

A photograph of a large, red mushroom with white spots, likely a Amanita muscaria, growing in a field of dry grass. The mushroom is the central focus, with its bright red cap and white spots contrasting sharply with the dry, brownish grass. The text 'Pharmacokinetics' is overlaid in yellow on the mushroom's cap.

# Pharmacokinetics

metabolism

A red mushroom with white spots is centered in the image, resting on a bed of dry, brown grass. The mushroom has a textured, slightly cracked surface. The background is a dense field of dry grass, creating a natural, outdoor setting. The overall lighting is somewhat dim, giving the scene a slightly somber or mysterious feel.

**by the end of this lecture you  
should be able to**

- **use your knowledge of drug metabolism to modify your treatment plan in any species or class of animal**

**How would you anaesthetise this one?**



# pharmacokinetics

- absorption
- distribution
- metabolism = biotransformation
- elimination

# metabolism

A large, red mushroom with white spots is the central focus of the image. It is growing on a bed of dry, brown pine needles. The mushroom has a thick, slightly textured cap and a short, white stem. The background is a dense layer of pine needles, creating a textured, natural setting.

- **most species differences in drug effects can be attributed to differences in metabolism**

# metabolism

- **most drugs are metabolised before elimination**
  - a few drugs are eliminated unchanged by the kidney, eg penicillin
- **metabolites are more easily eliminated**

# metabolism

- **Phase 1**
  - reactive “handle” attached to molecule
  - some drugs bypass phase 1
- **Phase 2**
  - water soluble group conjugated to “handle”



# phase 1

- **oxidative reactions**
  - hydroxylation
  - dealkylation
  - deamination
- **reductive reactions**
- **hydrolysis**

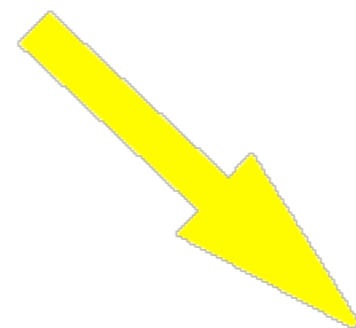
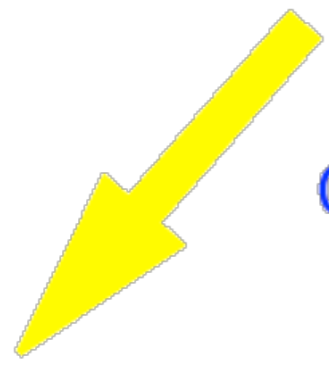
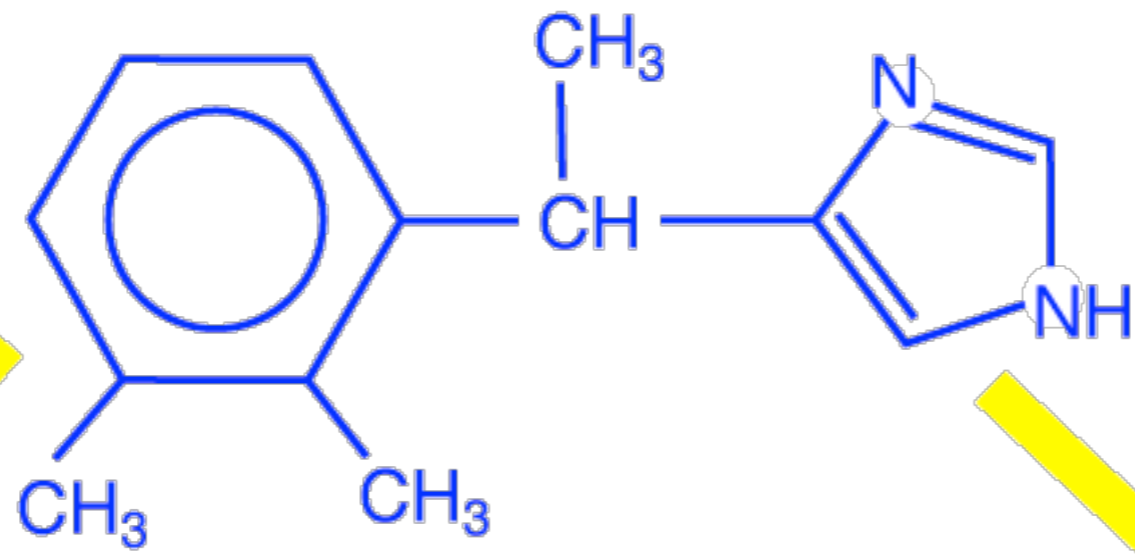


