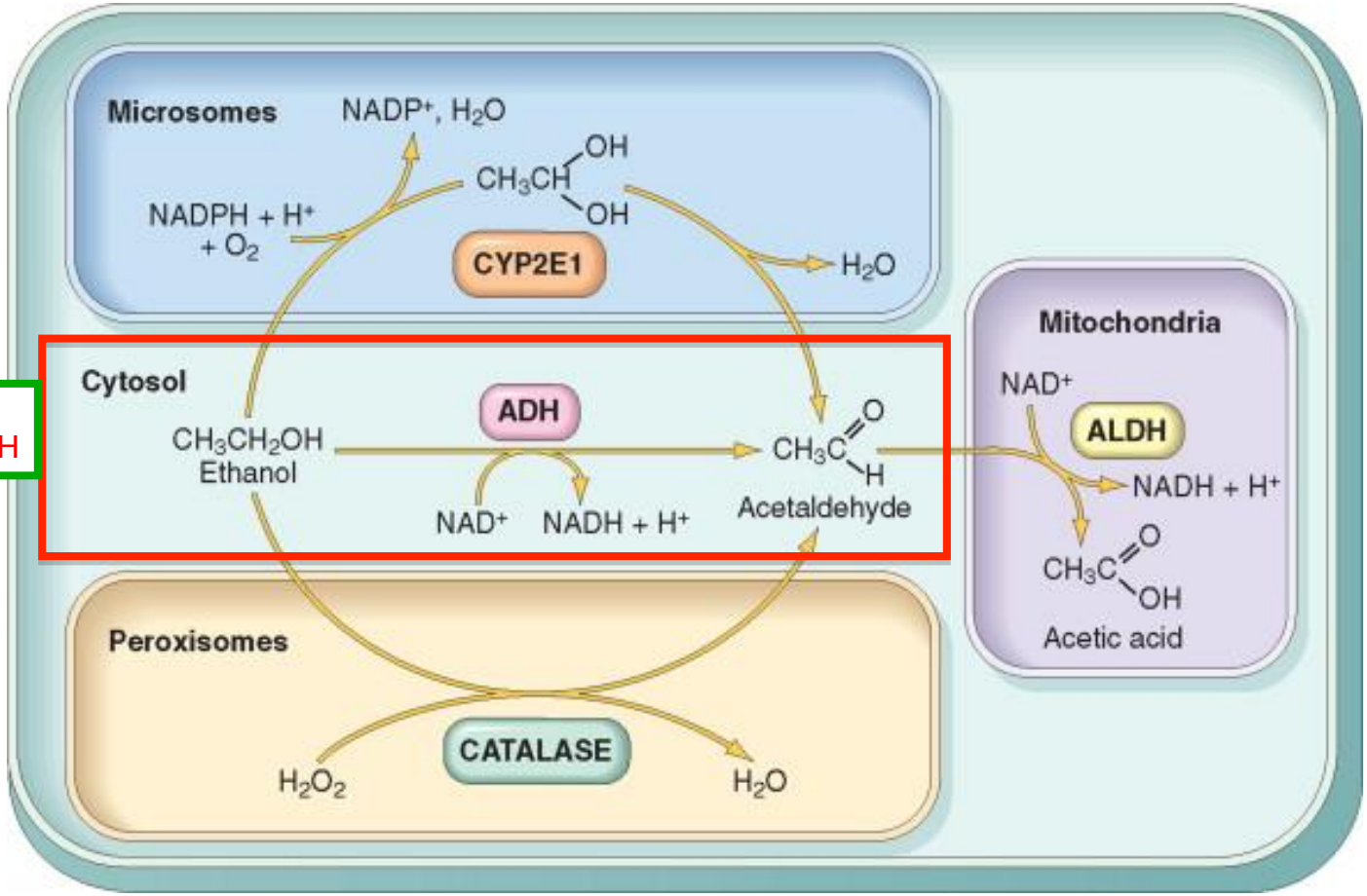
Alcohol

- Absorption and distribution
  - Absorbed unaltered in stomach and small intestine
  - Distributed to all body tissues in direct proportion to blood level
  - Amount in the breath is directly proportional to blood level

- Effects proportional to concentration:
  - 80 mg/dL: Legal definition of drunk driving in most locales (about three drinks)
  - 200 mg/dL: Drowsiness occurs
  - 300 mg/dL: Stupor occurs
  - Higher: Coma and possible respiratory distress

Alcohol

main mode of metabolism: ADH



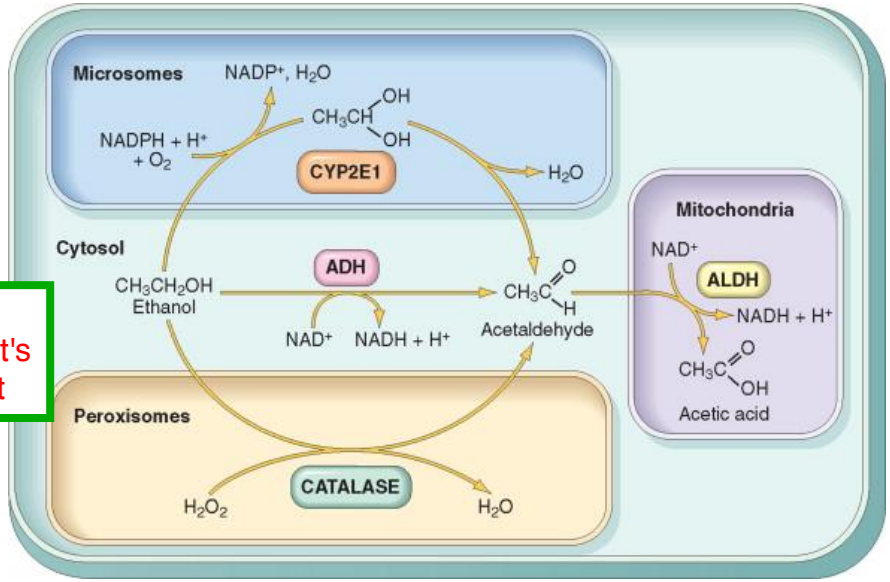
Three pathways -> Acetaldehyde

acetaldehyde is "bad stuff"

