

More Applications of Pharmacology & Toxicology

Week 4

Objectives

1 of 3

- List the toxic constituents of tobacco smoke and describe briefly the organ specific carcinogens found in tobacco smoke.
- Describe briefly the health hazards of smoking, list the causes of death attributed to tobacco smoking, and describe briefly the consequences of maternal smoking on fetus
- List the common drugs of abuse.
- Describe the effect of cocaine on neurotransmitters.
- Describe briefly the adverse health effects of intravenous drug abuse
- exogenous estrogen (Hormonal Replacement Therapy), and oral contraceptive pills.

Objectives

2 of 3

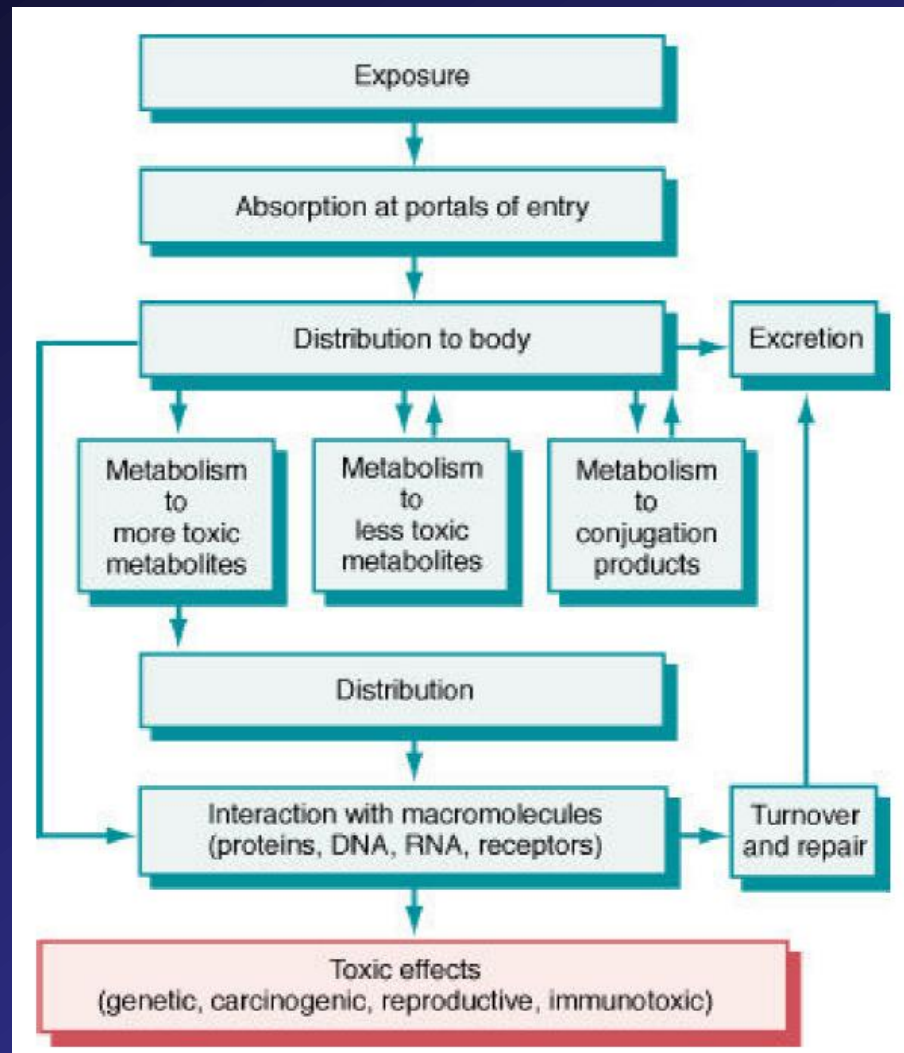
- Define “Xenobiotics” and explain how the body prevents their actions.
- Describe the disruption of normal cell functions by Xenobiotics and list the possible toxic effects of xenobiotics and examples of the target organs.
- List few examples of serious risks associated with the usage of certain personal care products.
- List examples of chemicals of concern in cosmetics / personal care products.
- Define “ Phthalates”, and describe its uses, its possible harmful effects on males and females and mention the possible routes of exposure.

Objectives

3 of 3

- List the different mechanisms of drugs interaction. Give examples of some drugs interactions and mention their impact
- Describe the health concerns of using herbal supplements and mention some example of their interactions with drugs and their possible harmful effects
- Describe the categories of diet-drug interaction and mention the possible adverse effects of these interactions
- Define “Endocrine disruptors”, give examples and describe their different mechanisms of action on th

Toxicokinetics & Toxicodynamics Review



Personal Exposure: Tobacco

- Tobacco has damaging effects on every organ in body
 - cancer, heart and lung disease, stroke, diabetes, COPDs, erectile dysfunction, increased risk for TB, eye disease
- 480,000 US deaths annually, 41,000 from 2nd hand smoke
- 16 million (1 in 20) Americans have smoking-related diseases
- 6 million die annually worldwide (to be 8 million in 2030)
- Longevity of smoker reduced 10 years
- 17.8% (42 million) Americans are smokers (20.5% of US males, 15.3% of US females)
- US Youth: 5.6 million of Americans ≤ 18 y age to die prematurely from smoking-related illness (1 in 13 ≤ 17 age alive today)
- 3200 young people smoke 1st cigarette every day, and 2100 per day "graduate" to regular smokers

Source: CDCP

Personal Exposure: Tobacco

Government (& Taxes)

- States collect \$25.6 billion (2015) in tobacco taxes & legal settlements but spend on \$490 million (2%) on prevention & cessation programs
- CDC-recommended levels of anti-smoking funding total \$3.3 billion for all states, but only ND & AK fund at recommended levels and DE, OK, HI, WY, and ME fund at half recommended level

