

A close-up photograph of a red mushroom with white spots, likely a fly agaric, growing in a field of dry grass. The mushroom has a bright red cap with numerous white, irregular spots. The background is a dense field of dry, yellowish-brown grass.

# **Pharmacokinetics**

**metabolism**



# pharmacokinetics

A red mushroom with white spots, likely an Amanita muscaria, is growing in a field of dry grass. The mushroom is the central focus of the image, with its bright red cap and white spots contrasting against the dry, brownish grass. The background is slightly blurred, emphasizing the mushroom.

- absorption
- distribution
- **metabolism = biotransformation**
- elimination



# metabolism

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





# metabolism

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



# metabolism

A red mushroom with white spots, likely a fly agaric, is growing in a field of dry grass. The mushroom is the central focus of the image, with its bright red cap and white spots contrasting sharply with the dry, yellowish-brown grass. The background is slightly blurred, emphasizing the mushroom.

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



A photograph of a red mushroom with white spots, likely an Amanita muscaria, growing in a field of dry grass. The mushroom is the central focus, with its bright red cap and white spots contrasting against the brownish-yellow grass. The text 'phase 1' is overlaid on the upper right portion of the mushroom's cap.

# phase 1

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

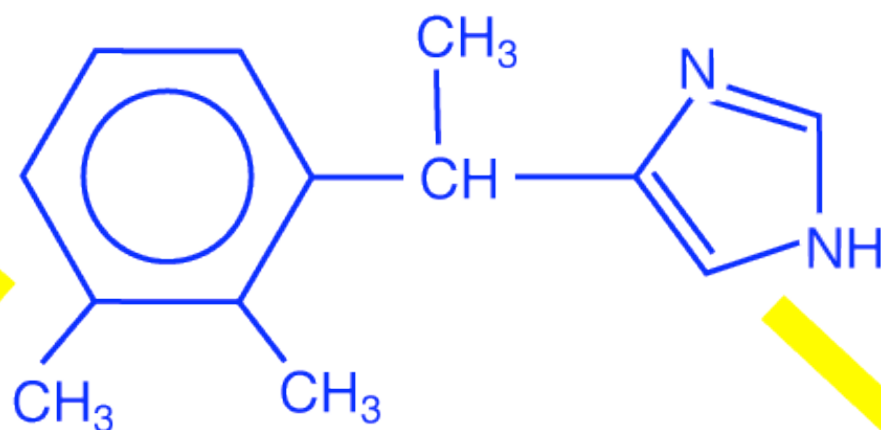


# oxidation

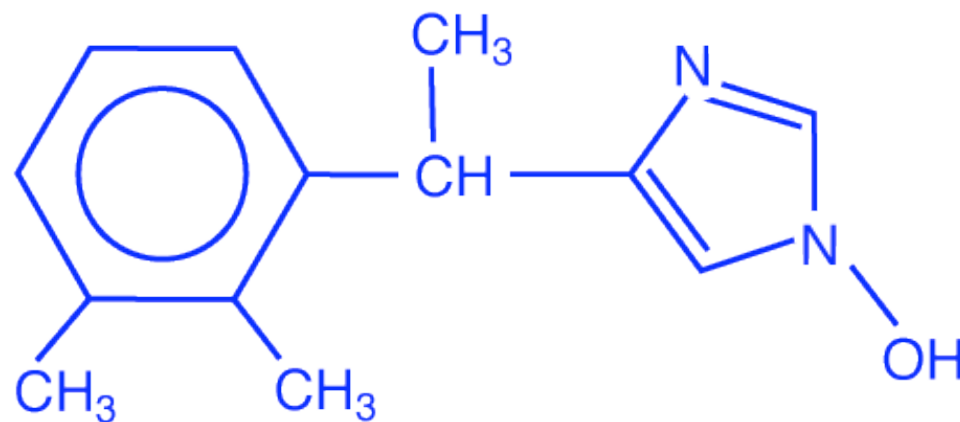
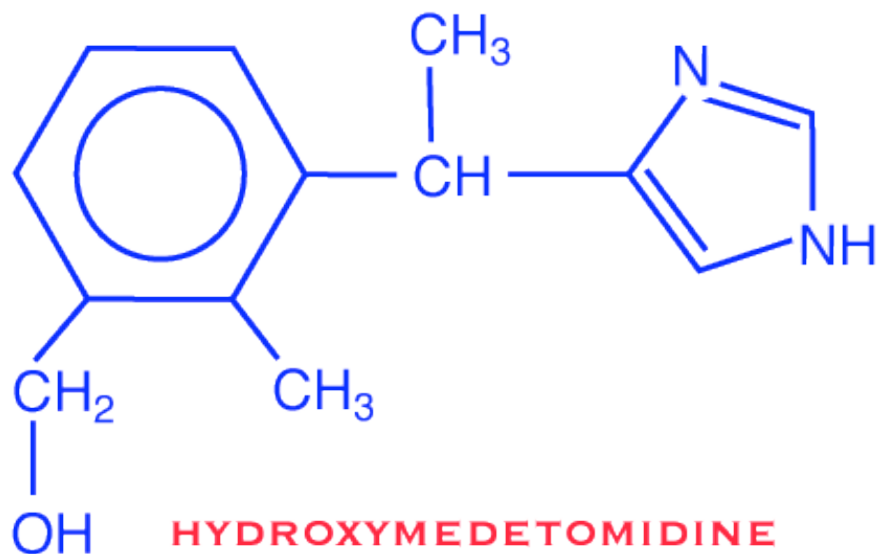
- **cytochrome P450 (microsomal mixed function oxidase)**
- **mainly in SER of liver cells**
  - **but also gut, lungs, kidneys, skin**
- **usually starts off with hydroxylation to produce a reactive intermediate**