# oxidation

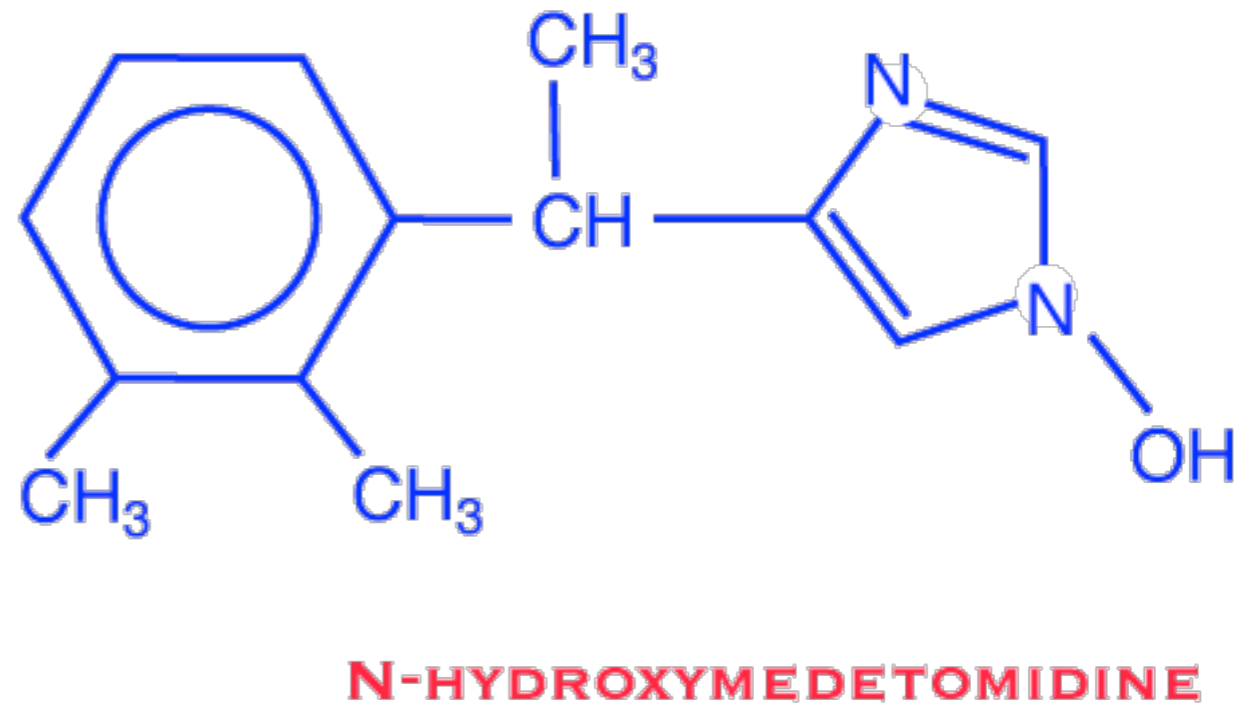
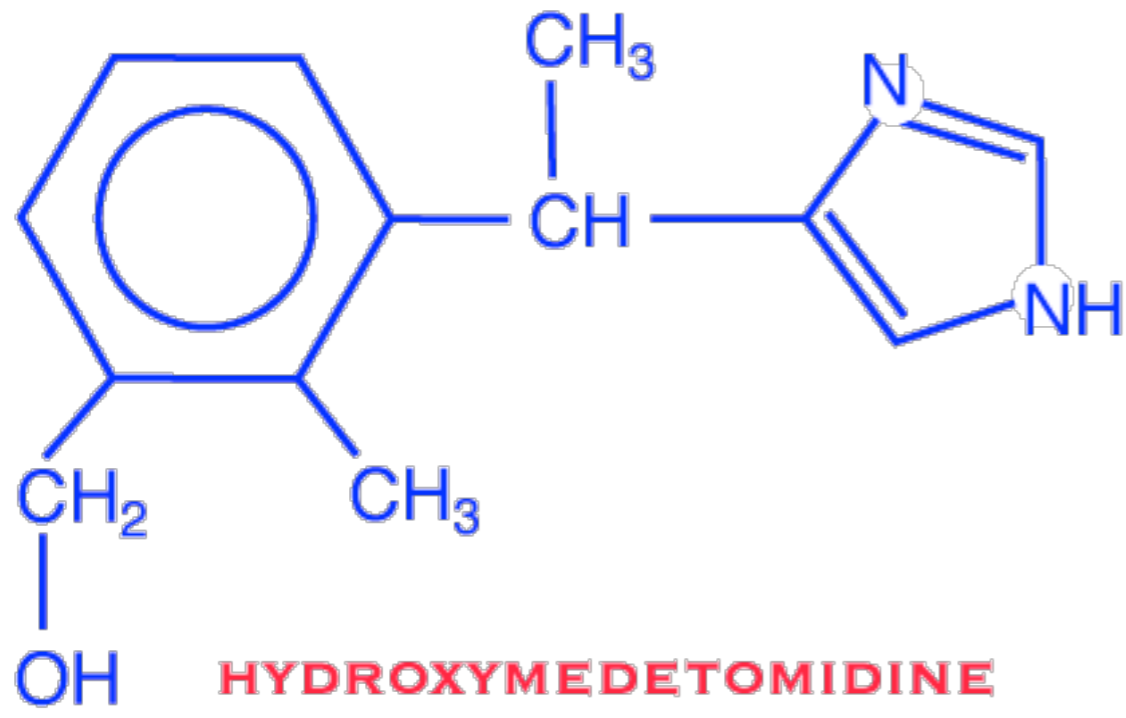
- **cytochrome P450 (microsomal mixed function oxidase)**
- **mainly in SER of liver cells**
  - **but also gut, lungs, kidneys, skin**
- **usually starts off with hydroxylation to produce a reactive intermediate**

**DEXMEDETOMIDINE**

**phase 1**



hydroxylation



# enzyme induction

- some drugs increase the rate of production of P450 enzymes
  - this increases the rate of metabolism of that drug and other drugs
    - phenobarbitone
    - alcohol
    - St John's wort
  - some drugs reduce the effect of P450
    - ketoconazole
    - cimetidine
    - quinidine

# cytochrome P450

A large, red, mushroom-shaped fungus with white spots, growing on a bed of dry pine needles. The fungus has a thick, textured cap and a short, white stem. The background is a dense layer of dry, brown pine needles.

