Course: *Toxicology, Path-438*

Applications of Pharmacology & Toxicology

Personal Exposure

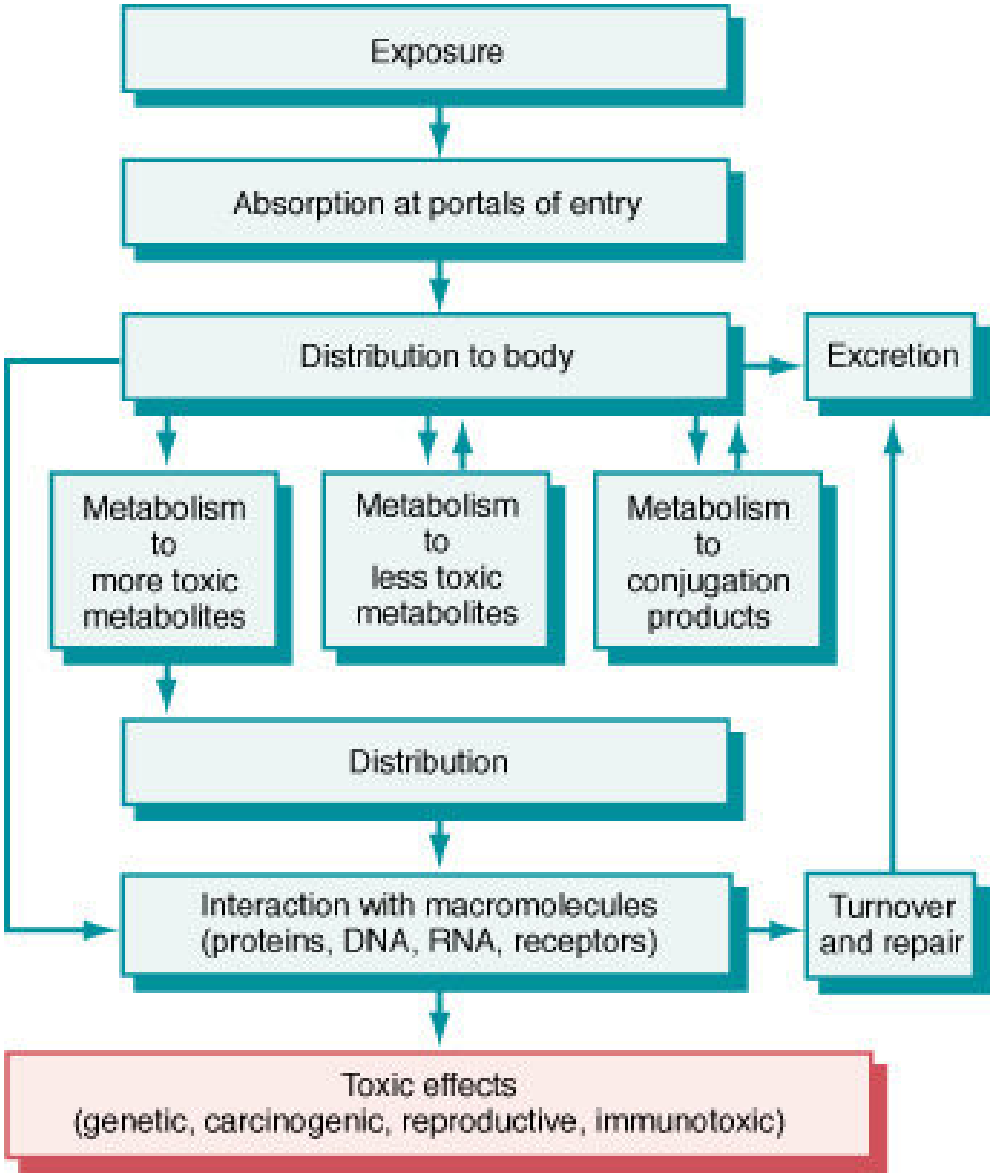
(Tobacco, Alcohol & Drug Abuse)

Acetaminophen Toxicity

Learning Objectives:

- 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
- Describe briefly the metabolism and toxic effects of alcohol abuse.
- 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.
- Describe briefly the dosing, metabolism, and toxicity of acetaminophen.
- Outline the diagnosis and management of acetaminophen poisoning.

Mechanism of Toxicity - *Absorption and Distribution of Toxicants:*



Personal Exposure – *Tobacco Use:*

- Use of tobacco products, including cigarettes, cigars, pipes, and snuff, is associated with more mortality & morbidity than other personal, environmental, or occupational exposure.

- Tobacco use contributes to premature deaths and chronic diseases of cardiovascular and respiratory systems.

- Smoking in teenagers & adults is quite common everywhere in the world.

- Tobacco can act alone as well as in synergistic fashion with other exposures e.g. increased risk of lung cancer in cigarette smokers exposed to asbestos.