Costs

- \$9.17 billion in 2012 (\$25 million/day, \$1 million/hour) to promote smoking, heavy price discounting in industry
- \$300 billion/y = \$170 billion direct medical costs + \$156 billion lost productivity (premature death + exposure to 2nd hand smoke)

Stopping Addiction

- 7 in 10 adults wanted to stop smoking, 4 in 10 made attempt
- 100,000 expected to remain tobacco-free from a 2012 *Tips From Former Smokers* campaign

Sources: CDCP

Personal Exposure – Tobacco Use:

- Smoke from a burning cigarette is a “concentrated aerosol of liquid particles suspended in an atmosphere consisting mainly of nitrogen, oxygen, carbon monoxide and carbon dioxide” *
- **Tar** is the total particulate phase without water or nicotine
- > 4000 constituents, including 43 known carcinogens
- toxic & carcinogenic metals (e.g. arsenic, nickel cadmium, & chromium).
- toxic promoters: acetaldehyde and phenol
- toxic irritants: NO_2 & formaldehyde (HCHO)
- Carbon monoxide: stronger binding affinity to heme in hemoglobin than O_2

* Guerin, Banbury Report #3 (1980)

Nicotine (Toxicokinetics)

- $pK_a = 8.0$ (weak base)
- Absorption
 - Oral ingestion pH-dependent: products (chewing tobacco, snuff, nicotine gum) alkalinized to facilitate absorption in buccal mucosa
 - Inhalation also bypasses intestinal & hepatic metabolism
- Distribution
 - 5% plasma protein binding
 - $V_d = 2.6$ times body
 - autopsy samples: highest concentrations in liver, kidney, spleen lung, lowest in adipose tissue

Nicotine

- Metabolism

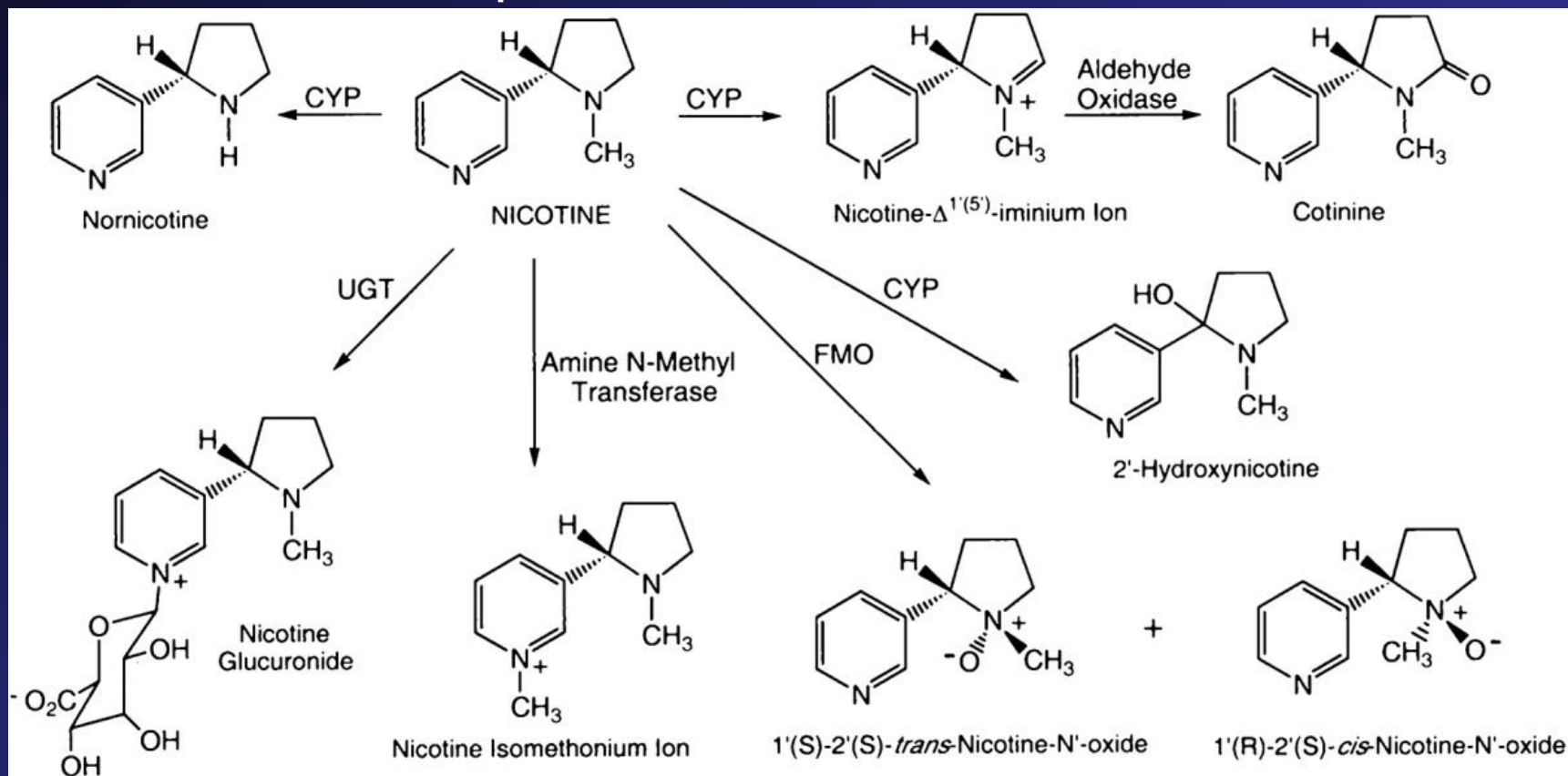
- Liver CYP2A6: to cotinine (compliance marker)
- Other CYP and nonCYP enzymes modify functional groups
- extensive metabolite products (see next slide)