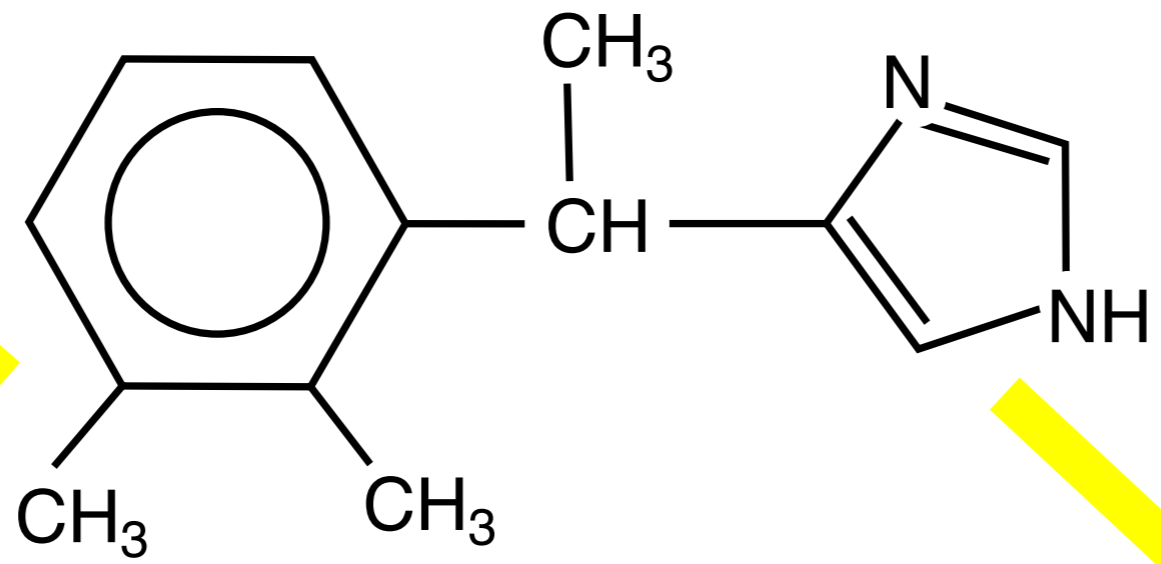
- **CYP1 - 3 used for drugs**
- **CYP4 - 12 used for endogenous compounds**
  - **steroids**
  - **fatty acids**
  - **etc**

# people

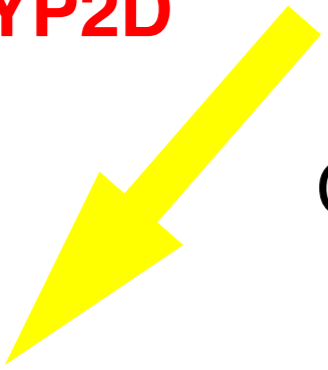
- **CYP3A4 - 55%**
- **CYP2D6 - 25%**
- **CYP2C9, 10, 19, 19 - 20%**