Personal Exposure – *Tobacco Use - Constituents of Smoke:*

- Mainstream cigarette smoke inhaled by the smoker is composed of a ***particulate phase*** **&** **a** ***gas phase*****;** ***tar*** is the total particulate phase without water or nicotine *(there are more* ***than 4000 constituents, including 43 known carcinogens):***
  - ***Carcinogenic metals*** ***(e.g. arsenic, nickel cadmium, & chromium).***
  - ***Promoters-acetaldehyde and phenol.***
  - ***Irritants-NO_2 & formaldehyde.***
  - ***CO*** ***(exposure to CO decreases the delivery of O_2 to tissues).***
  - ***Nicotine*** ***(it is an alkaloid that crosses BBB and stimulates nicotine receptor in the brain causing acute pharmacological effects mediated by catecholamine:*** ***increased heart rate & BP, increased coronary artery flow, increased contractility &cardiac output, and mobilization of free fatty acids).*** ***Nicotine is responsible for tobacco addiction.***

Organ Specific Carcinogens in Tobacco Smoke:

- **Larynx, lung:** ***Polycyclic aromatic hydrocarbons, 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):** ***Polycyclic aromatic hydrocarbons, NNK, NNN***
- **Oral cavity (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.*
  - *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 aero-digestive tract, lung, bladder, cervix, pancreas and stomach.*
- *Ischemic heart disease.*
- *Cerebrovascular disease.*
- *Arteriosclerosis.*
- *Chronic respiratory disease.*

Consequences of Maternal Smoking on Fetus:

- **Fetal hypoxia:**
  - **Low birth weight.**
  - **Prematurity.**
  - **Increased incidence of spontaneous abortions.**

- **At the time of delivery:**
  - **Premature rupture of membranes.**
  - **Placenta previa (**is an obstetric complication in which the placenta is inserted partially or wholly in lower uterine segment. It is a leading cause of antepartum vaginal bleeding).
  - **Abruptio placenta (**complication of pregnancy, wherein the placental lining has separated from the uterus of the mother. It is the most common pathological cause of late pregnancy bleeding).

Personal Exposure – *Alcohol Abuse:*

- Ethanol is the most widely used & abused agent through out the world. A blood alcohol concentration of *80–100mg/dL* is the legal definition of driving under the influence of alcohol in many states and countries.

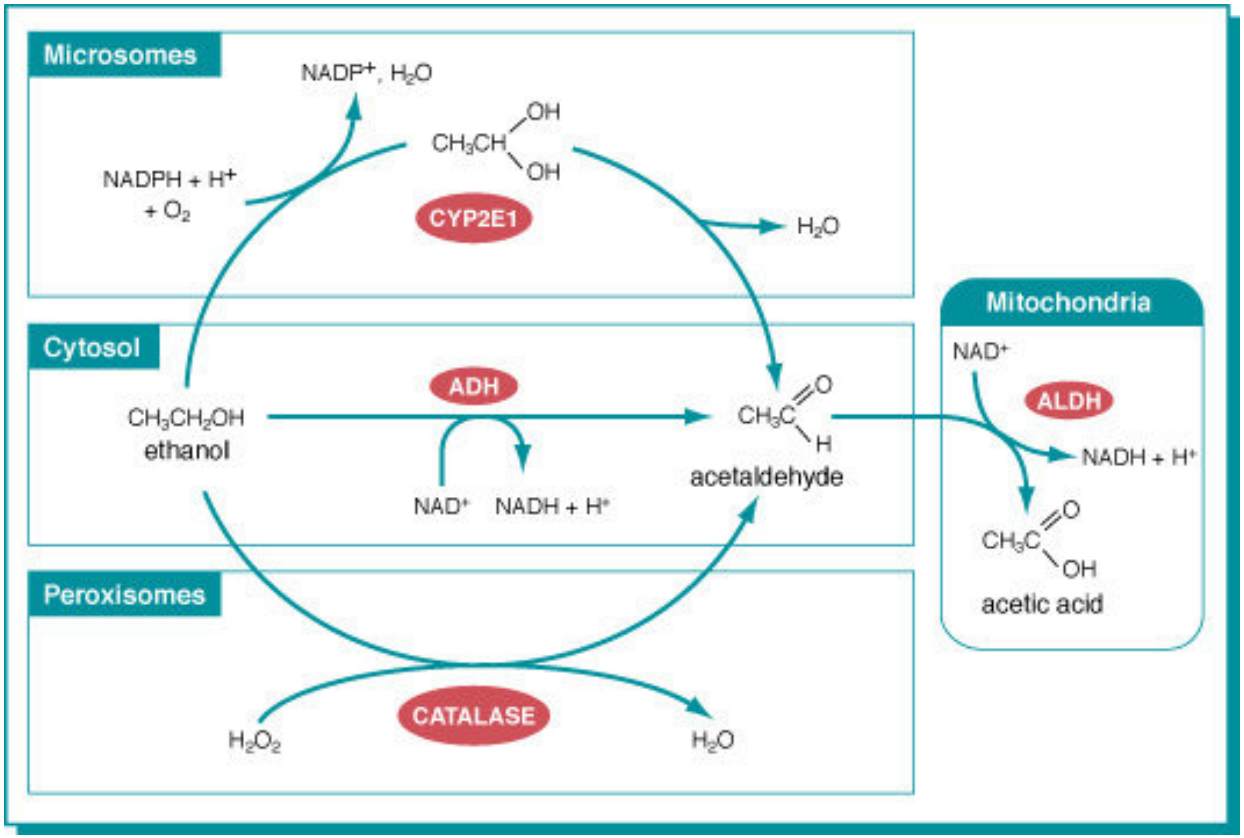
- In *occasional drinkers*, a blood alcohol level of 200 mg/dL produces *inebriation, with coma, death, and respiratory arrest at 300-400 mg/dL*. *Habitual drinkers* can tolerate blood alcohol levels up to *700 mg/dL*.