- Excretion

- Glomerular and tubular secretion: organic cation transporters (not MDR: Pgp)
- Fecal-biliary identified
- Sweat

Primary biotransformation pathways identified for nicotine

Does not encompass all metabolites



Organ Specific Carcinogens in Tobacco Smoke

Larynx, lung

- polycyclic aromatic hydrocarbons (PAHs)
- polonium 210
- 4-(methylnitrosoamino)-1-(3-pyridyl)-1-buta-none (NNK)

Esophagus

- N'-Nitrosonornicotine (NNN)

Pancreas

- NNK

Bladder

- 4-Aminobiphenyl, 2-naphthylamine

Oral cavity

- smoking: PAHs NNK, NNN
- snuff: NNK, NNN, polonium 210

Health Hazards of Smoking

- The inhaled smoking agents in cigarette smoke may act directly on the –mucous membranes, may be swallowed in saliva, or may be absorbed into bloodstream from abundant alveolar capillary bed.
- Inhaled smoke causes a variety of systemic diseases than can lead to death:
- Carcinogenic effect: Increase in the incidence of cancer of the organs listed earlier.
- Cigarette smoke act synergistically with other risk factors in the development of atherosclerosis and in turn ischemic heart disease, peripheral vascular disease and cerebrovascular accidents.

Health Hazards of Smoking

- Respiratory tract infections, exacerbation of other lung diseases
- Chronic obstructive lung disease-chronic bronchitis and emphysema
- Higher rates of accidents at work place
- Increases the prevalence of peptic ulcer
- Effects of side-stream (passive smoking)

Causes of Death Attributed to Cigarette Smoking

- Cancer
 - upper aerodigestive tract: lips, mouth, tongue, nose, throat, vocal cords, upper esophagus & trachea
 - lung, bladder, cervix, pancreas and stomach
- Ischemic heart disease
- Cerebrovascular disease
- Arteriosclerosis
- Chronic respiratory disease

Maternal Smoking Effects on Fetus & Infant

- fetal hypoxia
- low birth weight
- premature birth
- increased spontaneous abortion incidence
- premature rupture of membranes
- *placenta previa*: obstetric complication where placenta inserted partially or wholly in lower uterine segment, causes antepartum vaginal bleeding
- *abruptio placenta*: pregnancy complication wherein placental lining separates from uterus, most common cause of late pregnancy bleeding

Drugs of Abuse

CNS Depressants

- ethanol, barbiturates, benzodiazepines

CNS Stimulants

- Cocaine, amphetamine

Narcotics

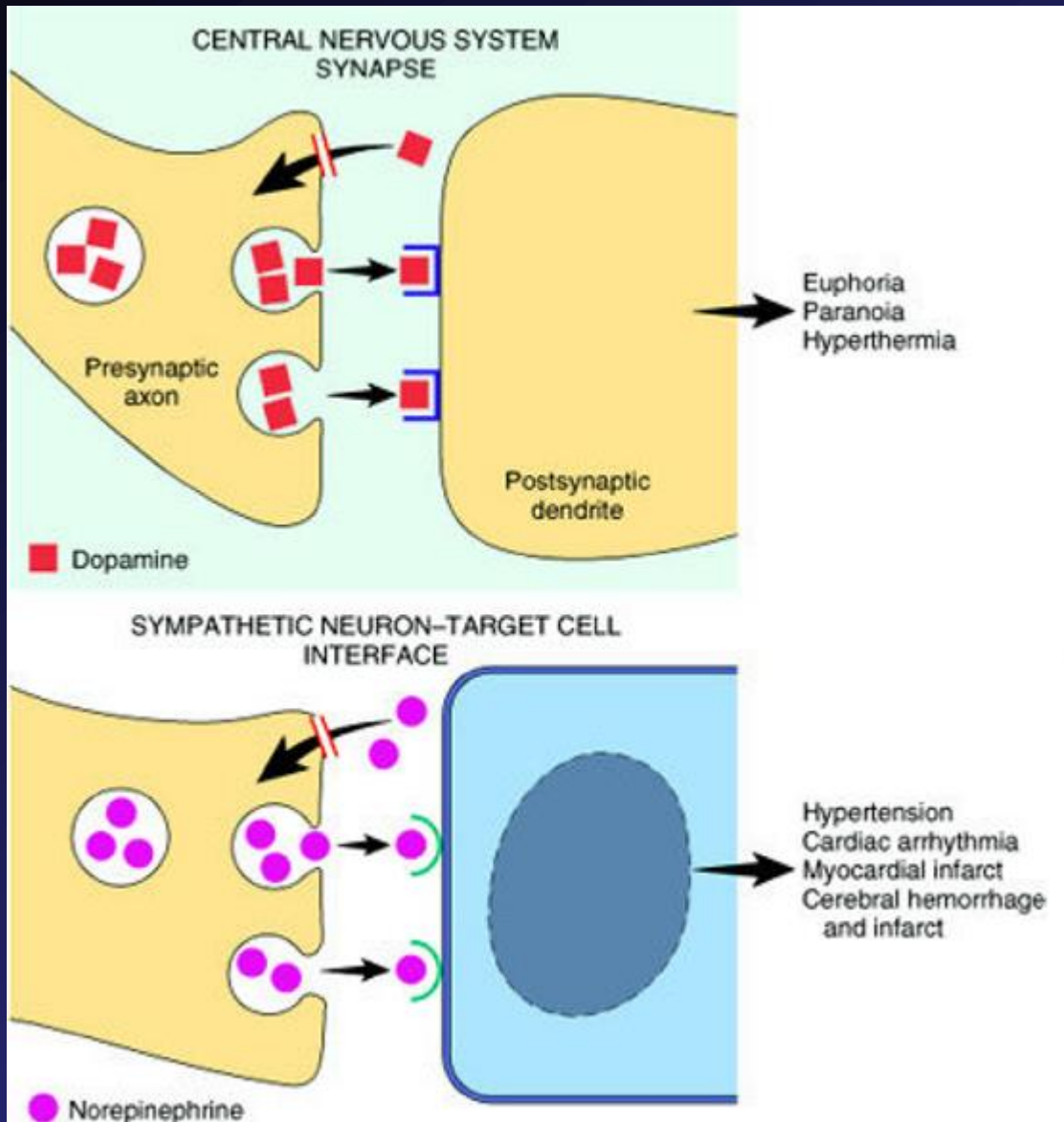
- opiates: morphine, heroin, codeine
- synthetic opioid: meperidine
- propoxyphene