dog

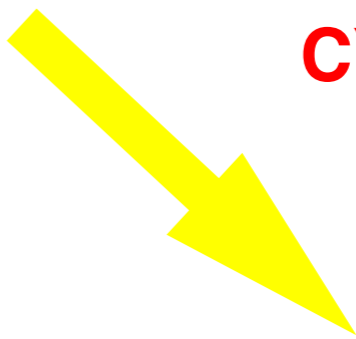
DEXMEDETOMIDINE



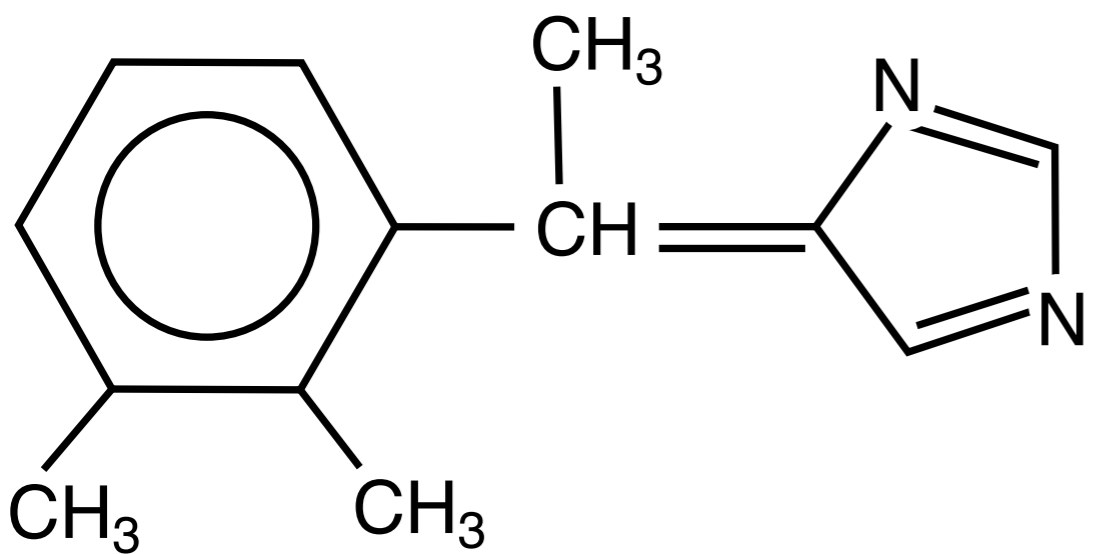
CYP2D



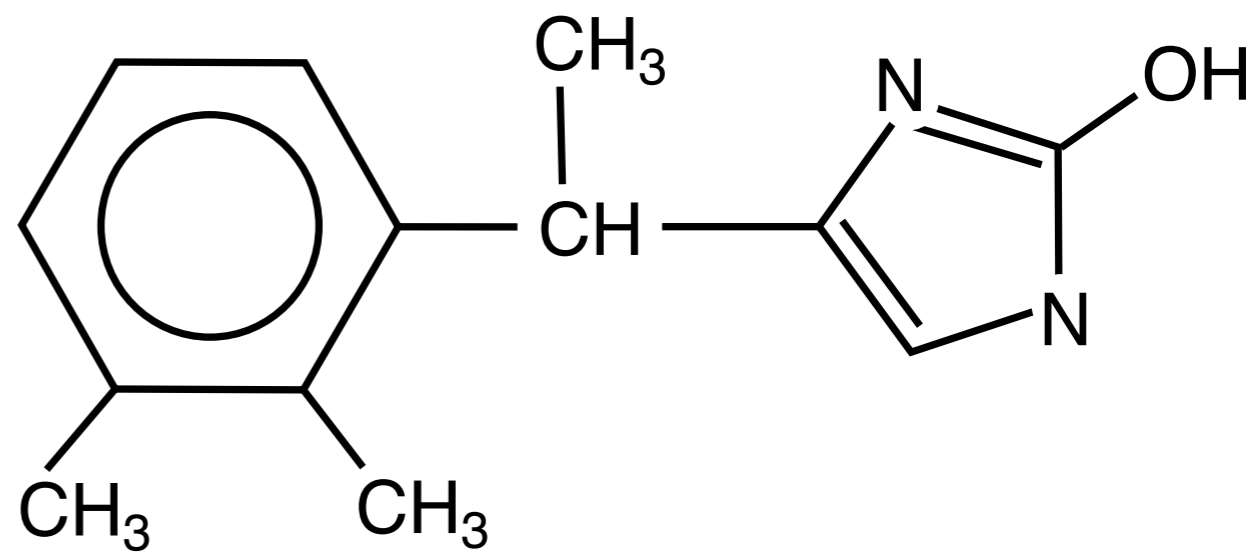
CYP3A



DEHYDROMEDETOMIDINE



HYDROXYMEDETOMIDINE



# abnormal phenotypes

- **people**
  - CYP2D6 common
  - CYP2C19 less common
  - some people have CYPs which turn harmless compounds into toxins / carcinogens
- **domestic animals**
  - ??????

# abnormal phenotypes

A large, bright red mushroom with white spots, growing on a bed of dry pine needles. The mushroom is the central focus of the image, with its vibrant red color contrasting sharply with the dry, brownish-green needles. The text is overlaid on the left side of the image.

- **slow metabolism**
  - unexpected side effects
- **fast metabolism**
  - drug does not work