Alcohol

- Most ethanol metabolism takes place via **ADH** in the cytosol of hepatocytes
- **Microsomal oxidation** system most important at high EhOH concentrations
  - Alcoholics have **chronic induction** of the CYP system, which can cause **increased susceptibility to other compounds** metabolized by the same enzymes (e.g. certain drugs, anesthetics)
- Catalase mechanism relatively unimportant

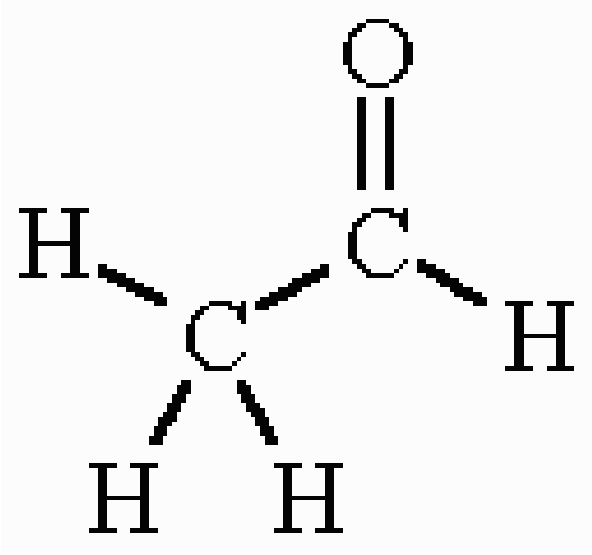
we know this, but it's important



Alcohol

- Acetaldehyde bad stuff
  - Converted to acetate in mitochrondria via aldehyde dehydrogenase (ALDH)

- ALDH deficiency
  - Unable to oxidize acetaldehyde
  - Nausea, flushing, tachycardia, and hyperventilation after drinking
  - 50% of Asian people have less active forms of the ALDH enzyme



Alcohol

- Known mechanisms of injury
  - Acetaldehyde toxicity:
    - Direct toxic effects
    - Carcinogen
  - NAD depletion largely responsible for liver damage
    - Oxidation of alcohol by ADH converts NADH -> NAD
    - NAD required for fatty acid oxidation in liver and for glycolysis
    - Deficiency causes fat accumulation and lactic acidosis
  - Production of reactive oxygen species
    - Metabolism in the liver by CYP produces ROS which cause cellular injury via lipid peroxidation of cell membranes

Alcohol

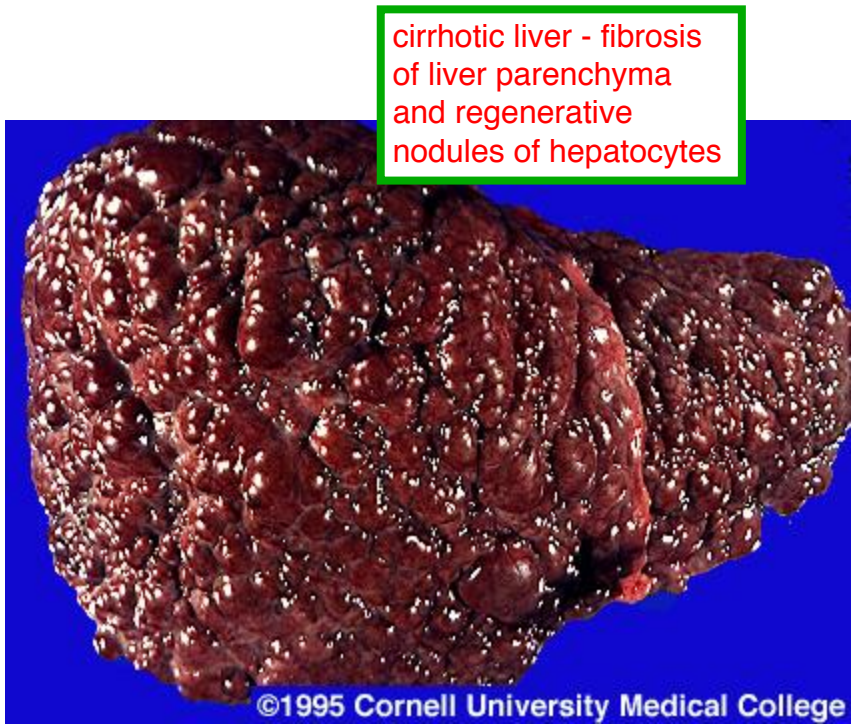
- Acute effects
  - CNS depressant
    - Low levels: Disordered motor and intellectual behavior
    - High levels: Depression of cortical neurons and medullary centers may cause respiratory arrest
  - Gastritis
  - Fat accumulation in the liver (steatosis)

it's possible to have ONE binge drinking episode and die -
Acute alcohol poisoning causes respiratory depression, vomiting may result in aspiration since cough reflex centers in the CNS are depressed, electrolyte imbalance may cause lethal cardiac arrythmias, hypoglycemia and metabolic acidosis also occur.