DEXMEDETOMIDINE

phase 1



hydroxylation



**N-HYDROXYMETOMIDINE**



# 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 red mushroom with white spots, likely an Amanita muscaria, is growing in a field of dry grass. The mushroom is the central focus of the image, with its bright red cap and white spots contrasting sharply with the dry, brownish-yellow grass. The background is slightly blurred, emphasizing the mushroom.

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



A red mushroom with white spots growing in grass. The mushroom is the central focus, with its cap showing a vibrant red color and numerous white, irregular spots. It is surrounded by dry, brownish grass. The text 'people' is overlaid on the upper part of the mushroom cap.

# people

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



# abnormal phenotypes

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



# abnormal phenotypes

A red mushroom with white spots, resembling a fly agaric, is growing in a field of dry grass. The mushroom has a bright red cap with irregular white patches and a thick, white, ringed stem. The background is a dense field of dry, yellowish-brown grass.

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



# drug interactions

A red mushroom with white spots, likely an Amanita muscaria, is the central visual element. It is positioned in the upper right quadrant of the slide, partially overlapping the title and the first bullet point. The background is a dark, textured surface of dry grass or straw, which is slightly blurred to emphasize the mushroom.

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



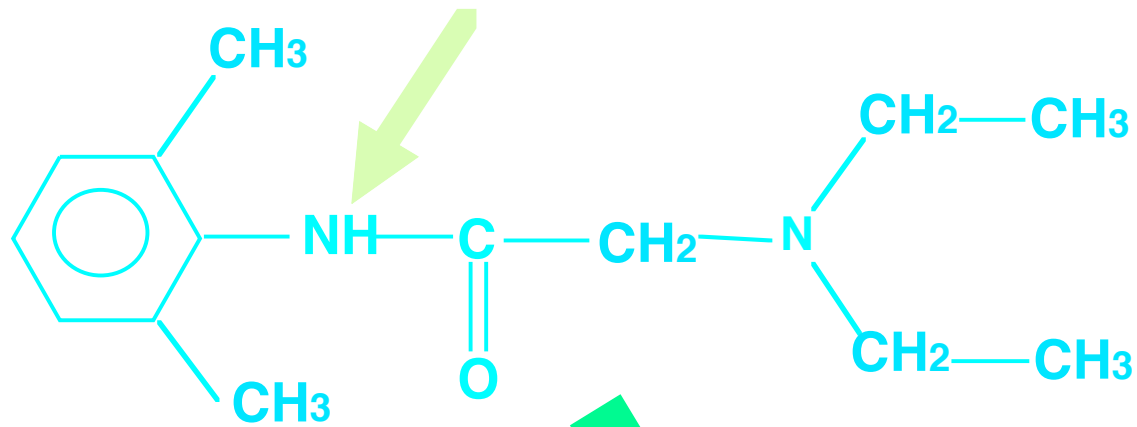
A red mushroom with white spots on a bed of dry grass. The mushroom is the central focus, with its cap showing a vibrant red color and several small, white, irregular spots. The background is a dense layer of dry, brownish-yellow grass, creating a textured, natural setting. The overall lighting is soft, highlighting the mushroom's texture and the surrounding foliage.