# drug interactions



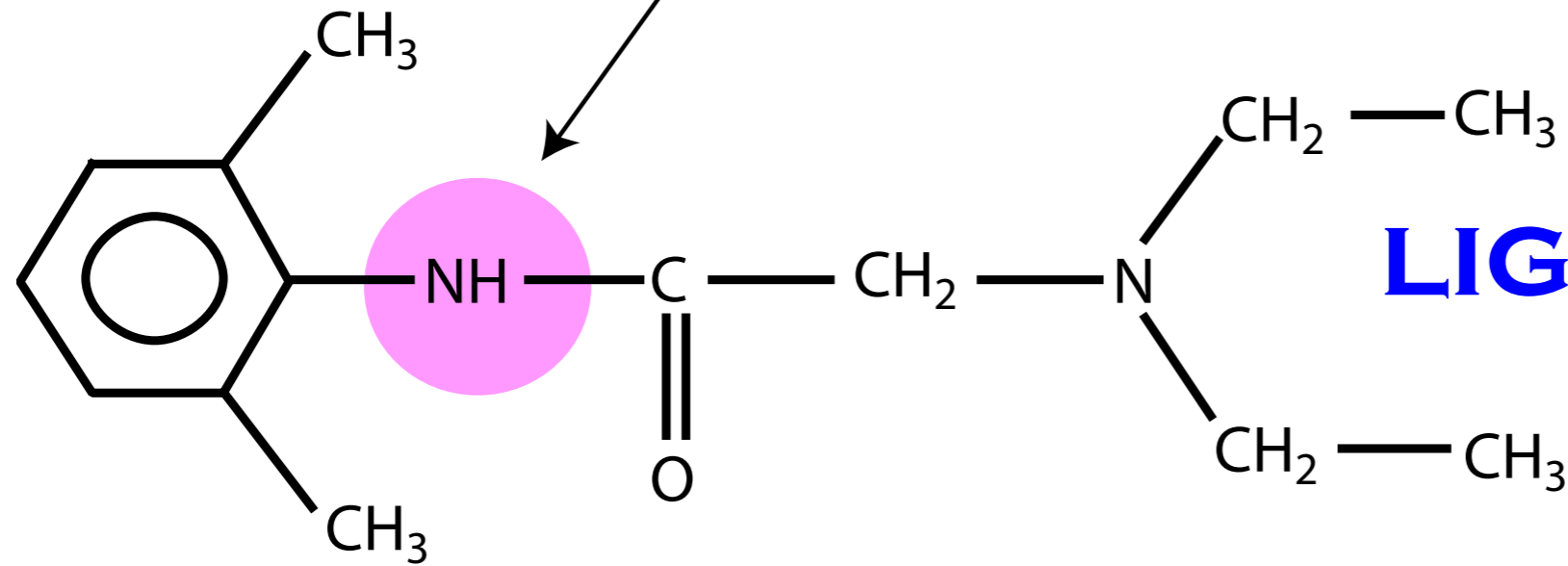
- **induction of P450**
  - phenobarbitone, rifampicin
  - environmental toxins
- **inhibition of P450**
  - piperonyl butoxide
  - grapefruit juice
- **competition for P450**
  - ketoconazole & many drugs

# phase 1

- **reductive reactions**
  - especially ketones, eg warfarin
  - usually also in liver
- **hydrolysis**
  - especially esters, eg suxamethonium, and also amides, eg lignocaine
  - usually in plasma