Hallucinogens/Psychedelics

- marijuana, mescaline (peyote),
lysergic acid diethylamide (LSD),
psilocybin (mushrooms)

Intravenous Drug Abuse

- Narcotics –overdose causes convulsions, cardiac and respiratory arrest, death
- Chronic use: tolerance and dependence
- All IV drug users are susceptible to infections
 - High incidence of HIV infection, AIDS
 1. Four sites most commonly affected
 2. skin and subcutaneous tissue
 3. heart valves, liver (viral hepatitis)
 4. lungs
 - Organisms causing right-sided endocarditis and tricuspid valve damage: most commonly *Staphylococcus aureus*; others include fungal infections (*Candida*) and other organisms



- Cocaine inhibits the reuptake catecholamine dopamine transporter in the presynaptic axon terminal, which means dopamine remains in the synaptic cleft, continuing to stimulate the postsynaptic neuron
- It can also inhibit reuptake of norepinephrine (NEpi) in neurons which use NEpi to stimulate effector cells and tissues, creating dangerous physiological effects

Therapeutic Drugs

- Exogenous estrogen (hormone replacement therapy “HRT”):
 - Used widely in postmenopausal women
 - Adverse effects:
 - Endometrial carcinoma- increased risk
 - Breast carcinoma- slightly increased risk
 - Beneficial effects:
 - CVS - estrogens tend to elevate the levels of HDL, and reduce the level of LDL

Therapeutic Drugs

- Oral contraceptives:
 - Adverse effects
 - Breast carcinoma-slight increase in the risk
 - Hypertension – slight increase in BP
 - Gall bladder disease
 - Thromboembolism-clearly associated with increased risk
 - Hepatic adenoma-well defined association with this tumor
 - Beneficial:
 - Protect against ovarian cancer

Xenobiotics

- A **xenobiotic** is a chemical which is found in an organism but is not normally produced or expected to be present in it
- It can also cover substances which are present in much higher concentrations than are usual. Specifically, drugs such as antibiotics are xenobiotics in humans because the human body does not produce them itself, nor are they part of a normal diet.
- Natural compounds can also become xenobiotics if they are taken up by another organism, such as the uptake of natural human hormones by fish found downstream of sewage treatment plant outfalls, or the chemical defenses produced by some organisms as protection against predators

How Does the Body Prevent the Actions of Xenobiotics ?

- 1) Redistribution

- 2) Excretion

 - sites of excretion*

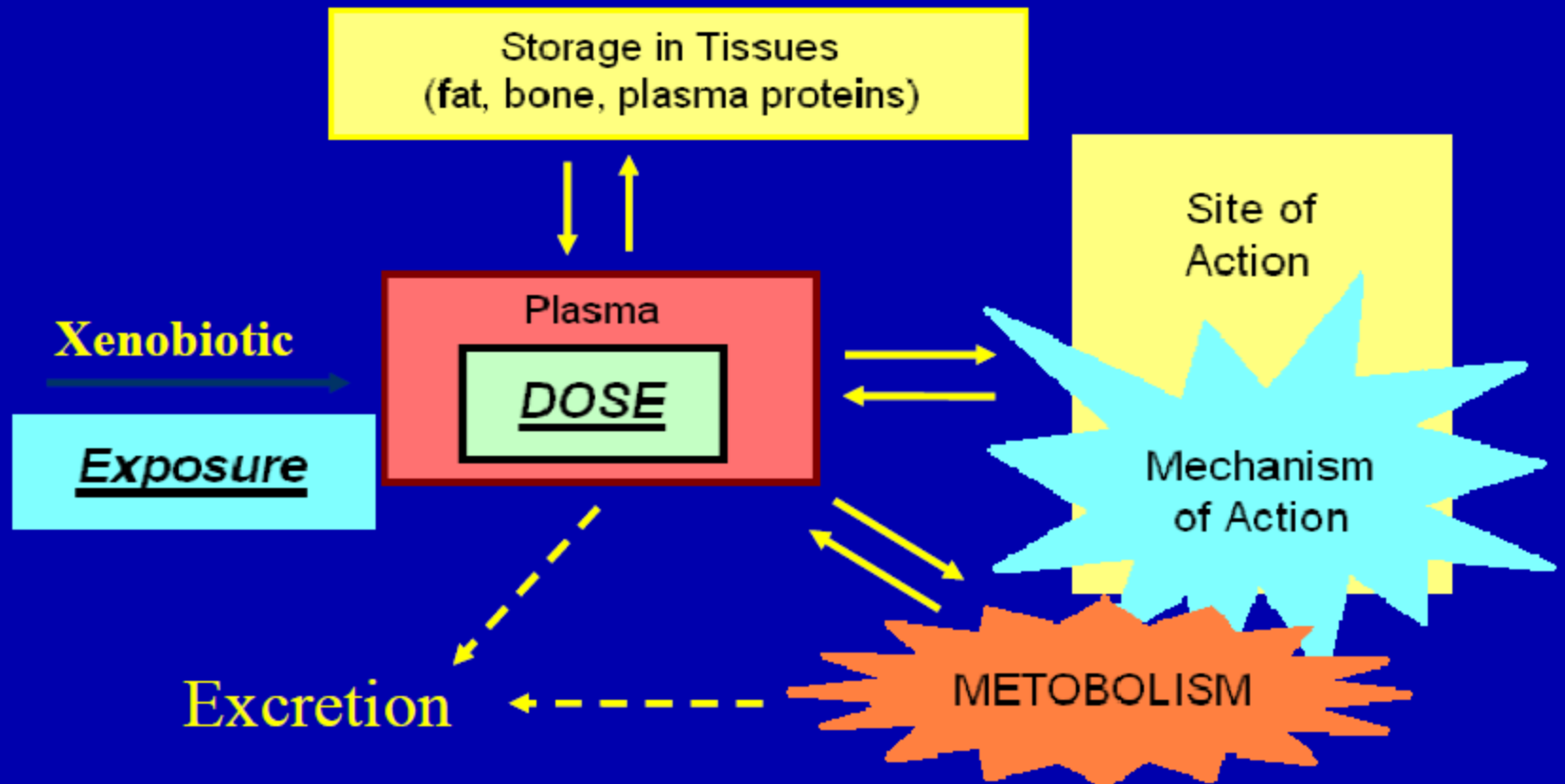
 - kidney in urine
 - liver as water-soluble forms (conjugates) in bile