# 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

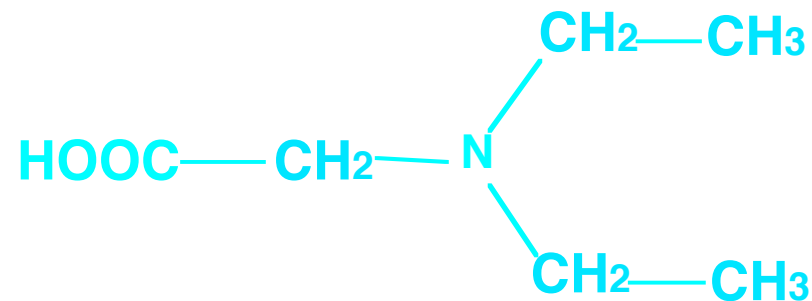
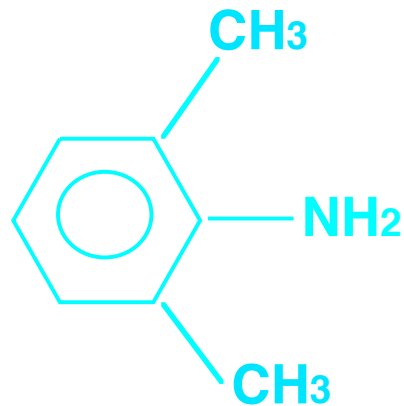
# hydrolysis

amide link



lignocaine

very rapid!





A red mushroom with white spots on a bed of dry grass. The mushroom is the central focus, with its cap showing a vibrant red color and scattered white patches. The background is a dense layer of dry, brownish-yellow grass, creating a textured and natural setting. The overall lighting is soft, highlighting the mushroom's texture and the surrounding foliage.