- Metabolic tolerance develops in chronic alcoholics by 5-10x induction of *cytochrome P-450 enzyme CYP2E1*.

- Chronic alcohol use results in *psychologic & physical dependence (addiction)* which may be of genetic basis.

- Metabolism in gastric mucosa and in liver: Enzymes are *alcohol dehydrogenase*, *CYP2EI* and *catalase*.

Metabolism of Ethanol:



- ***ADH*** **in the gastric mucosa & liver, cytochrome P-450 (*CYP2E1*) and *catalase* in liver.**
- ***Women have lower levels of gastric ADH activity than men do; therefore, they may develop higher blood alcohol levels than men after drinking the same quantity of ethanol.***

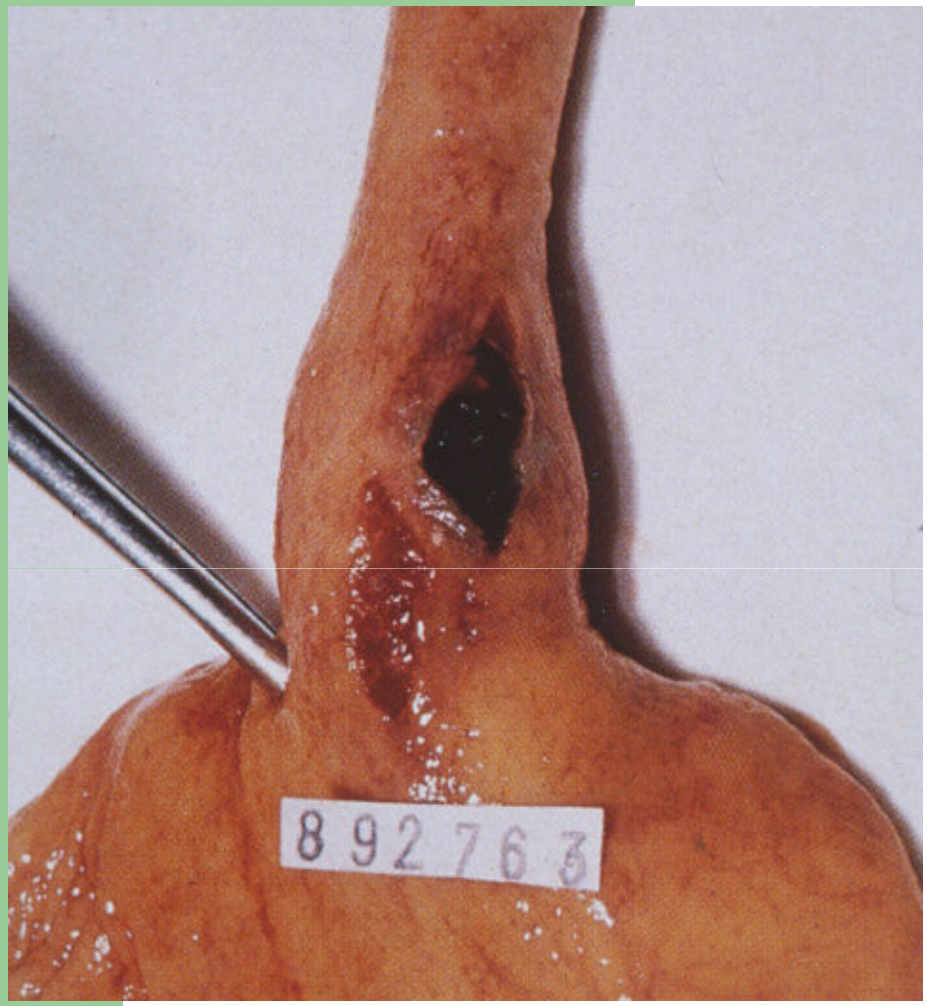
Toxic Effects of Alcohol (Review):

- Toxicity of alcohol is caused by *metabolites* of *ethanol-acetaldehyde* and *acetic acid:*
  - *Acute action as CNS depressant.*
  - *Chronic ethanol use causes wide range of systemic effects, some are due to vitamin and nutritional deficiency.*
- Many organs & systems in the body are affected:

(NEXT TABLE)

