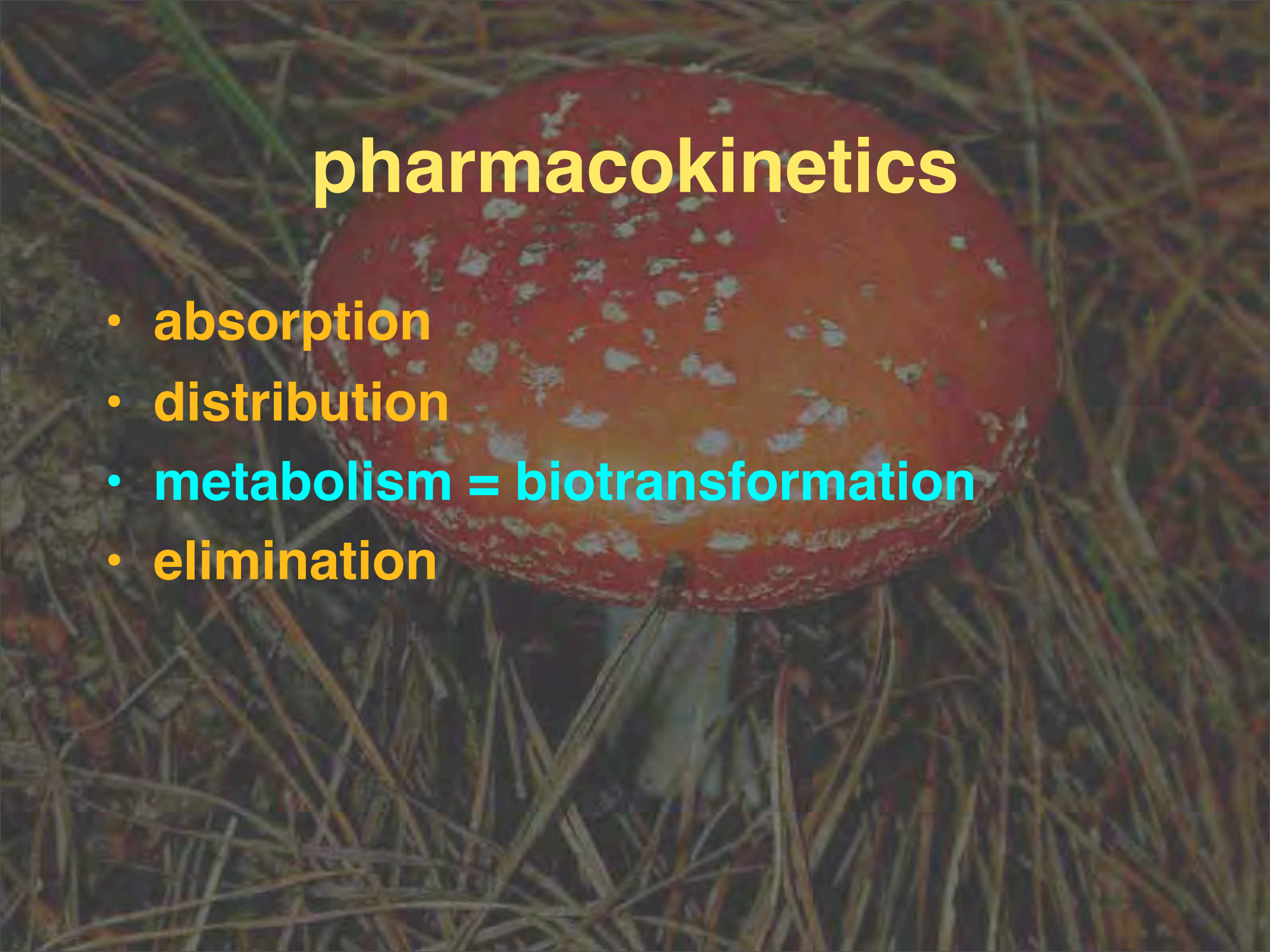

Pharmacokinetics
metabolism



pharmacokinetics

- absorption
- distribution
- metabolism = biotransformation