Alcohol

- Chronic effects
  - Alcoholic hepatitis and cirrhosis
  - Gastrointestinal bleeding due to portal hypertension, ulcers
  - Thiamine deficiency
    - Peripheral neuropathy
    - Wernicke-Korsakoff syndrome
  - Encephalopathy
  - Cardiomyopathy
  - Pancreatitis
  - Cancer

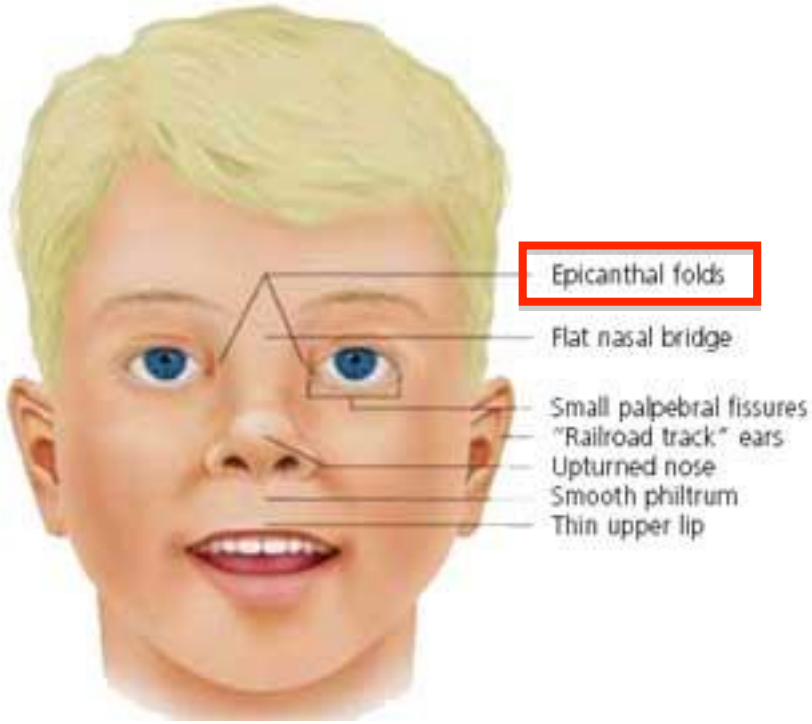
not uncommon



Alcohol

- Effects in pregnancy
  - **First trimester** is particularly vulnerable period
  - **Fetal alcohol syndrome**:
    - Microcephaly
    - Growth retardation
    - Facial abnormalities
    - Mental deficiencies

no one knows what the threshold is



Outline

- Pollution and poisons
- Tobacco
- Alcohol
- Occupational exposures
- **Drugs**
  - Therapeutic
  - Recreational
- Physical agents

Therapeutic drugs

- Adverse drug reactions "I cannot stress to you how important this is to you"
  - **Extremely common**
    - Affect **about 10%** of patients admitted to the hospital
    - 1 in 10 of these is **fatal**
  - **Most drugs** have known side effects

Therapeutic drugs

list of big ones - "if you feel like memorizing stuff."

every drug has a list a mile long

Reaction	Major Offenders
BONE MARROW AND BLOOD CELLS[*]	
Granulocytopenia, aplastic anemia, pancytopenia	Antineoplastic agents, immunosuppressives, and chloramphenicol
Hemolytic anemia, thrombocytopenia	Penicillin, methyldopa, quinidine, heparin
CUTANEOUS	
Urticaria, macules, papules, vesicles, petechiae, exfoliative dermatitis, fixed drug eruptions, abnormal pigmentation	Antineoplastic agents, sulfonamides, hydantoins, some antibiotics, and many other agents
CARDIAC	
Arrhythmias	Theophylline, hydantoins, digoxin
Cardiomyopathy	Doxorubicin, daunorubicin
RENAL	
Glomerulonephritis	Penicillamine
Acute tubular necrosis	Aminoglycoside antibiotics, cyclosporin, amphotericin B
Tubulointerstitial disease with papillary necrosis	Phenacetin, salicylates
PULMONARY	
Asthma	Salicylates
Acute pneumonitis	Nitrofurantoin
Interstitial fibrosis	Busulfan, nitrofurantoin, bleomycin
HEPATIC	
Fatty change	Tetracycline
Diffuse hepatocellular damage	Halothane, isoniazid, acetominophen
Cholestasis	Chlorpromazine, estrogens, contraceptive agents
SYSTEMIC	
Anaphylaxis	Penicillin
Lupus erythematosus syndrome (drug-induced lupus)	Hydralazine, procainamide
CENTRAL NERVOUS SYSTEM	
Tinnitus and dizziness	Salicylates
Acute dystonic reactions and parkinsonian syndrome	Phenothiazine antipsychotics
Respiratory depression	Sedatives

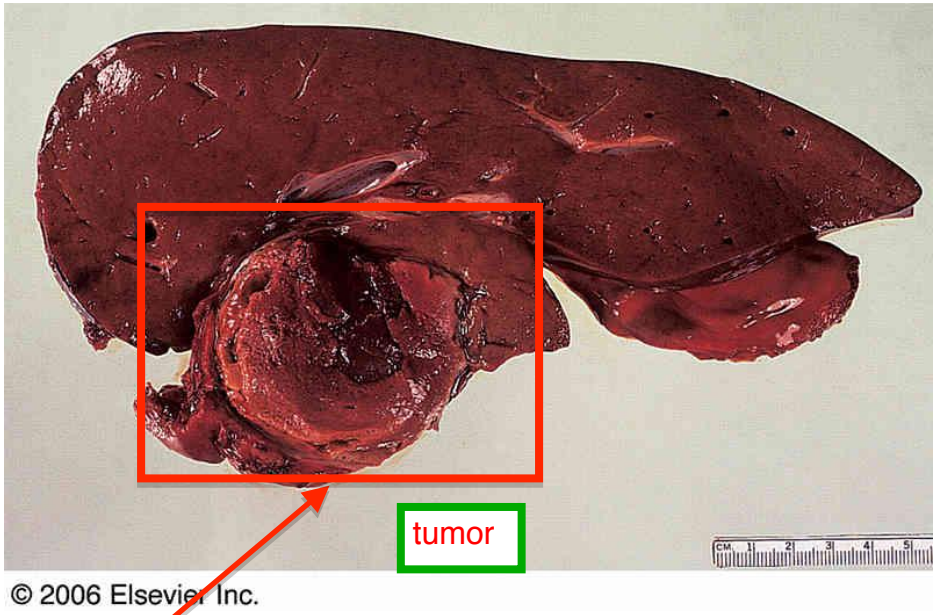
Therapeutic drugs

- Hormone replacement therapy
  - slightly
  - **Increased** risk of breast cancer
  - **Decreased** disk of cardiovascular disease if started early
  - **Increased** risk of venous thromboembolism