# hydrolysis

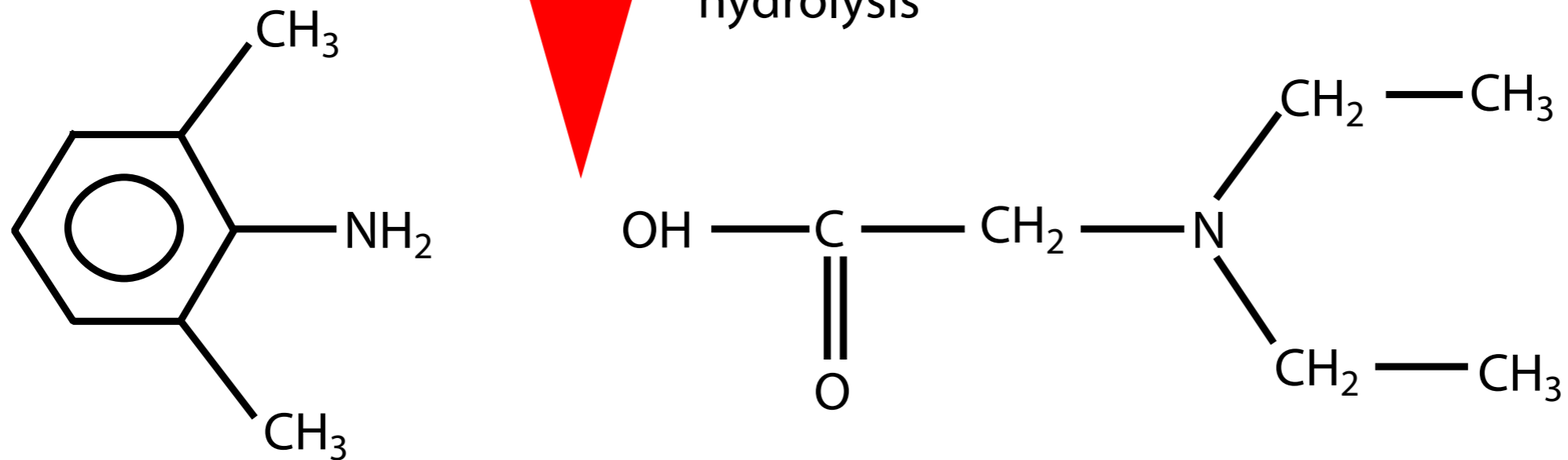
amide link



**LIGNOCAINE**



hydrolysis



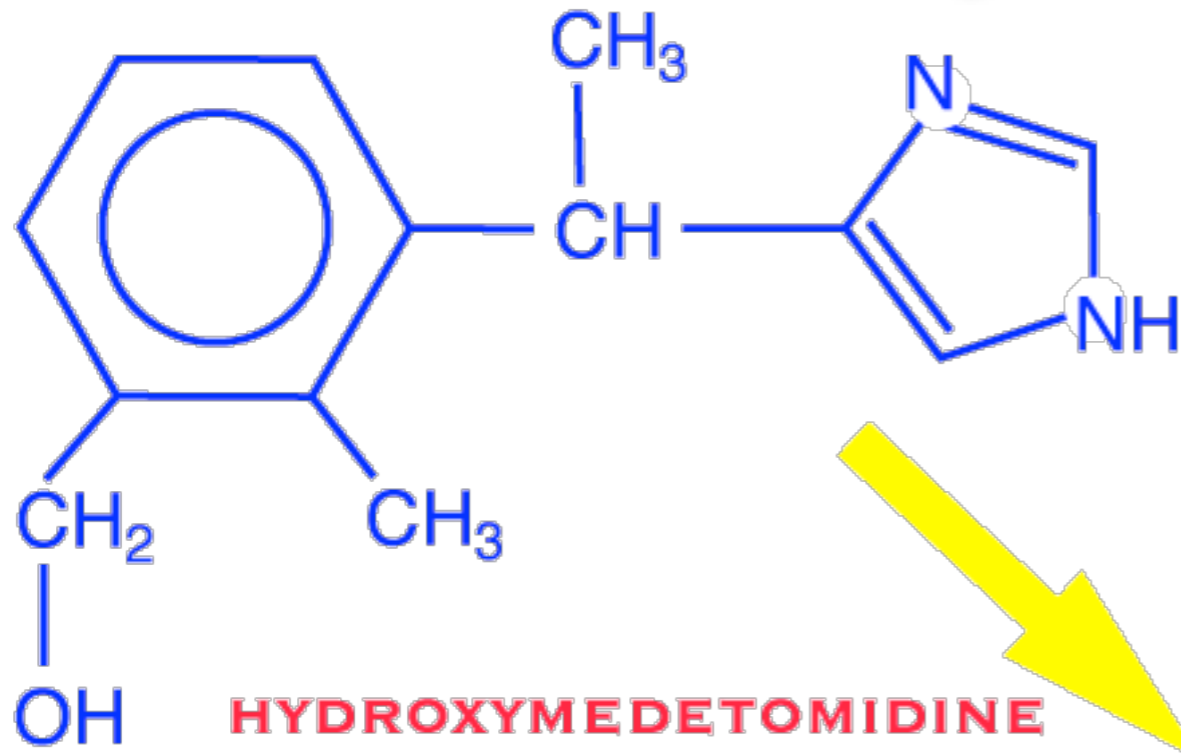
## phase 2

- conjugation with a polar group
- mainly in hepatocytes
- reduces reuptake in kidney
- some excreted in bile
  - bilirubin
  - endogenous steroids