- elimination

metabolism

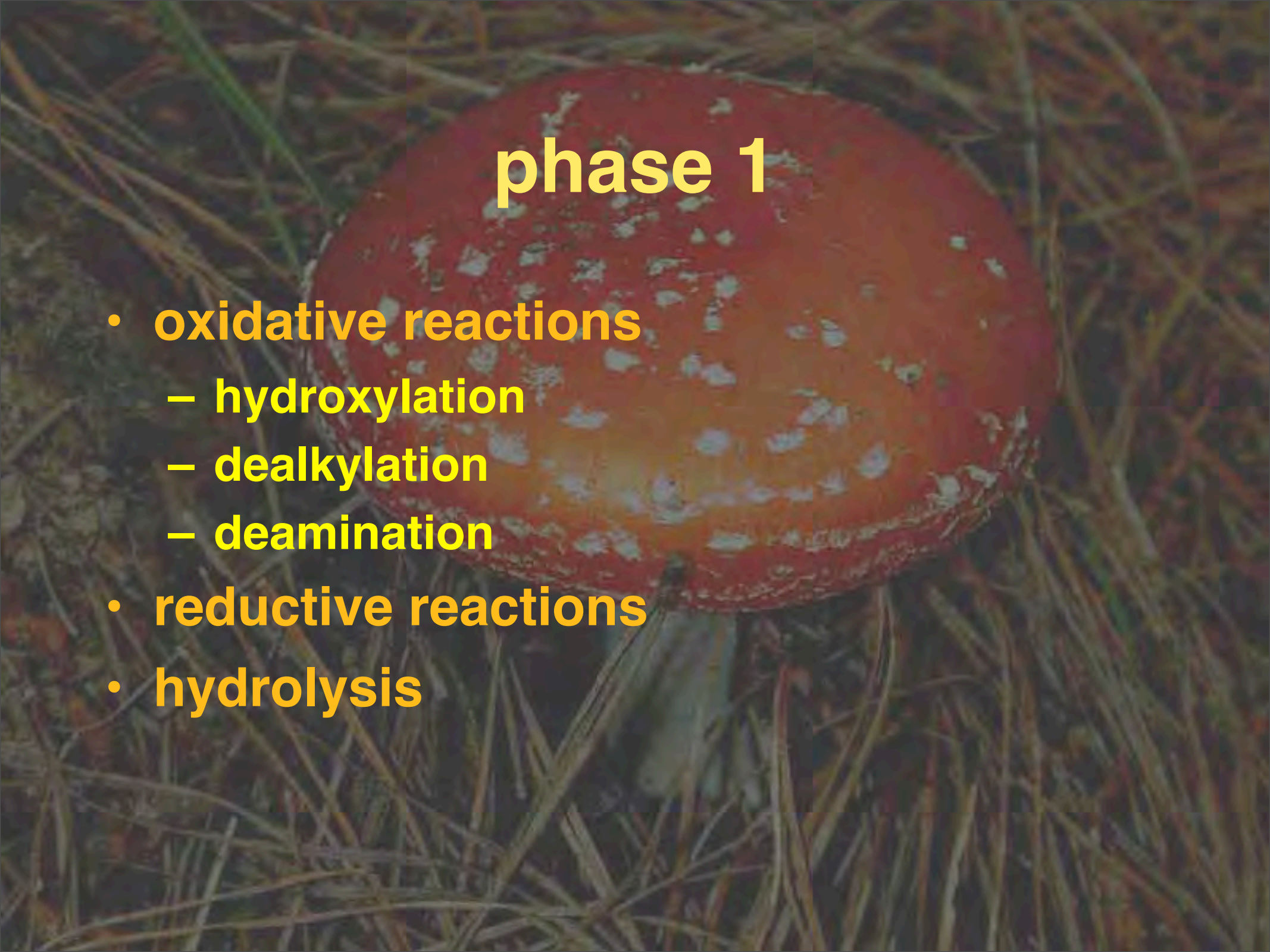
- most species differences in drug effects can be attributed to differences in metabolism