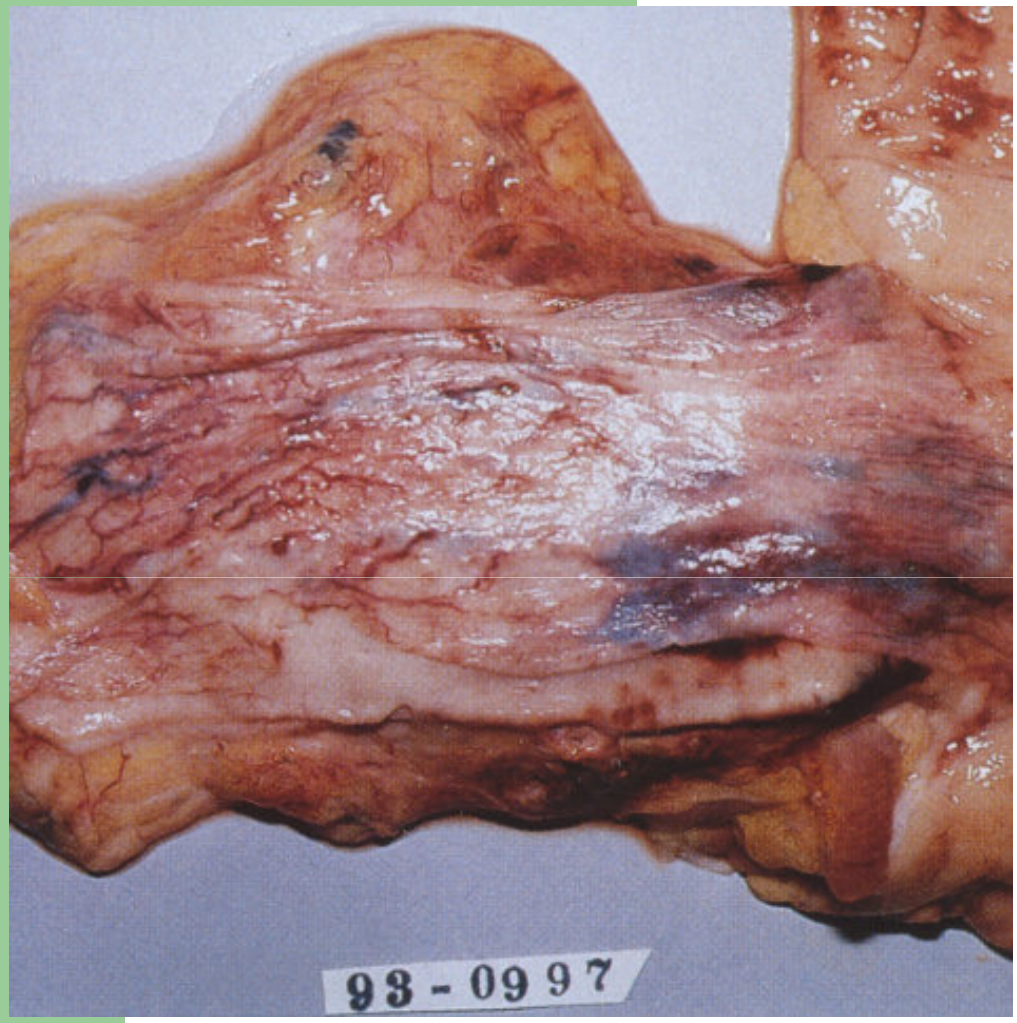
Mechanisms of Disease Caused by Ethanol Abuse:

Organ System	Lesion	Mechanism
Liver	Fatty change, alcoholic hepatitis Alcoholic cirrhosis- HCC	Toxicity
Nervous system	Wernicke syndrome Korsakoff syndrome Cerebellar degeneration Peripheral neuropathy	Thiamine deficiency Toxicity & thiamine def. Nutritional def. Thiamine deficiency
CVS	Cardiomyopathy Hypertension	Toxicity Vasopressor
GIT	Gastritis & Pancreatitis	Toxicity
Reproductive system	Testicular atrophy & spontaneous abortion	??
Skeletal muscle	Rhabdomyolysis	Toxicity
Fetal alcohol syndrome	Growth retardation, Mental retardation, and birth defects	Toxicity



Mallory-Weiss Syndrome:

Alcohol-induced vomiting and retching ("dry heaves") may tear the esophagus above or at the cardioesophogeal junction, resulting in massive hemorrhage and the vomiting of blood. Mallory-Weiss syndrome is quite often a lethal lesion. The longitudinal tears in the lower esophagus are readily apparent.