- 3) Metabolism – the major mechanism for terminating xenobiotic activity, and is frequently the single most important determinant of the duration and intensity of toxic responses to a xenobiotic

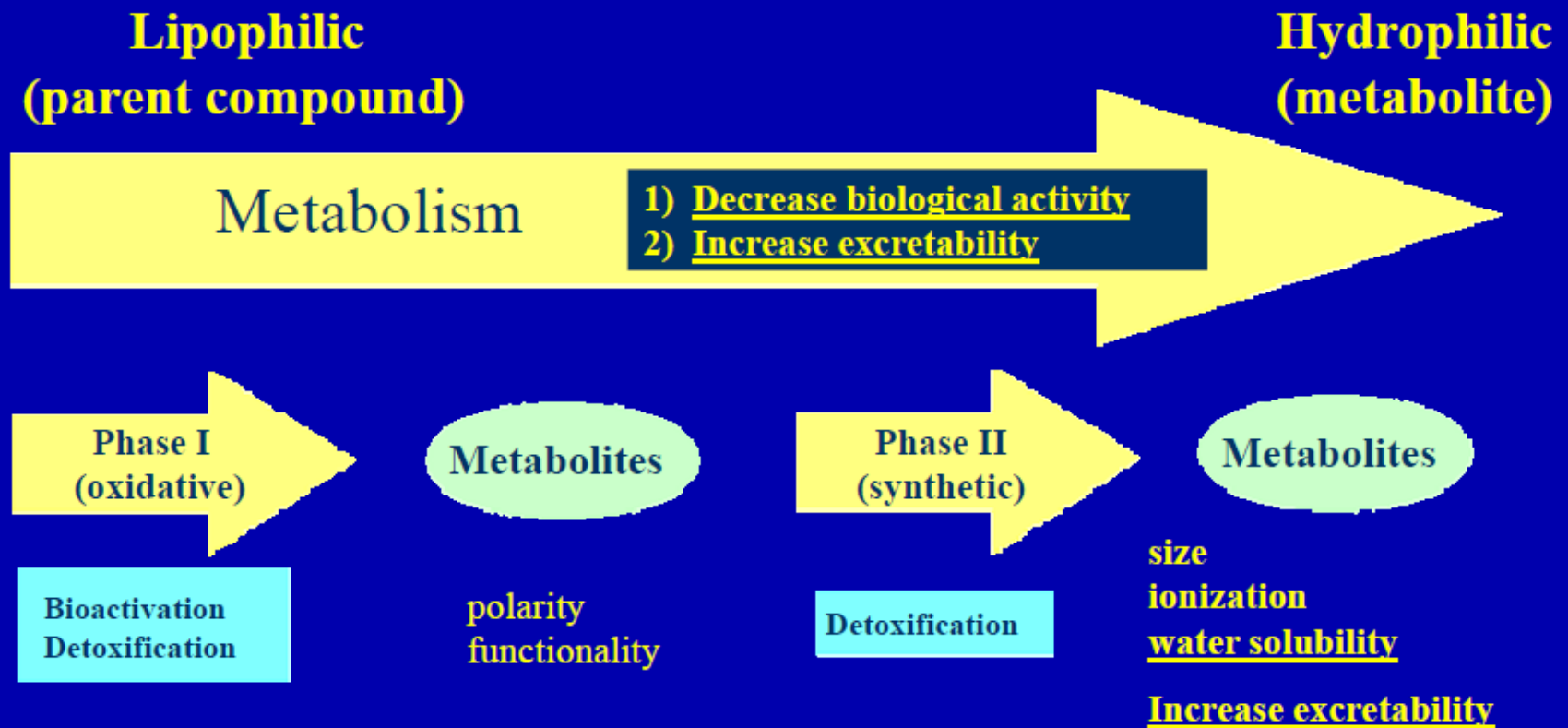
 - *sites of metabolism*: liver, kidney, lung, GI, and others

Note: 1) & 2) are highly dependent on 3)

TOXICOKINETICS



General Scheme of Xenobiotic Metabolism



Personal Care Products

Why are Personal Care Products Potentially Harmful

- Small-sized (low molecular weight) molecules in formulations
 - easy and quick dermal penetration into bloodstream
 - build up in organs and storage depot tissues

Is the cosmetic counter really a dangerous place?

