ACETAMINOPHEN OVERVIEW

acetyl-para-aminophenol (APAP)

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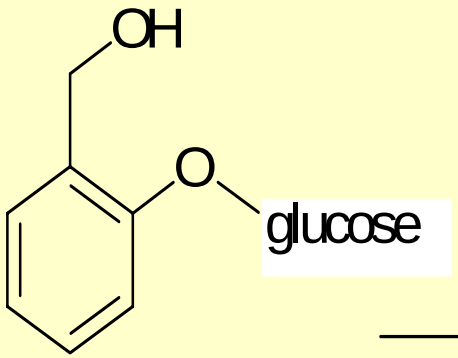
Nonprescription Drugs Advisory Committee Meeting, 19 September 2002

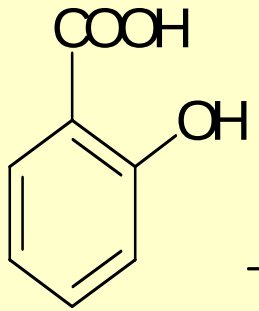
Center for Drug Evaluation and Research

Flight from Pain



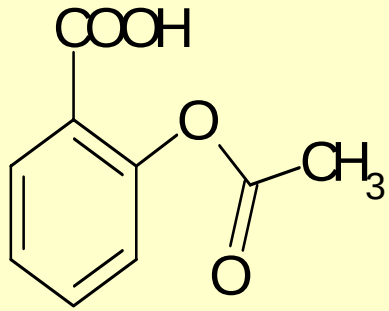
salicin
(willow bark)

prehistoric; Leroux 1829



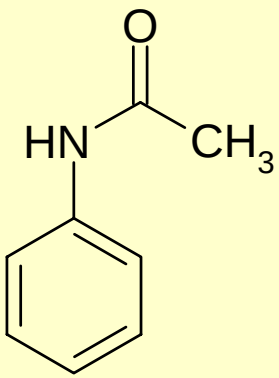
salicylic acid

Na-salicylate: 1875

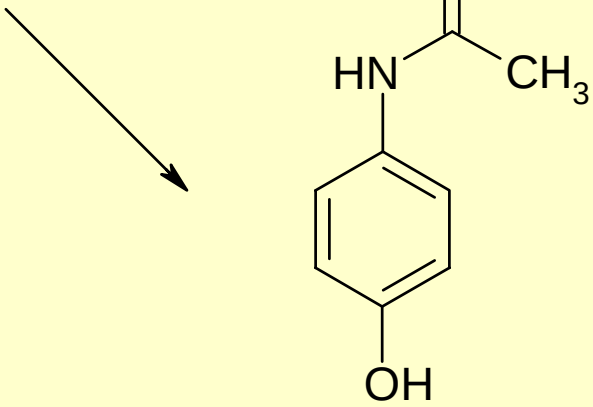


acetylsalicylic acid (ASA)
Gerhardt 1853; Bayer 1879
Dreser "aspirin" 1899

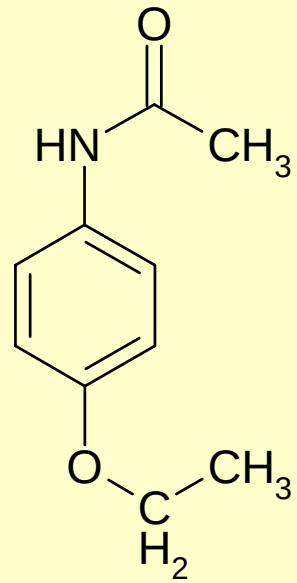
Coal-tar Analgesics



acetanilide
"afebrin" 1886



N-acetyl-*p*-aminophenol
acetaminophen; paracetamol; APAP
Von Mering, 1893



phenacetin 1887

Aspirin to Acetaminophen (APAP)