metabolism

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

metabolism

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

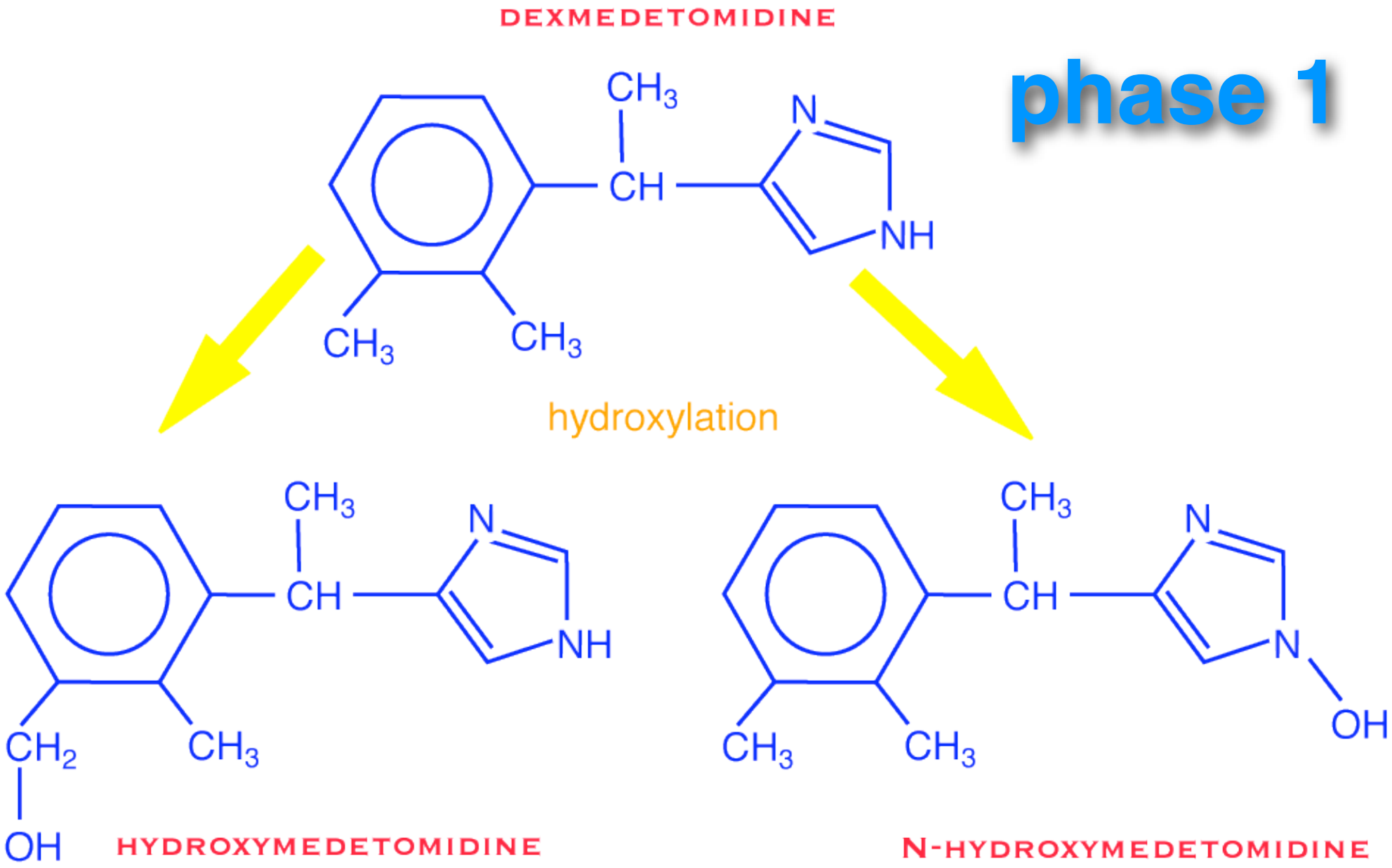


phase 1