Therapeutic drugs

- Oral contraceptives
  - **Increased** risk of venous thromboembolism
    - **Increased** risk of cardiovascular disease, particularly in smokers
    - **Decreased** risk of ovarian and endometrial cancer
    - **Increased** risk of hepatic adenoma

this is the big one - the 35 yr old woman on an airplane who dies



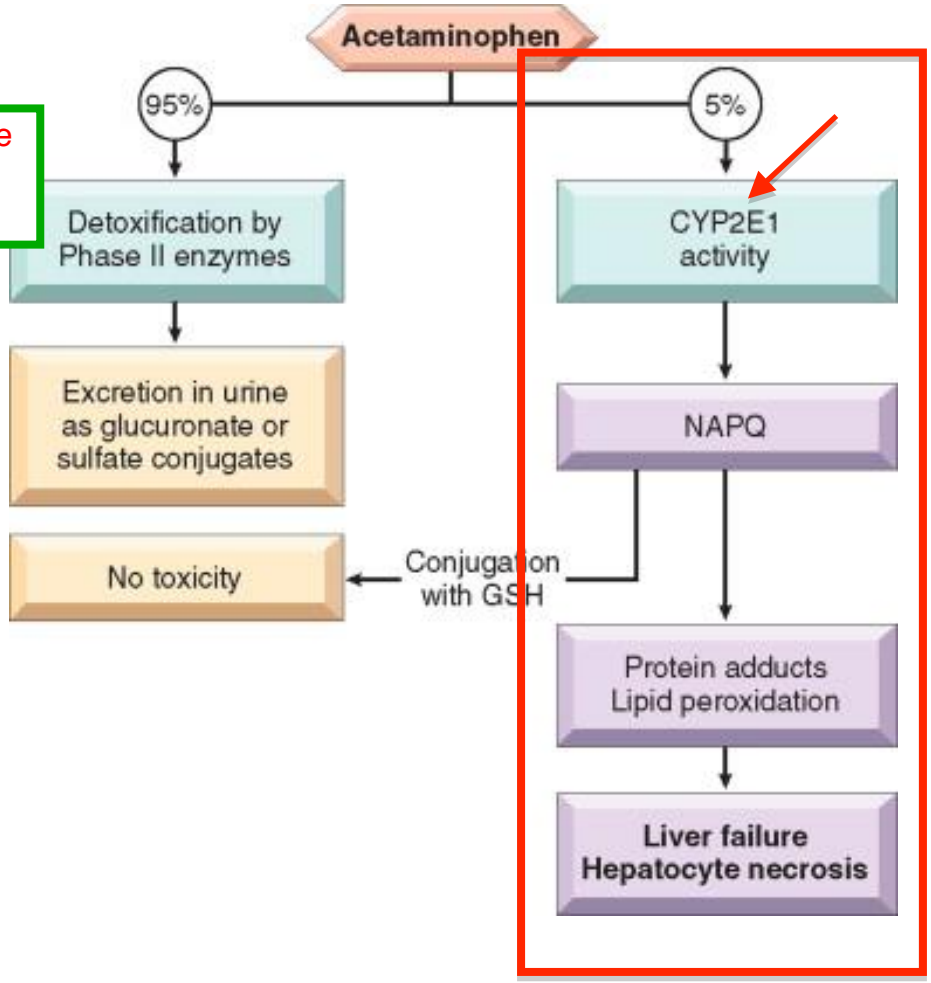
the other big one

Therapeutic drugs

- Acetaminophen
  - Overdoses responsible for more than 50,000 ER visits per year
  - Depletion of glutathione causes increased NAPQI, which is toxic to liver cells

many people don't realize this and accidentally kill themselves

via CYP



Therapeutic drugs

more of a curiosity than a clinically important manifestation

- Minocycline
  - Skin and thyroid pigmentation

thyroid turns black "like a crayon"

minocycline causing these dots

– Bonus question: What other disease causes black skin pigmentation?

next slide

– Bonus question: What other disease causes black skin pigmentation?

- **Ochronosis (alkaptonuria)**

black "tinge"