## phase 2

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

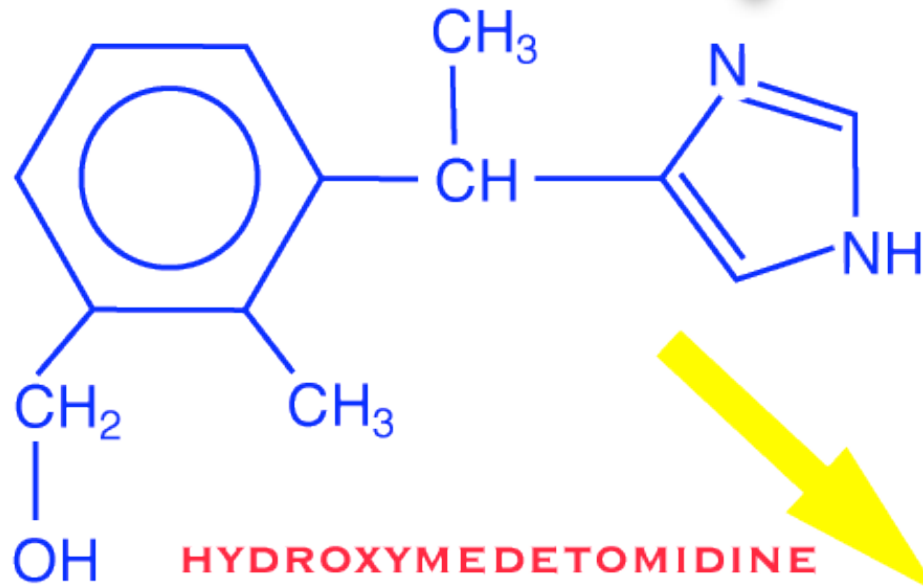


# conjugation

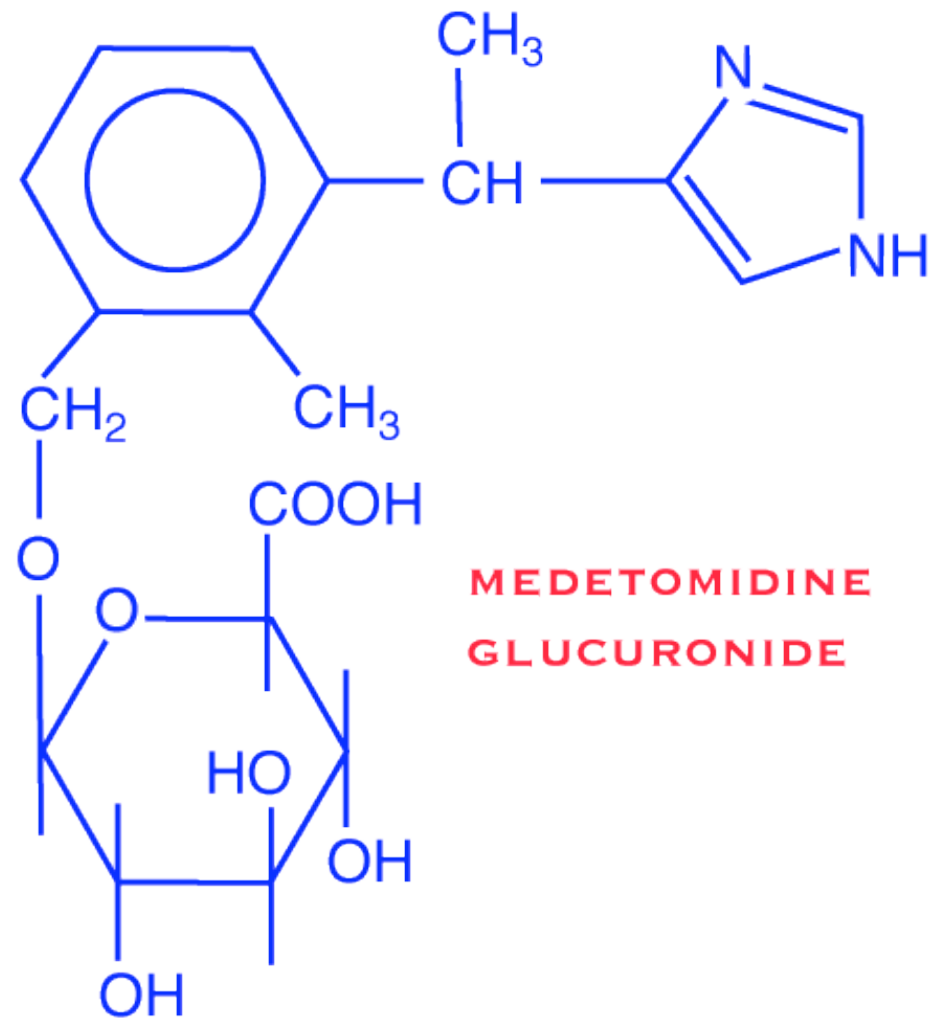
- glucuronide - not cats
- sulphate - not pigs
- acetyl - not cats & dogs
- methyl
- glycine
- ornithine - only birds