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

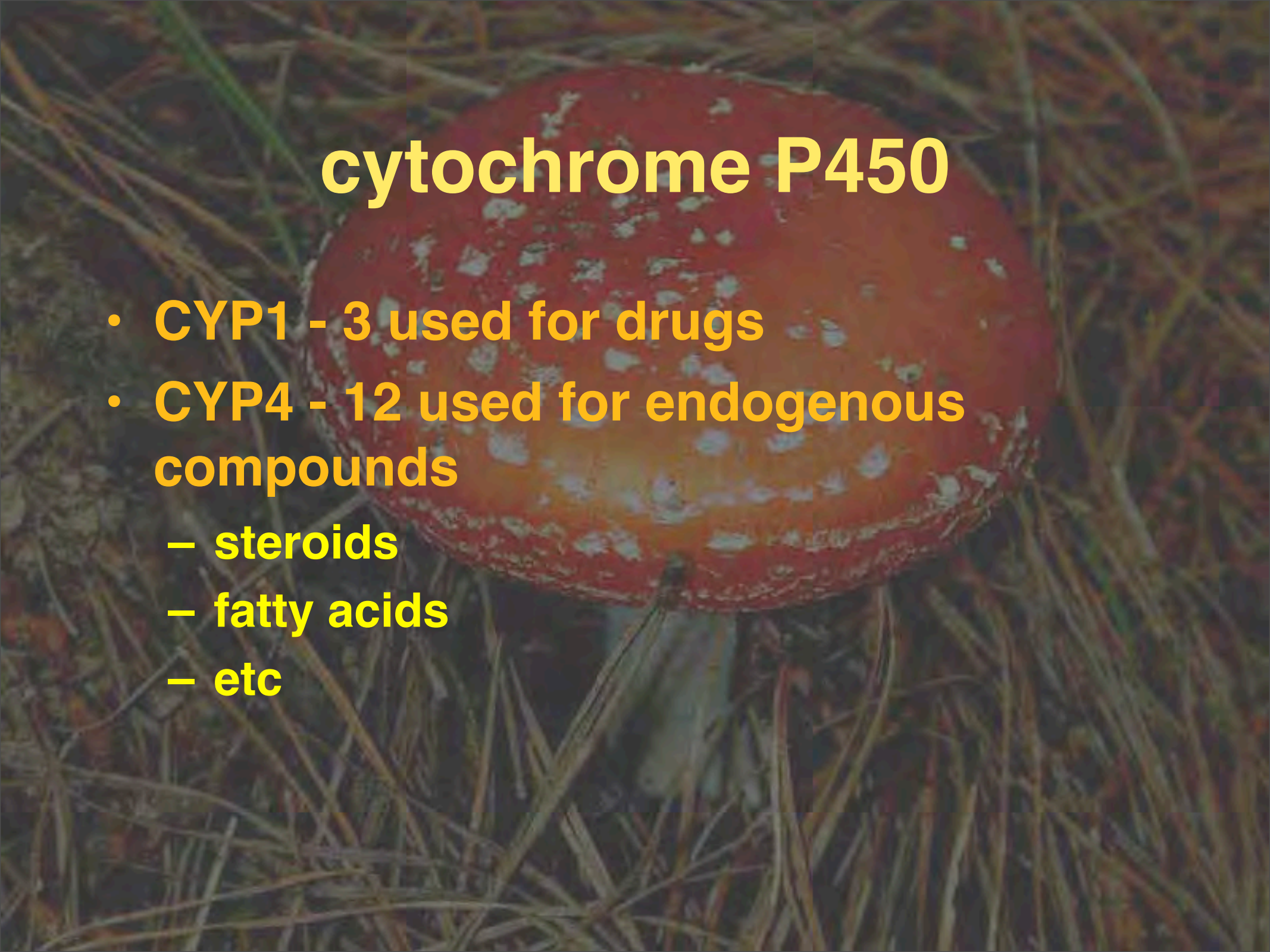
oxidation

- 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
HYDROXYMEDETOMIDINE
N-HYDROXYMEDETOMIDINE