Recreational drugs

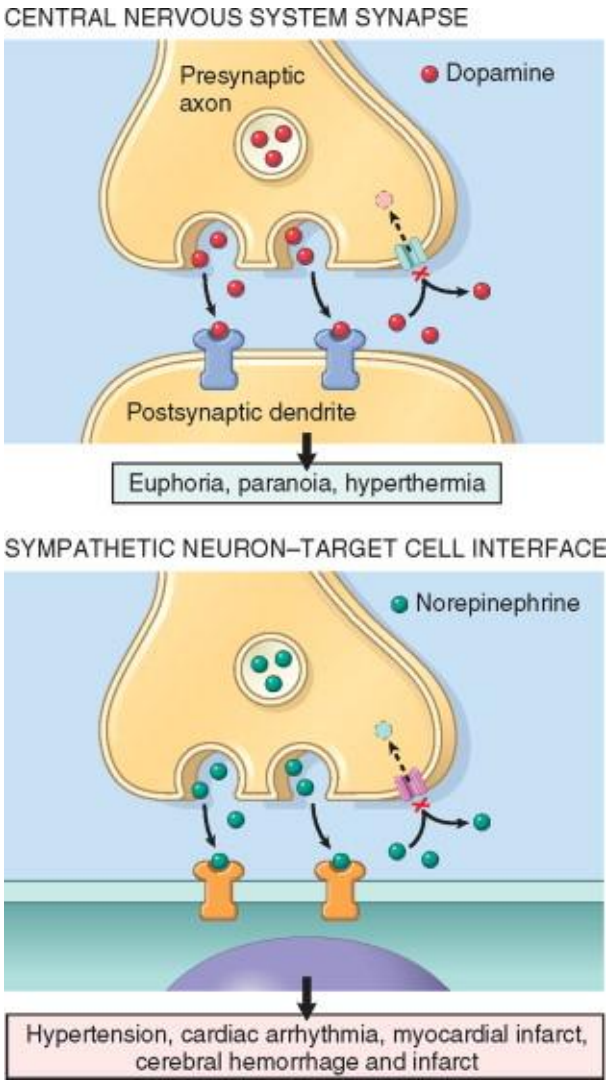
- Cocaine
  - Extracted from coca leaves
  - Usually prepared as a water-soluble powder or as crack
  - Typically injected, snorted, or smoked
  - **Purity varies widely**

Crack cocaine

can grind up other stuff to mix in that can be bad for you when you inject

Recreational drugs

- Cocaine
  - Powerful stimulant; blocks reuptake of dopamine, norepinephrine, and epinephrine and stimulates presynaptic epinephrine release



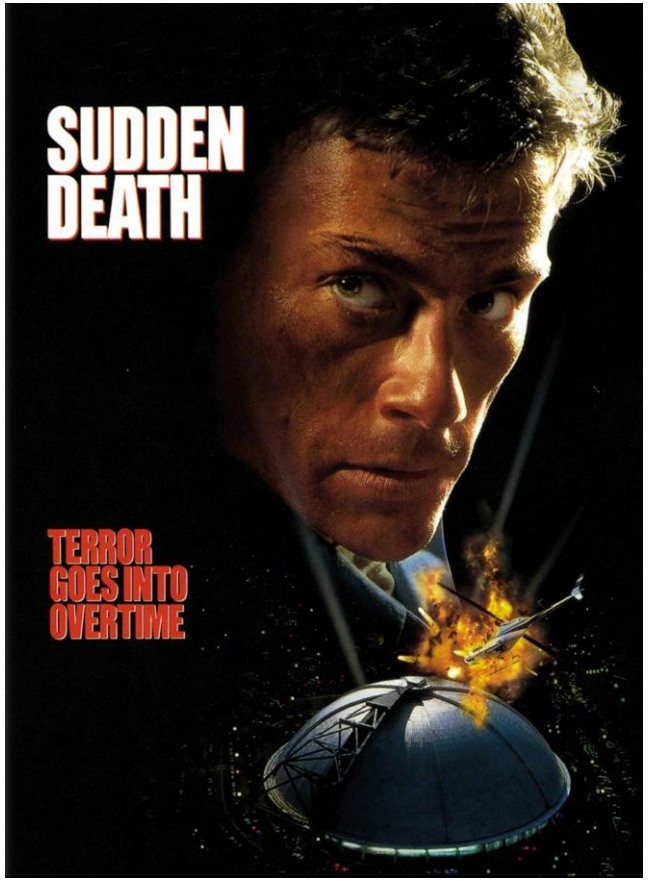
Recreational drugs

- Cocaine
  - Cardiovascular effects:
    - Tachycardia
    - Hypertension
    - Vasoconstriction
    - Enhanced platelet aggregation and thrombosis
    - Arrhythmias

sudden death of a young person

  - CNS effects:
    - Fever
    - Seizures
  - Pregnancy:
    - Fetal hypoxia
    - Spontaneous abortion

due to vascular effects



Recreational drugs

- Heroin
  - Derived from poppy plant
  - Closely related to morphine
  - Usually injected intravenously or subcutaneously
  - **Purity varies widely**
    - Often cut with talc or quinine