- risks and conditions: irritation or allergic reaction, swelling and lesions, contact dermatitis, flushing, headaches, dizziness, nausea, diarrhea, hair loss, and vomiting

Personal Care Products

- More serious risks and conditions
hyper/hypo-pigmentation, violent coughing, labored breathing, eye “problems” and damage, disruption of cell development, destruction of proteins and cellular structure, premature aging, mental depression
- Even more serious risks and conditions
 - hypoxia, narcosis
 - damage to immune system, respiratory system, reproductive organs, brain, liver, and kidney

Personal Care Products

- According to industry estimates, on any given day a consumer may use as many as 25 cosmetic products containing more than 200 different chemical compounds
- 89% of the ingredients used personal care products have not been screened for safety by FDA or anyone else

Examples of chemicals of concern in cosmetics / personal care products:

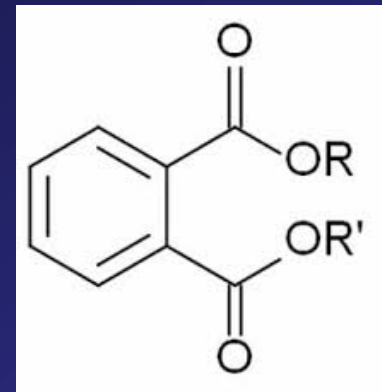
- carcinogens: acrylamide, formaldehyde, petroleum distillates–diethanolamine, 1,4-dioxane
- endocrine disruptors/reproductive toxins: phthalates, parabens, toluene
- neurotoxins: lead acetate, mercury.

Nail Salons & Their Workers

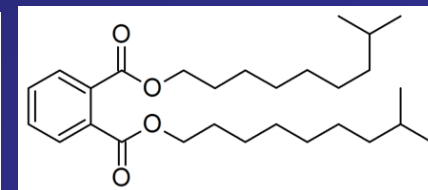
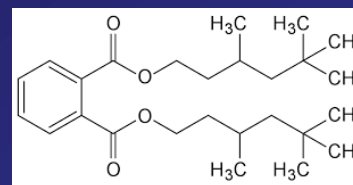
- 400,000 employed nationwide (96% women)
- Exposed to acetone, toluene, formaldehyde, phthalates, methylacrylates, toluene sulfonamide formaldehyde (TSF) resin, and other volatile organics
- Occupational Safety & Health Administration (OSHA) exposure standards do not address low-dose, long-term (chronic) exposure
- State government regulation may be very inadequate
- Some safer products are available -but workers may not be aware of them
- Use of special ventilation products: ventilated tables

Phthalates

Chemicals softening & increasing flexibility of plastic & vinyl: polyvinyl chlorides (PVC) mixed with these to make softer



- Diisononyl phthalate (DINP)
heat & cold & volatility resistance
- Diisodecyl phthalate (DIDP)
used to reduce volatility, resist heat, resists aging, in electrical insulation
- Dibutyl phthalate (DIBP)
ingredient in nail polish, explosives, lacquer, plastic for molds
- Di-2-ethylhexyl phthalate (DEHP)
used to make PVC



Environmental Phthalates

- Phthalates represent 80–90 % of global plasticizer consumption
- Used primarily as plasticizers in polyvinyl chloride (PVC) products
 - Child's toys, kitchen floors, building materials
 - Medical devices: Plastics in IV tubing/parts, blood bags
- Perfumes: slows evaporation, makes scent last longer
Other uses: polish from chipping, hair sprays, new car smell (Partly the pungent odor of phthalates volatilizing from a hot plastic dashboard), nail extenders, bath soaps, detergents, aftershave lotions
- Highest level of exposure reported for women of child-bearing age: High levels of DEP, DBP, BBP
Likely sources exposures through cosmetics: hair sprays, nail polishes and perfumes, which are common uses of DBP

Reproductive Development & Phthalates

- Low dose levels of phthalates may produce risks for reproductive anatomy/function during development
- Male experimental animals (rats) had dramatic changes in male sexual characteristics when exposed in utero to DBP & DEHP far below acute toxicity levels
 - Hypospadias (anomaly of the urethra).
 - Damage of Sertoli cells
 - Low sperm count + reductions in semen quality
 - DNA damage to sperm.
- Effects on females
 - Premature breast development.
 - Premature birth.
 - Carcinogenic.
- At higher doses, mice and rats show liver damage

Drug Interactions

- Drug interaction can be unidirectional or bidirectional: drug 1 can alter drug 2 ADME or each can influence each other

Classification of mechanism of interaction

- Alteration in absorption
 - complexation/chelation
e.g. antacids + tetracycline and this causes tetracycline complexes with divalent cations forming an insoluble complex
 - altered GI transit
e.g. anticholinergics + acetaminophen and this causes delay in absorption of acetaminophen
 - altered gastric pH
e.g. H-2 blockers + ketoconazole: dissolution of ketoconazole is decreased, resulting in reduced absorption

Drug Interactions

- Alteration in hepatic metabolism

- induction of metabolism

- e.g. phenobarbital + warfarin: phenobarbital increases the metabolism of warfarin, resulting in reduced anticoagulation

- inhibition of metabolism

- e.g. cimetidine + theophylline: cimetidine reduces the clearance of theophylline causing an increase in adverse effects

- Alteration in plasma protein binding

- e.g. phenytoin + valproic acid: protein binding of valproic acid is reduced.