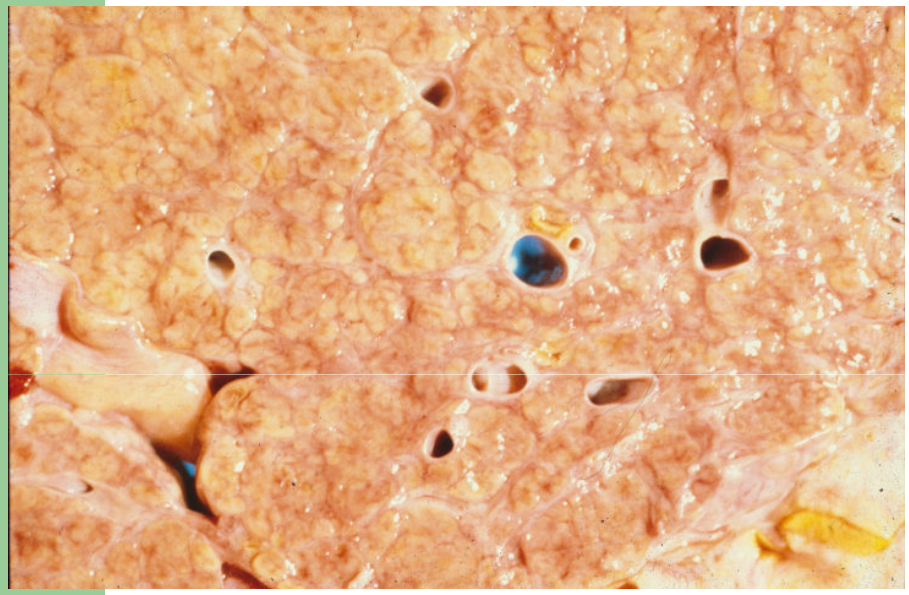


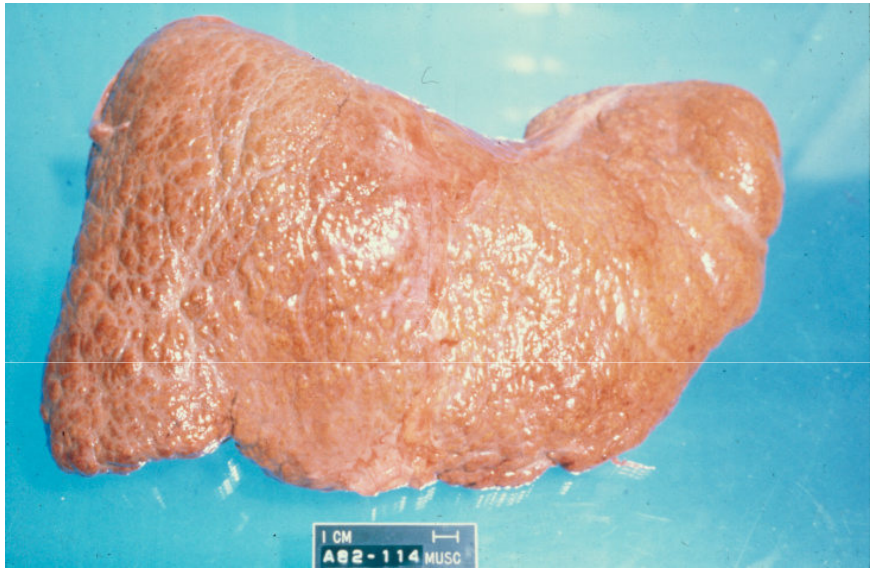
Esophageal Varices:

The variceal veins in the lower esophagus have been bleeding as evidenced by the dark blue submucosa. Esophageal varices are caused by portal hypertension caused most often by alcoholic cirrhosis.

The mortality of esophageal varices exceeds 50-75% on the first bleed. A patient surviving the first episode will have a 50% chance of a second bleed within a year with an even more dismal prognosis.