he once saw a patient with quinone toxicity

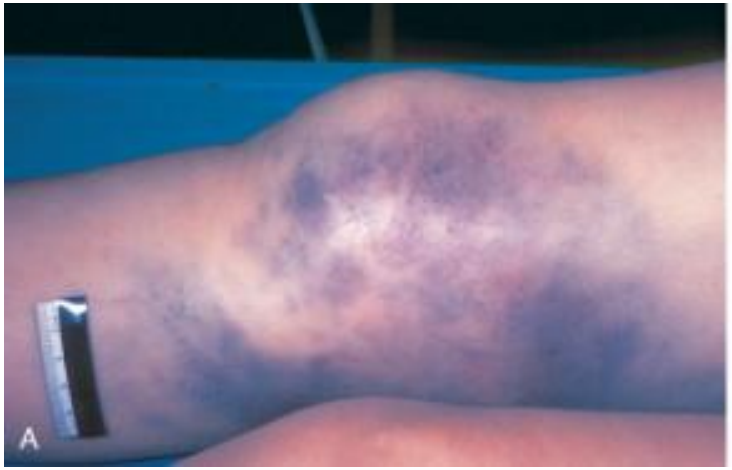
Recreational drugs

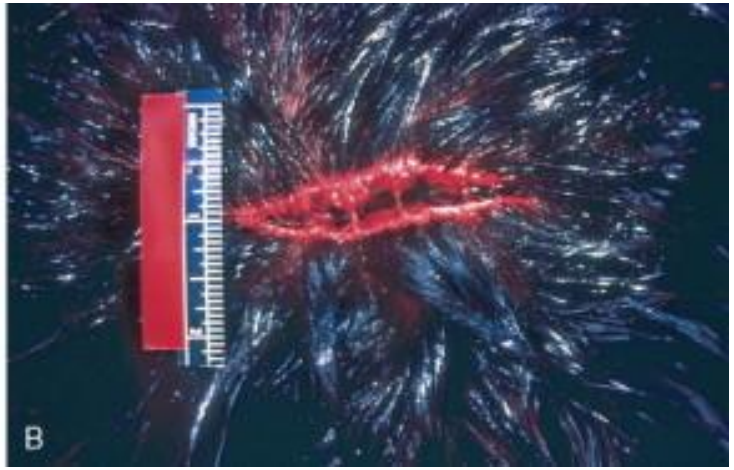
- Heroin — the most dangerous recreational drug
  - Sudden death
    - Overdose
    - 1-3% yearly mortality among heroin users
    - Respiratory depression, arrhythmia, cardiac arrest
  - Infections — dirt / crud from shared needles
    - Endocarditis: Usually involves **right-sided heart valves**, caused by ***Staph. aureus***
    - Skin and other sites
  - Lung, renal, and skin injury

Physical agents

Physical agents

- Mechanical trauma
  - Car accidents, stabbings, shootings, falls, beatings, etc





IMPORTANT TERMS TO KNOW:

Contusion

rupture of small capillaries
- can occur in brain / liver
- swelling can affect function of organs

Laceration (bridging strands)
(compare with incised wounds)

tear

Physical agents

- Mechanical trauma

IMPORTANT TERMS TO KNOW:

Abrasion scraped

Fracture

Physical agents

- Thermal injury
  - 500,000 burning / scalding injuries treated per year in the United States
  - 4000 fatalities per year due to burns and smoke inhalation
  - Marked improvements in treatment over the past three decades
    - 90% survival in 40,000 hospitalizations (2007)

in children

have very good treatment

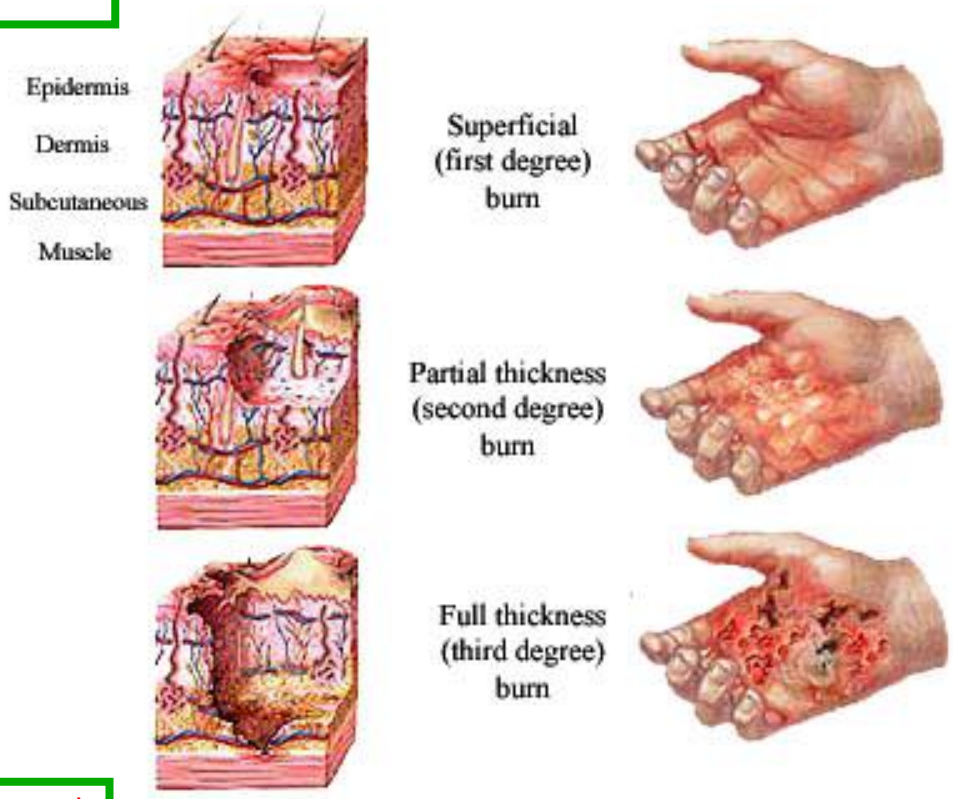
Physical agents

- Thermal injury
  - **Superficial** (first-degree): Epidermis only
  - **Partial thickness** (second-degree): Epidermis and dermis
  - **Full thickness** (third- and fourth-degree): Subcutaneous tissue, muscle

don't really use the "degrees" of burn any more

blistering

charring - may not be painful because the nerves are burned



Physical agents

- Thermal injury
  - Shock
    - Rapid fluid shift into interstitial compartment
    - Extensive protein extravasation
    - Hypovolemic shock