Drug Interactions

- Alteration in renal clearance

- increase in renal blood flow

- e.g. hydralazine + digoxin: hydralazine increases the renal clearance of digoxin

- inhibition of active tubular secretion

- e.g. probenecid + penicillin: probenecid prolongs the half-life of penicillin, allowing single dose therapy

- alterations in tubular reabsorption

- e.g. antacids + aspirin: antacids reduce the tubular reabsorption of salicylate via an increase in urine pH

Herbs / Herbal Products

- Widespread consumer use as dietary supplements
- Not controlled by FDA if not marketed to prevent, diagnose, cure, treat, or mitigate disease
 - If FDA can show "unsafe," can remove from market
- Efficacy
 - Many salutary benefits claims unproven
 - Limited studies support traditional use/benefits
- Safety
 - GRAS: natural forms Generally Regarded As Safe
 - Variations in preparations may produce toxic form

Herbs / Herbal Products

- Interactions

- Some could prolong or inhibit actions of other herbs or drugs

- Contamination

- some products found to contain lead & other toxic metals, even added, to the preparation
 - other contaminants include molds, bacteria, pesticides

- Adulteration of imported products, including addition of synthetic drugs not identified on labels

Examples of Herb-Drug Interactions

Herb	Drug	Interaction
American ginseng	Estrogens, corticosteroids	Enhances hormonal response
American ginseng	Breast cancer therapeutic agent	Synergistically inhibits cancer cell growth
American ginseng, karela	Blood glucose regulators	Affect blood glucose levels
Echinacea (possible immunostimulant)	Cyclosporine and corticosteroids (immunosuppressants)	May reduce drug effectiveness
Evening primrose oil, borage	Anticonvulsants	Lower seizure threshold
Feverfew	Aspirin, ibuprofen, and other nonsteroidal anti-inflammatory drugs	Negates the effect of the herb in treating migraine headaches
Feverfew, garlic, ginkgo, ginger, and Asian ginseng	Warfarin, coumarin (anticoagulating drugs, "blood thinners")	Prolong bleeding time; increase likelihood of hemorrhage
Garlic	Protease inhibitor (HIV drug)	May reduce drug effectiveness
Kava, valerian	Anesthetics	May enhance drug action
Kelp (iodine source)	Synthroid or other thyroid hormone replacers	Interferes with drug action
Kyushin, licorice, plantain, uzara root, hawthorn, Asian ginseng	Digoxin (cardiac antiarrhythmic drug derived from the herb foxglove)	Interfere with drug action and monitoring
St. John's wort, saw palmetto, black tea	Iron	Tannins in herbs inhibit iron absorption
Valerian	Barbiturates	Causes excessive sedation

Drug-Diet Interaction

Diet-drug interactions fall into the following categories:

- Medications can alter food intake by suppressing appetite or causing complications that interfere with food intake.
- Medications can alter absorption, metabolism & excretion of nutrients.
- Nutrients & other food components can alter absorption, metabolism & excretion of medications.
- Some interactions between food components & medications can be toxic

Effects of Drug on Diet

- Drug effects on food ingestion
 - nausea & vomiting affecting appetite
 - alteration of taste sensations
 - dry mouth
 - inflammation or lesions in mouth or GI tract
 - abdominal discomfort
 - constipation
 - diarrhea
 - drowsiness

Effects of Drug on Diet

- Drug effects on nutrient absorption
 - antineoplastic & antiretroviral medications: damage of intestinal mucosa
 - ciprofloxacin: prevents nutrient absorption
 - antacids: reduced gastric acidity lowers absorption of vitamin B₁₂, folate & iron
 - some drugs interfere with absorption of intestinal transporters
- Drug effects on nutrient metabolism
 - methotrexate: inhibits folate-mediated metabolism
- Drug effects on nutrient excretion
 - reduced mineral reabsorption in kidney tubules
 - increased excretion of vitamins, minerals (vit B₆)

Dietary Effects

- Dietary effects on drug absorption:
 - Stomach emptying rate
taking medications on empty stomach tends to increase absorption rate; taking medications on full stomach may delay its absorption rate (ex. Aspirin).
 - Stomach acidity
absorption rates affected by acid or alkaline medium
- Interactions with food components: may bind with drugs & inhibit absorption.

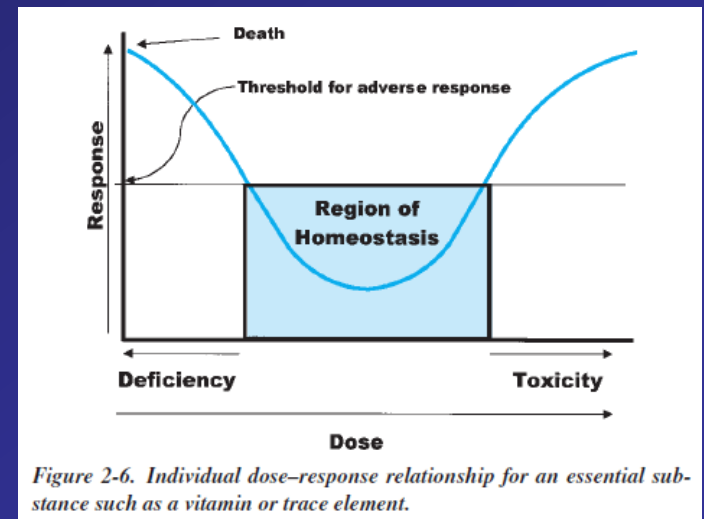
Dietary Effects

- Dietary effects on drug metabolism:
 - alteration in activities of enzymes that metabolize drugs
 - increased blood concentration of drug (stronger physiological effects): e.g. grapefruit and statins (lipid lowering drugs).
 - Decreased effectiveness of drug
e.g. warfarin and Vit. K
- Counteraction of drug effects in other ways

- Alterations in excretion causing toxicity or reduced effectiveness of the drug:
 - Increased or decreased reabsorption (e.g. Li and Na).
 - Alterations in drug actions
- Diet-drug interactions & toxicity
 - interactions can result in toxicity or exacerbate drug side effects
 - e.g. MAOIs “antidepressants” potentiates the pressor effect of the monoamine tyramine “found in cheese”
- Health professions must understand mechanism of action of drugs & diet-drug interactions for identification &/or prevention.