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

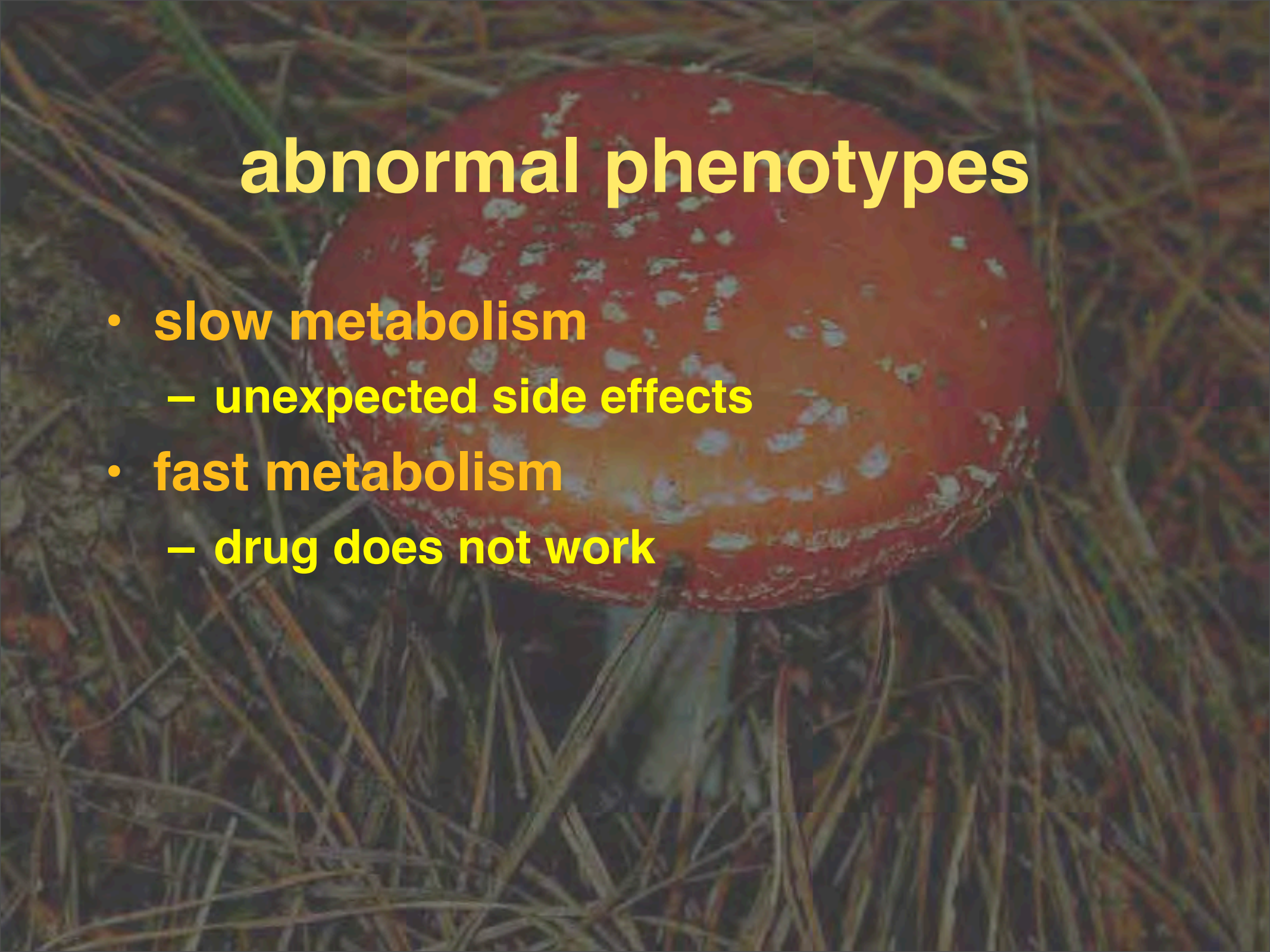
- CYP1 - 3 used for drugs
- CYP4 - 12 used for endogenous compounds
  - steroids
  - fatty acids
  - etc