- Aspirin **considered a wonder drug for >50 years (1899-1950). . .** *but found to cause gastrointestinal ulcers and bleeding, to cause CNS "salicylism," altered acid-base balance (respiratory alkalosis), inhibit cyclooxygenase, Reye's syndrome in children with viral infections. . .*

- Acetaminophen **approved 1950 and for OTC use about 1959 (proof of efficacy not required) . . .** *did not cause bleeding or GI ulcers, did not cause Reye's syndrome (noted in 1963, associated with aspirin 1980s) . . .* **..... *but, . .***

Br Med J 1966 (27 Aug); 2 (5512)

- **Davidson DGD, Eastham WN. (Edinburgh)** **pp 497-9**
  Acute liver necrosis following overdose of paracetamol.

- **Thompson JS, Prescott LF. (Aberdeen)** **pp 506-7**
  Liver damage and impaired glucose tolerance after paracetamol overdosage.

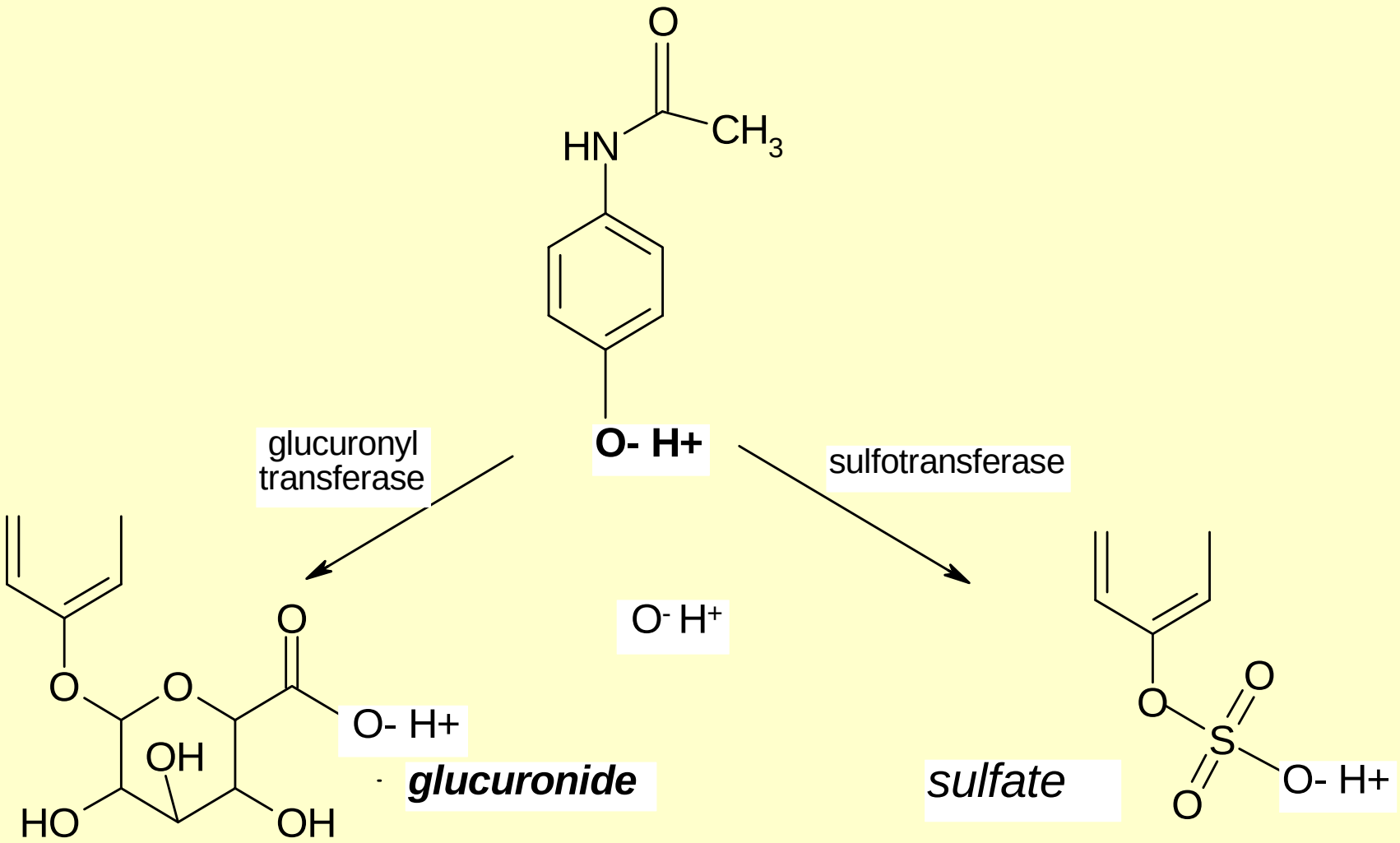
- **Editorial** **pp 485-6**
  Liver necrosis from paracetamol.