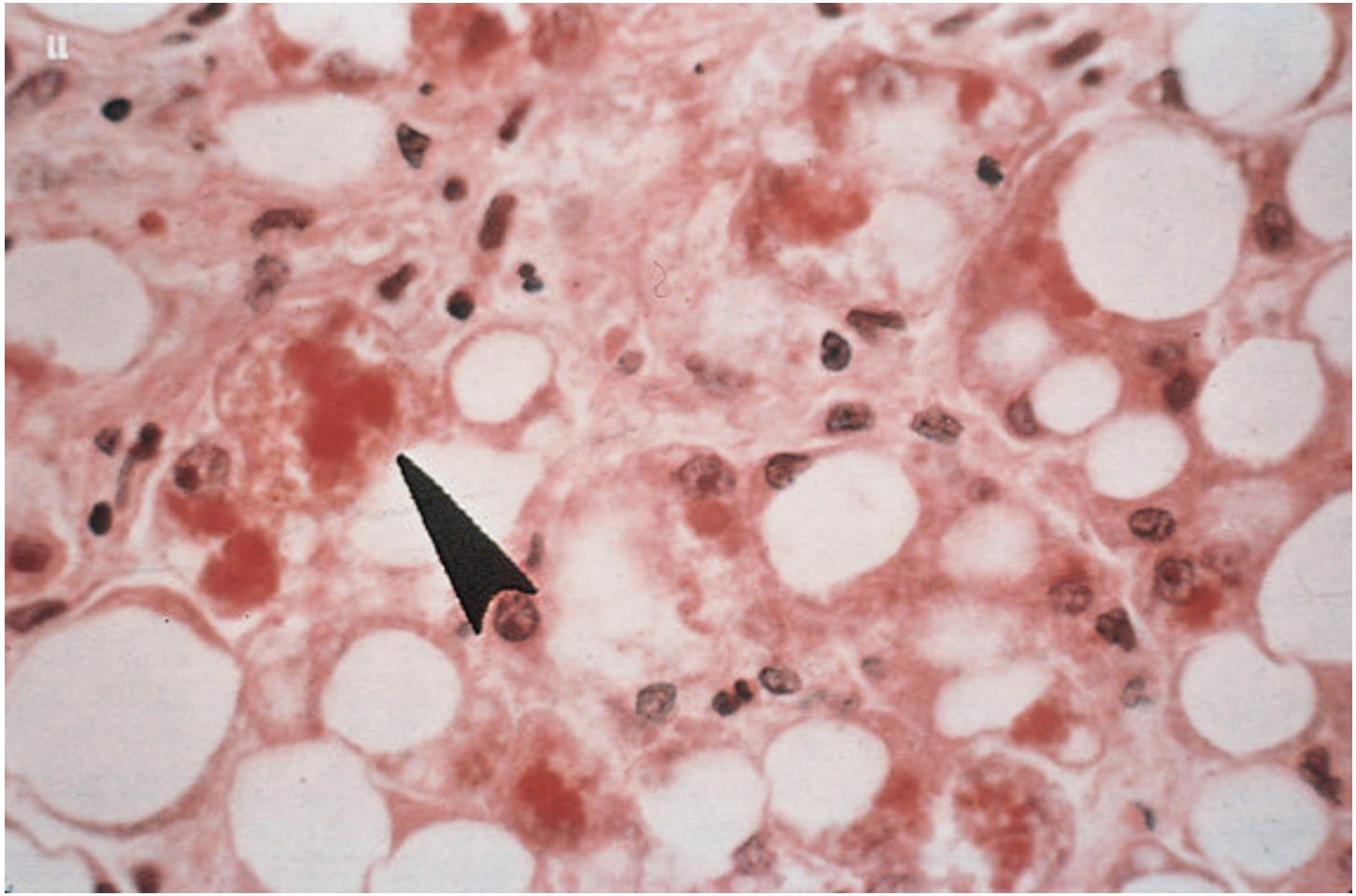
Alcoholic Liver Cirrhosis:





Alcoholic cirrhosis-This liver has a yellow appearance because of the fat present in the hepatocytes (steatosis).

Acute Alcoholic Hepatitis:



The liver cells show cytoplasmic accumulation of fat & hyaline (arrow). A scattered inflammatory infiltrate is present.

Ethanol and Cancer *(Review of Week-3 Lecture):*

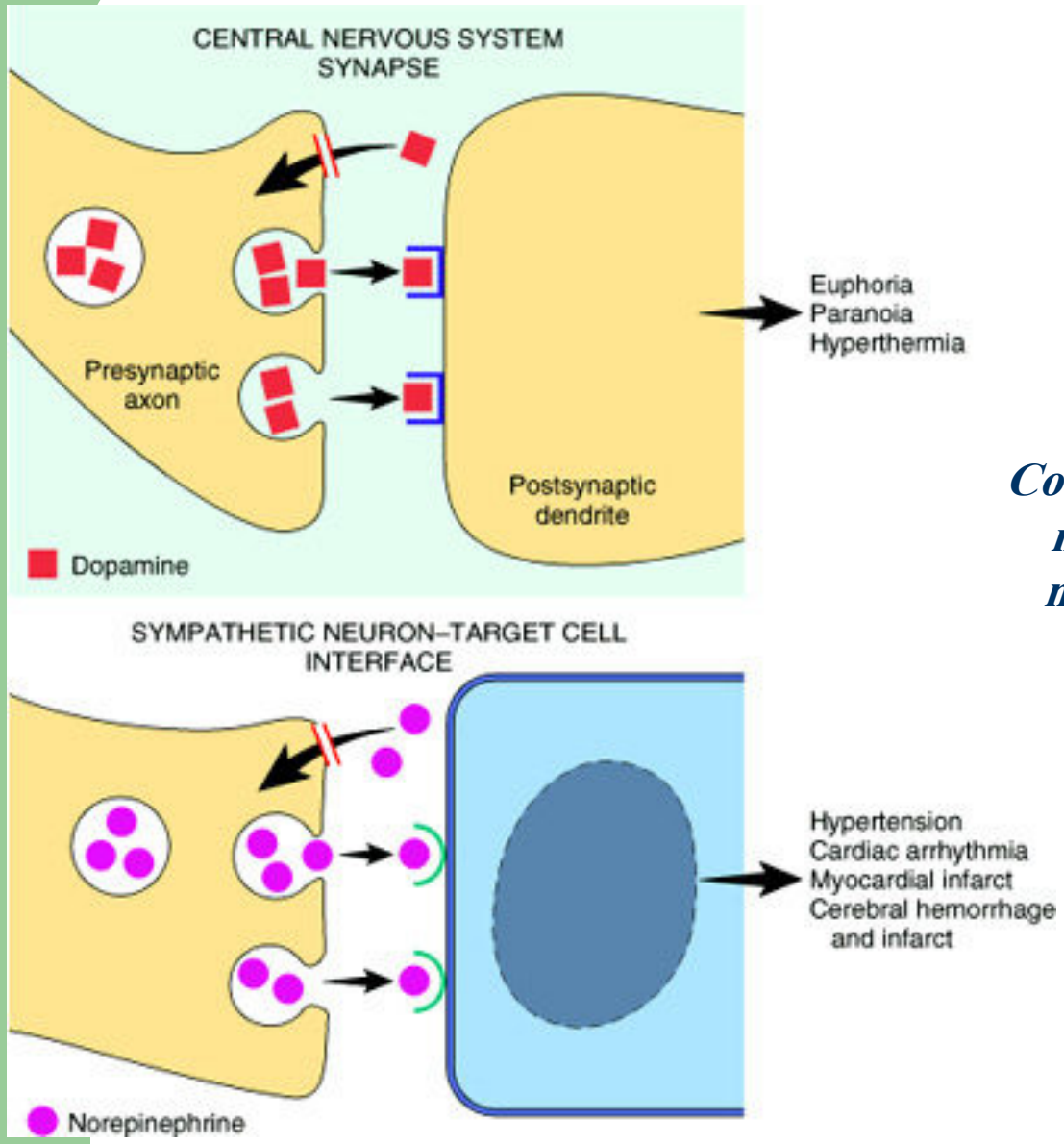
- **Use of alcohol is associated with increased incidence of cancer of *upper aerodigestive tract, esophagus, liver, and possibly the breast:***
  - ***Acetaldehyde acts as a tumor promoter.***
  - ***Induction of enzyme may lead to increased metabolic conversion of other carcinogens as well.***
  - ***Associated vit.A deficiency also contributes.***