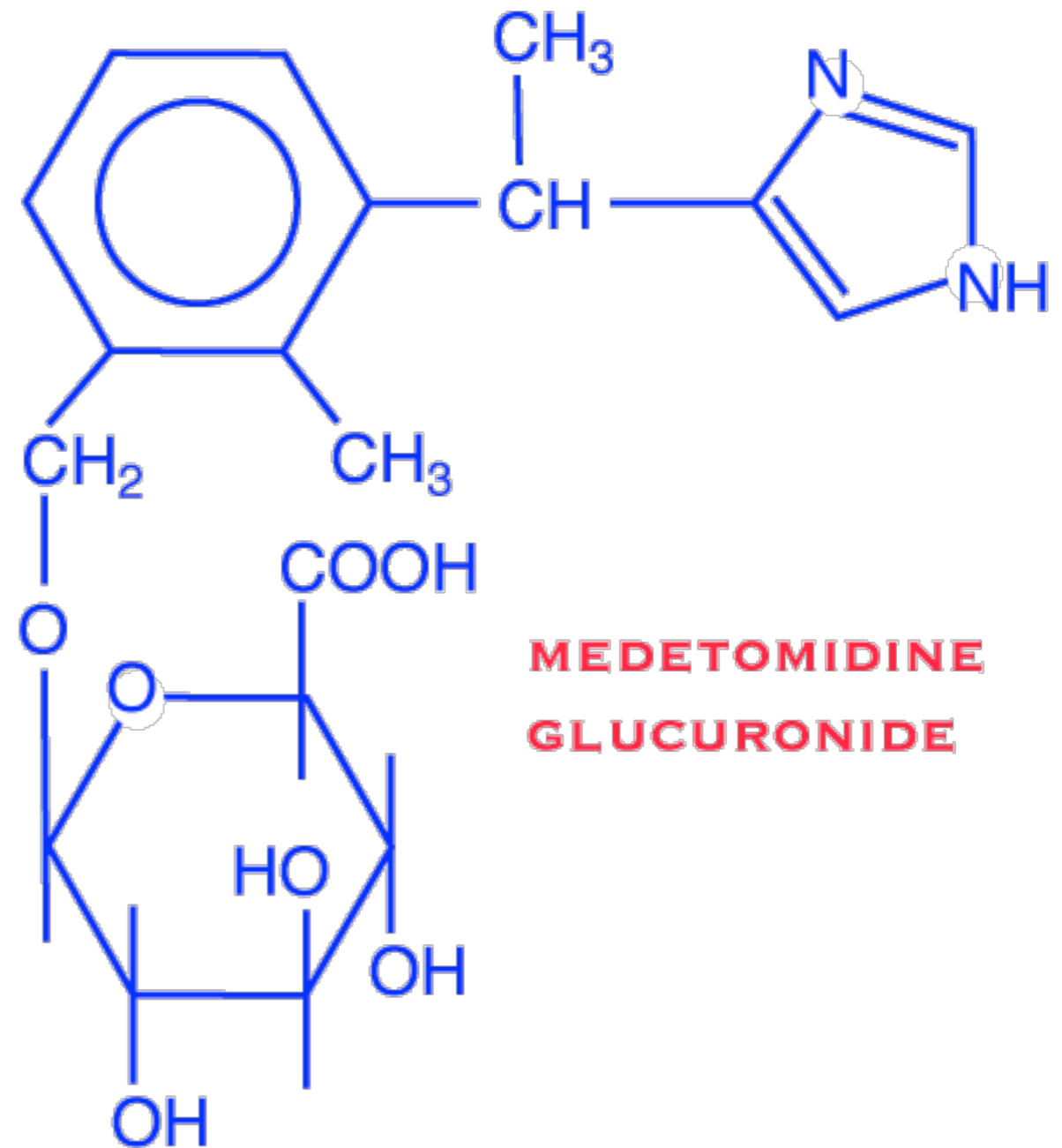
# conjugation

- **glucuronide - not cats**
- **sulphate - not pigs**
- **acetyl - not cats & dogs**
- **methyl**
- **glycine**
- **ornithine - only birds**

# phase 2

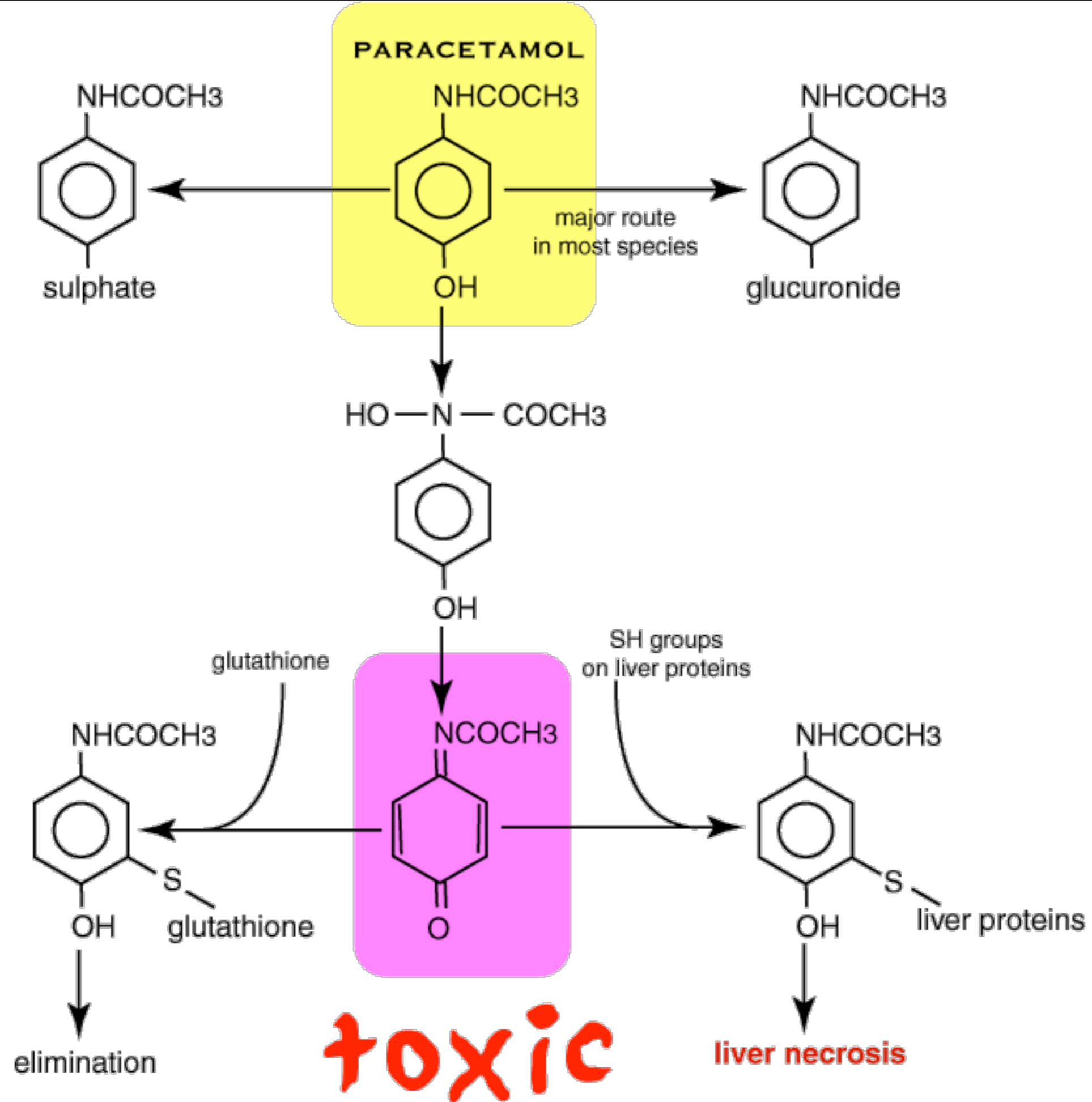


glucuronidation



# prodrugs

- **active drug - inactive metabolite**
  - detomidine - detomidine carboxylic acid
- **inactive drug - active metabolite**
  - cortisone - hydrocortisone
  - enalapril - enalaprilat
- **active drug - active metabolite**
  - morphine - morphine 6 glucuronide
- **active drug - toxic metabolite**
  - paracetamol - epoxide
- **beware liver disease**