An Insidious Agent

- **After acute ingestion of a large amount (8-20 g in adult) *may* (*or may not*) experience nausea, sweating, vomiting, drowsiness - - - subsides -**
- **“latent period” of no symptoms for 24-72 hours (*but a lot of metabolic changes going on*) - - -**

- **nausea, anorexia, vomiting, tender-swollen liver, with ALT and AST in -000s, PT (INR) elevated**
- **liver failure: encephalopathy, acidosis, jaundice, 2º? renal failure, hypoglycemia, bleeding, . . . death.**

Acetaminophen (APAP) Conjugates



J Pharmacol Exp Ther 1973 (Oct); 187
Acetaminophen-induced hepatic necrosis

- ***I. Role of drug metabolism*** **pp 185-194**
  Mitchell JR, Jollow DJ, Potter WZ, Davis DC, Gillette JR, Brodie BB

- ***II. Role of covalent binding <u>in vivo</u>*** **pp 195-202**
  Jollow DJ, Mitchell JR, Potter WZ, Davis DC, Gillette JR, Brodie BB

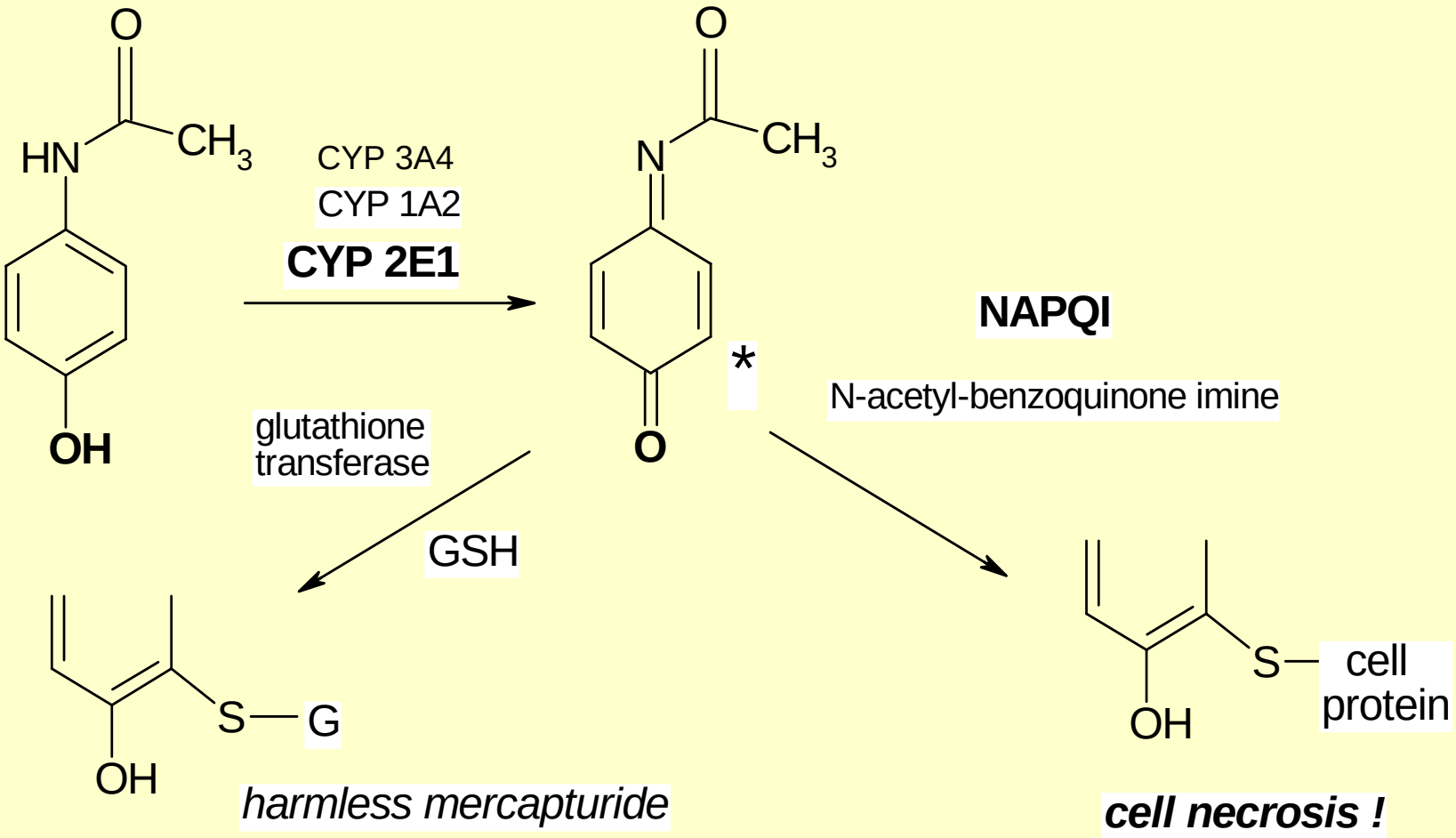
- ***III. Cytochrome P-450-mediated covalent binding <u>in vitro</u>***
  pp 203-210
- **Potter WZ, Davis DC, Mitchell JR, Jollow DJ, Gillette JR, Brodie BB**

- **IV. Protective role of glutathione** **pp 211-217**
  Mitchell JR, Jollow DJ, Potter WZ, Gillette JR, Brodie BB

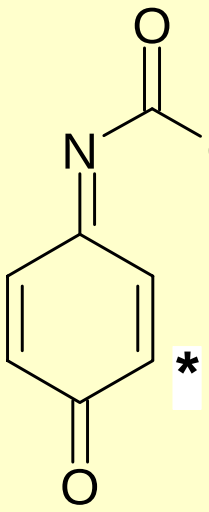
APAP-induced hepatic necrosis

- ***centrilobular liver necrosis in mice and rats related to drug** metabolism rate, **not to plasma levels of drug;***
- ***liver damage severity in mice related to** covalent binding **in vivo** **of metabolite to hepatocyte microsomal protein;***
- *cytochrome P-450-mediated* ***covalent binding of acetaminophen metabolites to cell microsomal protein;***
- *glutathione* ***depletion worsens, and glutathione addition prevents damage, without affecting metabolism***