people

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

abnormal phenotypes

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



abnormal phenotypes

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

drug interactions

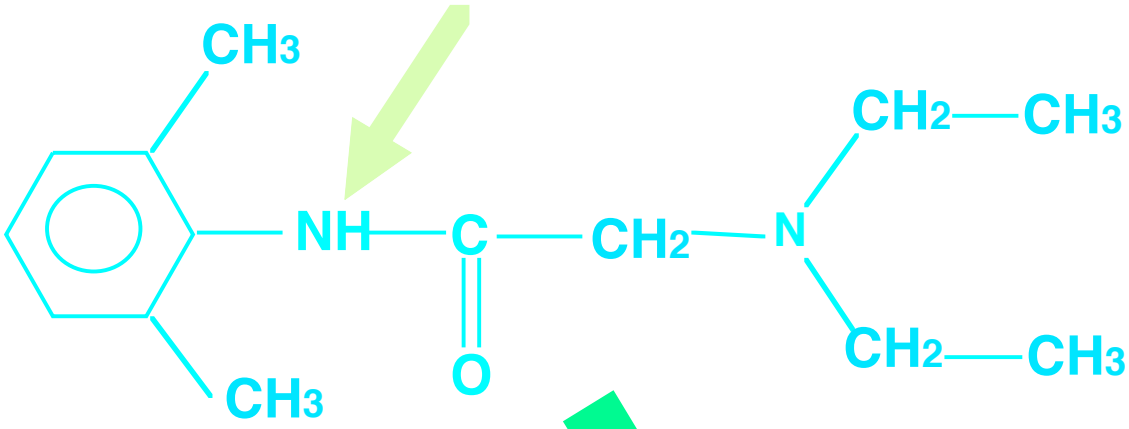
- induction of P450
  - phenobarbitone, rifampicin
  - environmental toxins
- inhibition of P450
  - piperonyl butoxide
  - grapefruit juice
- competition for P450
  - ketoconazole & many drugs