# stereoisomers

- many enzymes are stereospecific
- isomers may have different metabolic pathways
- usually only one isomer active
  - but others may be toxic, eg bupivacaine

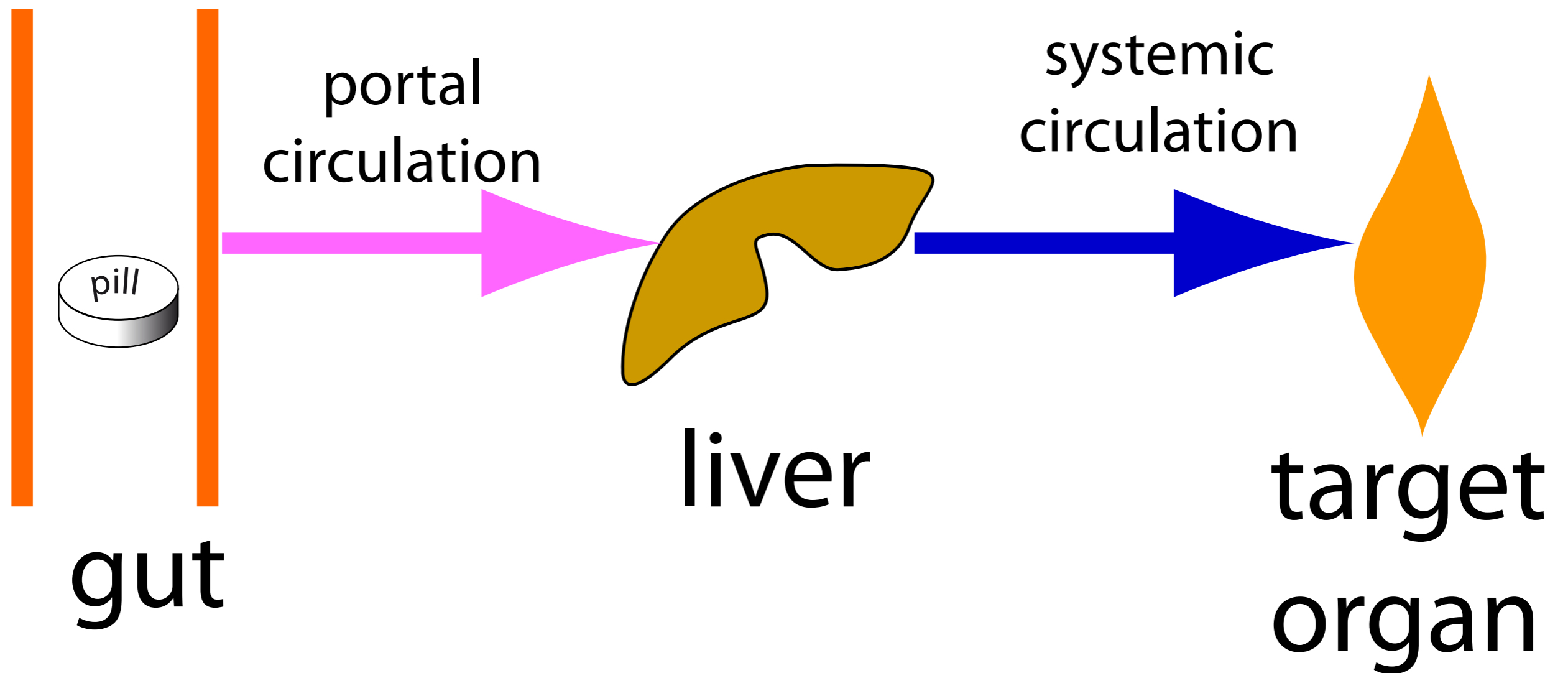
# abnormal metabolism

- **newborn animals**
- **old animals**
- **liver disease**
  - **or disease which reduces blood flow to liver**
- **individual variation**
  - **missing enzymes**

# **enterohepatic recirculation**

- **conjugated drug excreted in bile**
- **gut bacteria lop off conjugate**
  - **used for energy metabolism**
- **drug reabsorbed**
- **prolonged effects / animal recovers then effects reappear**

# first pass metabolism



**How would you anaesthetise this one?**



# metabolism

- **most drugs are metabolised by cytochrome P450 and conjugated with glucuronide in most species except cats**
- **some drugs will induce P450 to increase rates of metabolism**
- **prodrugs have to be metabolised to produce their action**
- **liver disease usually slows metabolism**