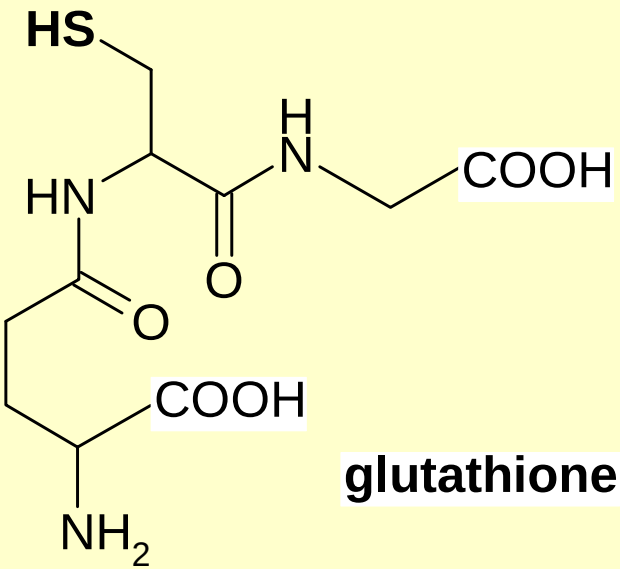
Acetaminophen Oxidation



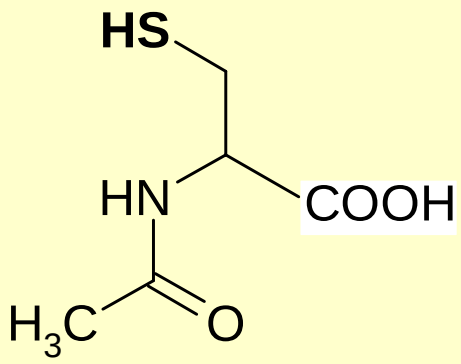
NAPQI Detoxification



NAPQI



glutathione



N-acetylcysteine

Four Lines of Defense

- excretion of unchanged APAP - < 5%
- glucuronide conjugation - about 55 - 60%
- conjugation with sulfate - about 30 - 35%
- mercaptide formation with GSH - about 5%

- -

- N-acetylcysteine conjugation - *last chance*

Moderate, Chronic Overdose

- about 30-50% of hep-toxic cases unintentional
- may have no prodromal symptoms
- doses of 4-8 g/day, after “inducers” dangerous ?
- may develop tolerance (M. Black’s case)

- acetaminophen (APAP) plasma levels not always helpful, and may be too late for effective treatment with Mucomyst (N-acetylcysteine), - - - - and no time for a liver transplant...

Factors Affecting Absorption and Metabolism

- dissolution
- gastric emptying
- absorption fraction
- glucuronidation
- sulfation
- renal function
- liver function
- mercaptides
- NAPQI formation