Personal Exposure – *Drug Abuse:*

Common Drugs of Abuse:

CNS depressants	Ethanol Barbiturates, benzodiazepines
CNS stimulants	Cocaine, amphetamine
Narcotics	Morphine, Meperidine, Propoxyphene
Hallucinogens	Marijuana, Mescaline

Effects of Cocaine on Neurotransmitters:



Cocaine inhibits the reuptake of the neurotransmitters dopamine & norepinephrine in the central & peripheral nervous system.

Intravenous Drug Abuse:

- **Narcotics –overdose causes *convulsions, cardio-respiratory arrest and death.***

- **Chronic use- *tolerance and dependence.***

- **All IV drug users are susceptible to *infections*:**
  - ***High incidence of HIV infection and AIDS.***
  - ***4 sites most commonly affected: skin and subcutaneous tissue, heart valves, liver (viral hepatitis) and lungs.***
  - ***Right sided endocarditis common –organisms: most commonly staph. aureus, others include fungal infections (Candida) and other organisms.***

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.***

- **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.***

Acetaminophen (Tylenol):

- **Tylenol or Paracetamol** or **Acetaminophen** chemically named N-acetyl-p-aminophenol, is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer).

- Paracetamol is classified as a mild analgesic. It is commonly used for the relief of headaches and other minor aches and pains and is a major ingredient in numerous cold and flu remedies.

- Most popular analgesic in North America. ***Lay people commonly underestimate its toxicity.***

Acetaminophen Poisoning- *Epidemiology:*

- Intentional (suicidal) & unintentional (chronic) poisonings.
- Tylenol is often thought to be benign, or is a "hidden ingredient" in other remedies.
- Tylenol is the most common single agent involved in poisonous ingestions in young children.
- Tylenol is also commonly involved (often mixed with other drugs) in episodes of intentional self harm by teenagers.
- Accounts for more overdoses and overdose deaths each year in North America than any other pharmaceutical agent:
  - In 2000, it accounted for 5% of overdoses and 23% of reported fatalities.

Acetaminophen Poisoning- *Dosing:*

- "Plain Tylenol":
  - Regular-strength: 325mg
  - Extra-strength: 500mg
- Pediatric syrup:
  - 160 mg/5 mL –Children
  - 80 mg/0.8 mL –Infants
- Other Tylenol formats include:
  - Tablets
  - Chew-tabs
  - Dissolvable
  - Capsules
  - Suppositories

Acetaminophen Poisoning- *Dosing & Toxicity:*

- Recommended Tylenol dosing is as follows:
  - Adult: 325-650 mg every 4-6 hours or 1000 mg 3-4 times/day; do not exceed 4 g/day.
  - Pediatrics: 10-15 mg/kg/dose every 4-6 hours as needed; do not exceed 5 doses (80mg/kg) in 24 hours.
- The minimum toxic dose for an ***acute ingestion*** of Tylenol (i.e. occurring ***within a time frame of four hours***) is **7.5g for adults** & **150mg/kg for pediatrics**.
- Ingestions occurring over a period of ***more than four hours*** are arbitrarily termed ***chronic ingestions.***
- The minimum toxic dose for *chronic ingestions* of Tylenol is less well defined: ***(> 7.5g/d in adults & > 150mg/kg/d in children if no risk factors e.g. alcoholism and drugs that potentiate CYP450 like Rifampin & anticonvulsants).***