massive edema

Physical agents

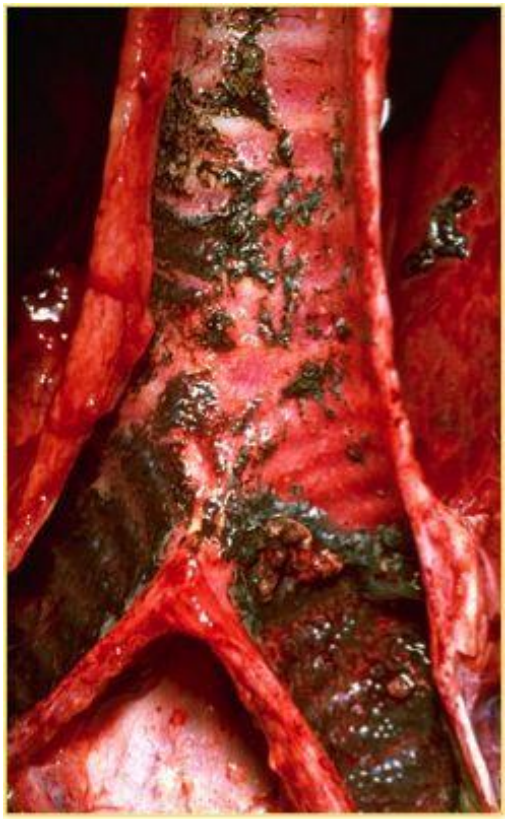
- Thermal injury
  - Sepsis
    - Burned skin, serum, and debris along with impaired blood flow and other weakened host defenses are fertile ground for infection
    - ***Pseudomonas aeruginosa*** is the most common offender, but others (e.g. Staph aureus) may also be involved

review: smells like grapes

Pseudomonas aeruginosa on *Pseudomonas* isolation agar

Physical agents

- Thermal injury
  - Respiratory insufficiency
    - Typically develops 24 to 48 hours after the burn
    - May result from direct thermal effects or from noxious gases in smoke
    - Airway inflammation and swelling may cause obstruction
    - Pneumonitis and pulmonary edema



Soot in airway

person inhaled smoke into lungs

Physical agents

last slide that he got to

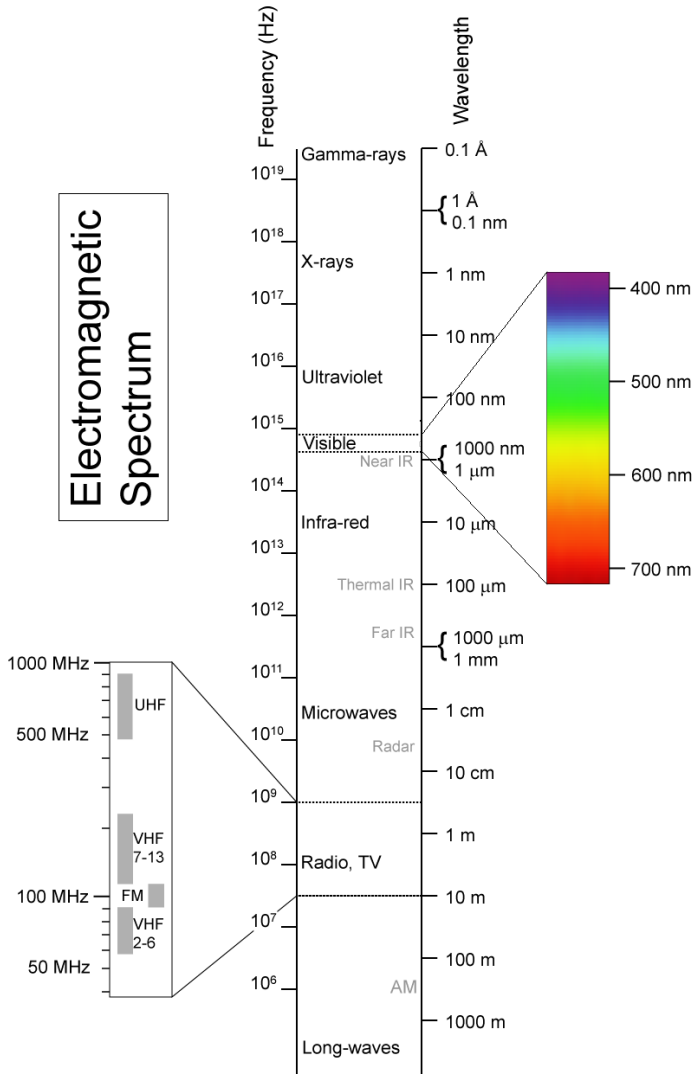
- Electrical injury
  - Two injury types:
    - **Burns**
    - **Arrhythmias** (ventricular fibrillation)
  - Severity depends on current (amperage), duration, and path of the current
  - Household current (120 or 220 VAC) is enough to kill