- protein adducts
- toxic O-reactants

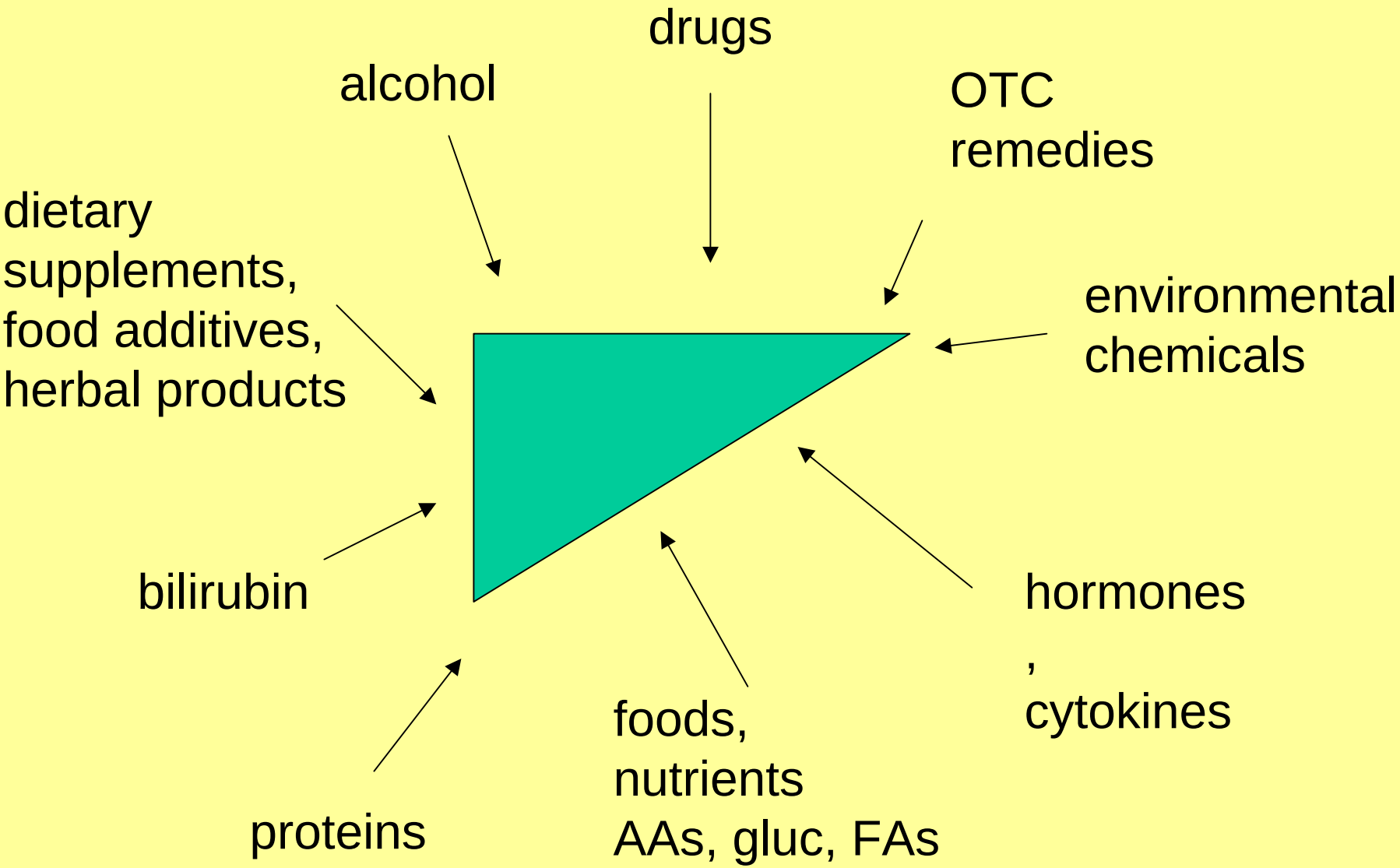
- solution, capsule, tablet
- varies up to 9-fold, (-) meals
- 1-3x in uptake, C_{max},AUC, $T_{1/2}$
- (-) Gilbert's, ranitidine
- (+) acetaminophen, estrogens
- (++) glucuronides, sulfates
- (++) $T_{1/2}$ with toxic overdose
- (+) GSH, N-Acys; (-) depletion
- (-) cimetidine, chronic APAP
- 60-fold inter-individual variation
- "overdose" for given person
- reperfusion, ischemia

Cytochrome P-450 2E1 Inducers

- **alcohol (ethanol)**
- **isoniazid**
- **acetaminophen**
- **aspirin**
- **chlorzoxazone**
- **other alcohols, acetone**
- **retinol (vitamin A)**
- **obesity; cigarette smoke**
- **clofibrate, ciprofibrate**
- **trichlorethylene, pyrazole**

Also, CYP 1A2 and 3A4 inducers, such as:

rifampacin, omeprazole, broiled beef; phenobarbital, phenytoin, lovastatin, prednisone, erythromycin, omeprazole.


drugs
alcohol
OTC
remedies
dietary
supplements,
food additives,
herbal products
environmental
chemicals
bilirubin
hormones
,
cytokines
foods,
nutrients
AAs, gluc, FAs
proteins

Variability of Absorption and Metabolism Among Individuals

- considerable variation at each step
  - absorption, glucuronidation, sulfation, oxidation, GSH conjugation - - - - - - - - result is 60-fold variation in toxic NAPQI formation among individuals
- many drug-drug and drug-compound interactions