Vitamins & Minerals

- *Vita* "life" + *amin(e)* "amino acid"
- The essential drug: deficiency as bad as overdose
- Coenzymes in countless metabolic pathways, including detoxifying reactions (NAD, FAD/FMN)
- Author of *Vitamania* C Price:
The healthiest and safest doses of vitamins are the ones naturally occurring in foods



Supplementation Industry Facts

- \$18 billion with 7% avg annual growth 2010-2015
- 1031 businesses employing 27,000
- Vitamin & mineral supplements may be prescribed in pathological deficiencies
- At least no harmful effect with overdosing most (water-soluble) vitamins
- Fat-soluble vitamin A and D could present problem in overdosing (hypervitaminosis)
- sources: IBISWorld

Endocrine Disruptors

Any chemical agent in the environment that can alter normal endocrine system actions leading to deleterious effects on an organism or its progeny

- **Direct-acting disruptors**

hormone or hormone-like agonists or antagonists interfering with hormone actions on target cells, interacting with receptors or effecting physiological activity

- **Indirect-acting disruptors**

alter hormone dynamics in circulation, change hormone metabolism, or interfere with hormone regulation

Examples of Endocrine Disruptors

- Pesticides: herbicides, insecticides
- Plasticizers
- Natural plant metabolites
- Pharmaceuticals: contraceptives, drugs
- Detergents
- Chemicals from cooking & burning
- Antibiotics
- Metals

Effects of Endocrine Disruptors

- Inability to maintain homeostasis
- Altered growth & development
- Altered responses to external stimuli
- Altered behavior
- Suppressed gametogenesis
- Elevated gestational losses
- Embryonic malformation
- Induced neoplasia or carcinogenesis

Mechanism of Endocrine Disruption

- Receptor Mediated
 - Agonistic & Antagonistic
 - Pesticides
 - Polychlorinated biphenyls (PCBs)
- Altered Enzyme Action
 - Nitrate/nitrite
 - Pesticides
 - Phthalates
- Altered Metabolism
 - Pesticides
 - Altered Hormone Availability
 - PCBs/ Polybrominated biphenyls (PBBs)
- Altered Gene Expression
 - Nitrates/nitrite
 - Pesticides
 - PCBs

Endocrine Disruption Effects on Females

- Impaired fertility
- Endocrine dysfunction: altered hormone profiles
- Reproductive system structure alteration
increasing incidence of uterine and oviduct abnormalities
- Brain and behavior
altered IQ and behavior, including sexual behaviors
- Cancer
increasing incidence of breast, ovarian, and uterine cancers
- Endometriosis
abnormal outgrowth of endometrial tissue beyond uterus
- Age at which puberty is reached
- Immune dysfunction
- Multigenerational effects

Effects on Males

- Declining fertility
 - fall in sperm count
- Endocrine dysfunction
 - altered hormone profiles
- Reproductive system structure alteration
 - increasing incidence of hypospadias (urethral opening not at penis tip but underside) and cryptorchidism (undescended testes)
- Brain and behavior
 - same as for female
- Cancer
 - increasing incidence of testicular & prostate cancers
- Age of Puberty.
- Immune dysfunction.
- Multigenerational effects

Metabolic Impact

- Toxicants disrupt metabolic pathways
 - Specific enzymes in the pathway
 - Altering proteins that may provide structure or function of vital organelles
- Mitochondrial Dysfunction

Genomic Impact

- Toxicants (or their metabolites = OTM) can enter nucleus and directly chemically modify DNA directly
- Toxicants OTM can alter other biochemicals that can modify DNA detrimentally
- Toxicants can alter the function of enzymes that maintain correct coding of DNA or its expression (DNA repair enzymes, RNA transcribing enzymes)
- Any of these can lead to altered cell biology or to cell death
- Altered cell biology includes loss of cells' ability to control its replication → cancer

Systems Biology (OMICS)

- Science now attempts to get a larger picture (the "whole picture") of what happens in diseased/disordered states, and compare it to healthy states
- It does this by doing experiments and assays to qualitatively and quantitatively determine all the RNA, proteins, and metabolites that are present during a disease state or after a toxicant is administered
- The catalog of these molecules represents the transcriptome, the proteome, and the metabolome, respectively, of cells and tissues. Comparative assessments are done against what is regarded as healthy
- This global analysis

Holistic Management

- Holistic medicine – healing taking into account the "whole person": body, mind, spirit, emotions
- If one part in disorder, then all parts affected
- Patient-centered wellness: diet, exercise, psychotherapy/relationship-spiritual counseling, etc
- "Complementary & alternative therapies": acupuncture, chiropractic care, homeopathy, massage/aroma therapy, naturopathy, etc
- "Western medications, surgical procedures"
- Practitioners: DCs, MDs, DOs, DOMs/DAOMs, NDs/NMDs, LAcS
- Academy of Integrative Health & Medicine (AIHM, formerly American Holistic Medicine Association)

Chiropractic Medicine

- American Chiropractic Association House of Delegates recently passed a resolution calling for "prescriptive authority" and for establishment of College of Pharmacology & Toxicology, but do not endorse the use of pharmaceuticals in the approach to health care

Philosophy of Chiropractic Med

- 70% of Americans now take at least one prescription drug
- Many healing approaches
- What should be the first approach ("resort")?
- Last resort?
- What are your obligations in discussing the resolution to the patient's chief complaint?