Lichtenberg figures (“ferning”) on lightning strike victim

Physical agents

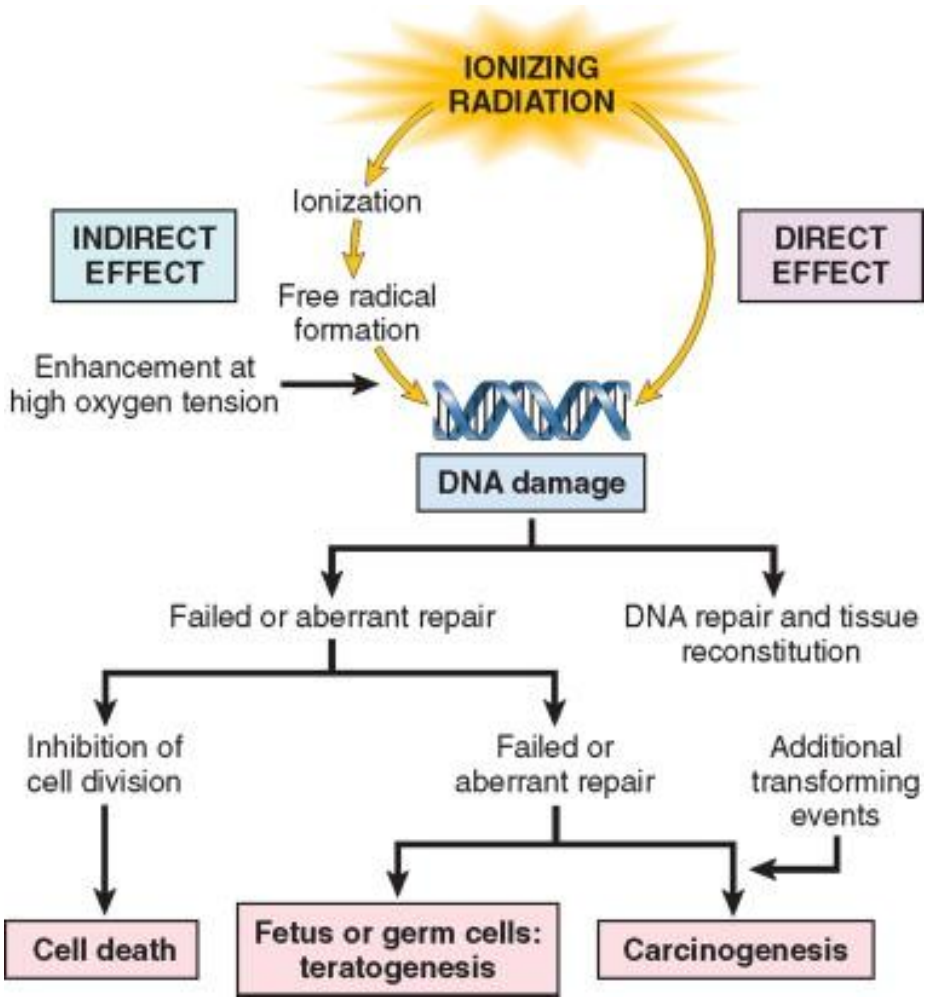
see the book for more info

- Ionizing radiation
  - Main sources:
    - **Gamma rays** (high-frequency electromagnetic rays)
    - **X-rays** (high-frequency electromagnetic rays)
    - **Alpha particles** (two protons and two neutrons)
    - **Beta particles** (electrons)
  - 25% of total dose of ionizing radiation received by the US population is man-made



Physical agents

see the book for more info



Physical agents

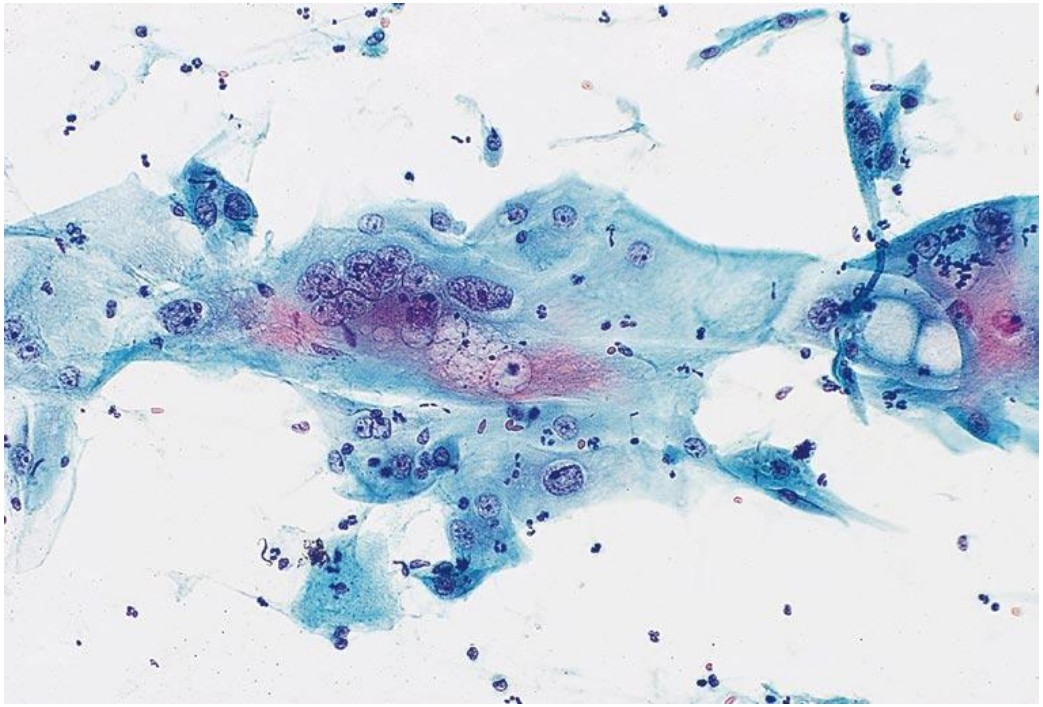
see the book for more info

- Ionizing radiation
  - Determinants of biological effects
    - **Rate of delivery**
      - Effects of radiation are cumulative, but divided doses may allow “repair” during intervals
    - **Field size**
      - Larger field size is much more dangerous
    - **Cell proliferation**
      - Rapidly dividing cells (gonads, bone marrow, GI mucosa) are much more susceptible
      - Non-dividing cells may be damaged at high doses due to impaired transcription of DNA
    - **Oxygen effects**
      - Poorly-vascularized tissues (e.g. the center of a tumor) are less susceptible

Physical agents

see the book for more info

- Ionizing radiation
  - Chromosomal effects
    - Double-strand breaks
    - Structural chromosomal changes (deletions, breaks, translocations)
    - Polyploidy and aneuploidy
  - Cytologic effects
    - Pleomorphism
    - Multinucleation
    - Abnormal mitotic figures
    - Giant cells



Radiation atypia in squamous cells (Pap smear)

see the book for more info

Major morphologic consequences of radiation injury

Particularly important systemic effects:

- **Hematopoietic system changes**
  - Occur within hours and persist for months
- **Fibrosis**
  - May occur weeks to months after radiation damage
- **Carcinogenesis**
  - Increased risk for cancers of the **thyroid** and for **leukemia and lymphoma**, in particular
  - Risk likely increased by radiation equivalent to ten diagnostic CT scans