## phase 2



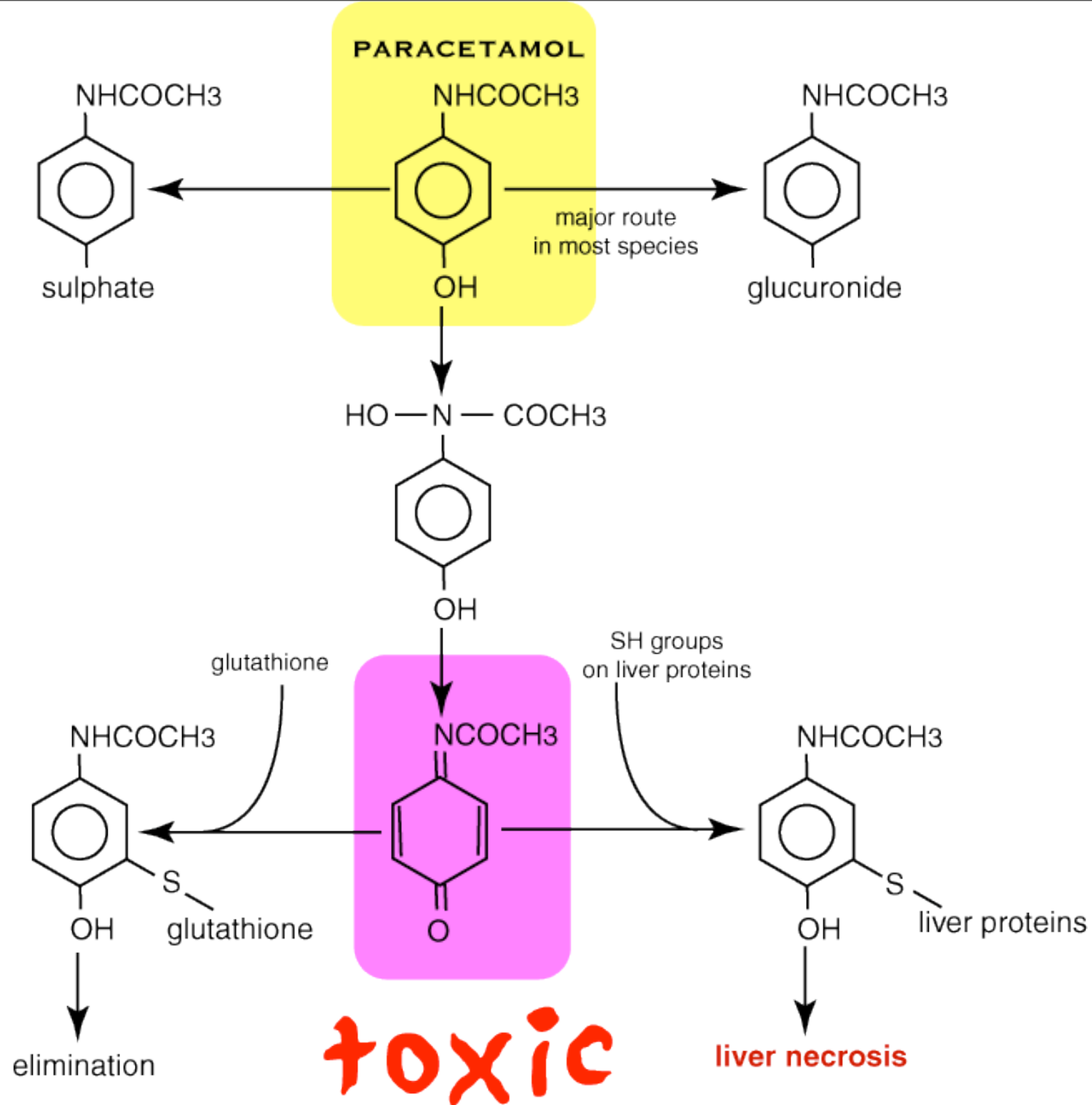
glucuronidation



# 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



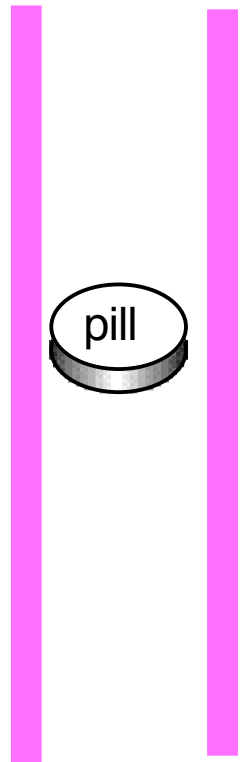


# enterohepatic recirculation

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

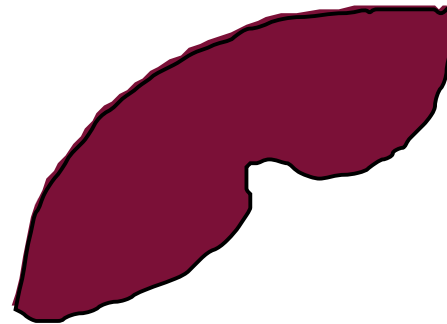


# first pass metabolism



gut

portal vein



liver

systemic  
circulation



target  
organ



**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**