Acetaminophen Poisoning- *Metabolism:*

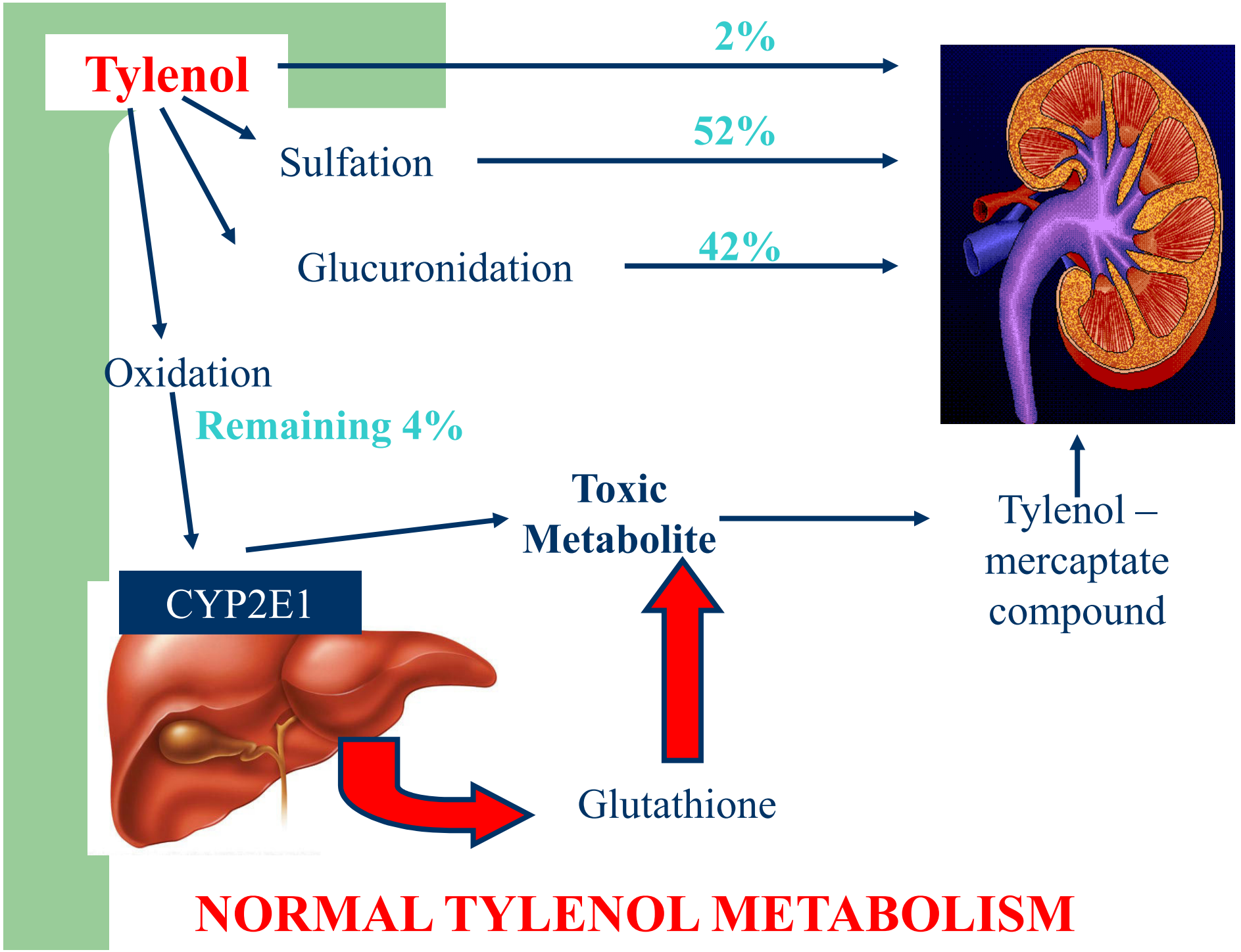
- Immediate-release Tylenol is rapidly absorbed in the gut, with peak serum levels typically achieved in 30m – 2hr. Peak serum levels can be delayed with sustained-release formulations & also with combination formulations.

- Acetaminophen in normal individuals is inactivated by sulfation (approximately 52%) and glucuronide conjugation (42%). About 2% of the drug is excreted unchanged. The remaining 4% is biotransformed by the cytochrome P-450 mixed-function oxidase system.

- The P-450 isozyme responsible for acetaminophen biotransformation is **CYP2El.** *Metabolism by CYP2El results in a potentially toxic metabolite that is normally detoxified by* ***conjugation with glutathione*** *and excreted as the* ***mercapturate***.

- Evidence extrapolated from animals estimates that when 70% of endogenous hepatic glutathione is consumed, the toxic metabolite becomes available for covalent binding to hepatic cellular components.

- However, patients who are concurrently using, or have recently used, agents that induce CYP2E 1, such as in the case of ***chronic ethanol exposure or phenobarbital use, may produce more than 4% of the toxic metabolite***. *It is therefore important to determine, whenever possible, whether or not the patient's CYP2E1 system may be induced when determining the risk of hepatic necrosis in any given individual*



NORMAL TYLENOL METABOLISM