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

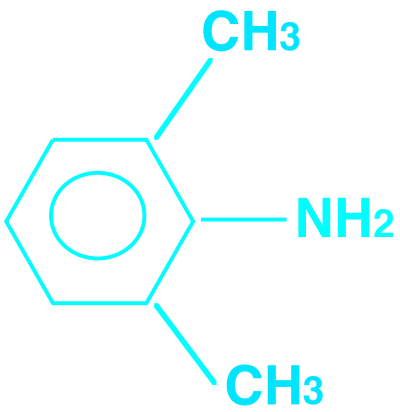
hydrolysis

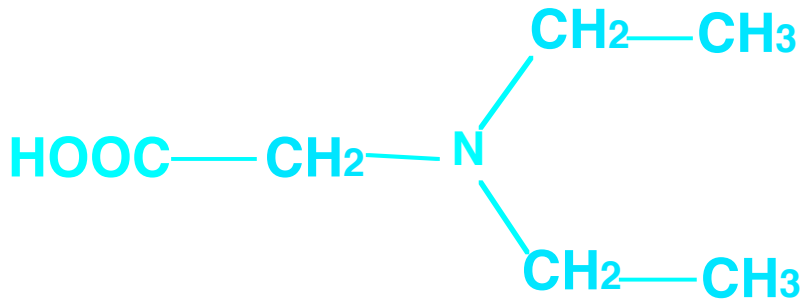
amide link

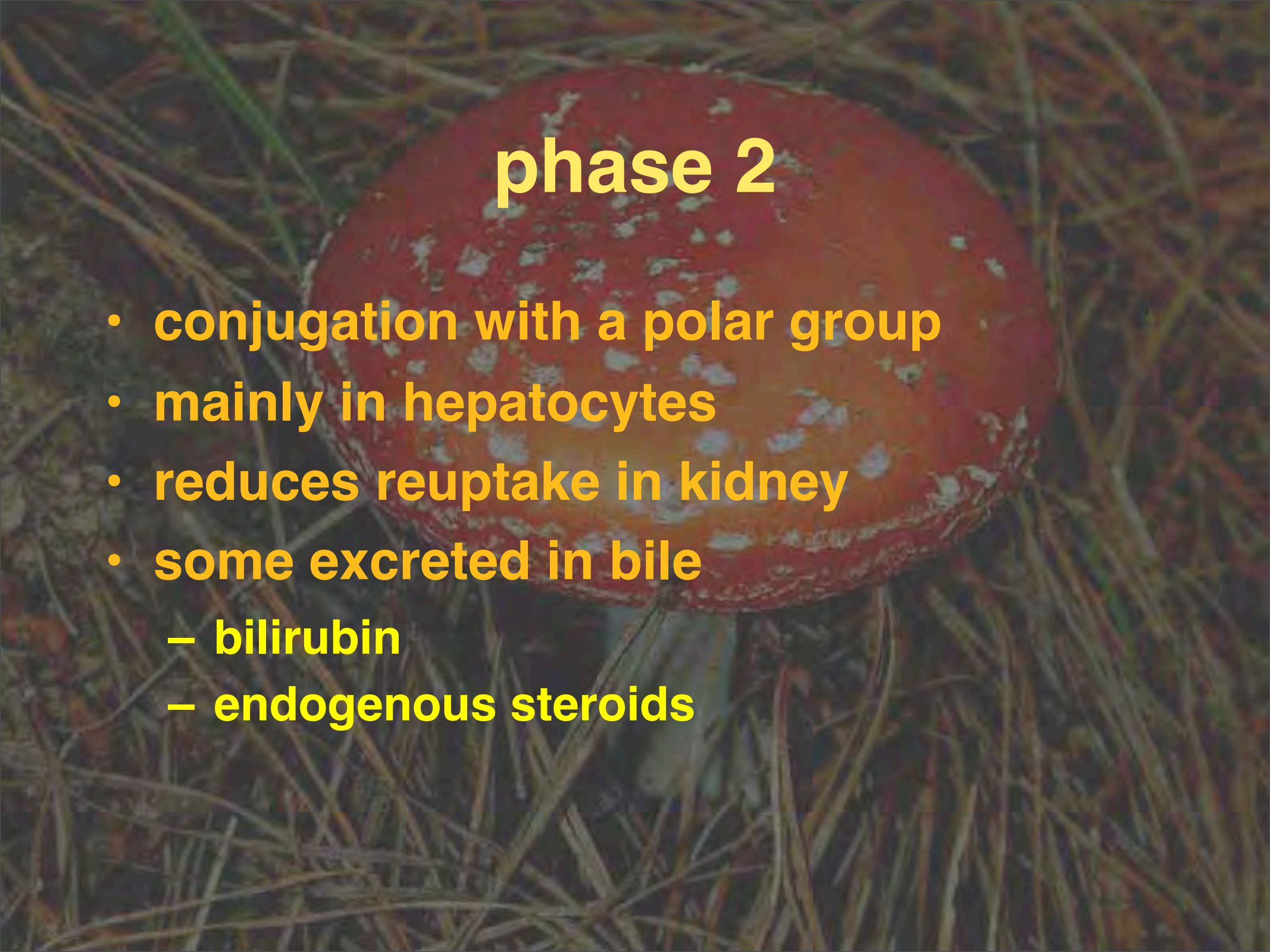


lignocaine

very rapid!







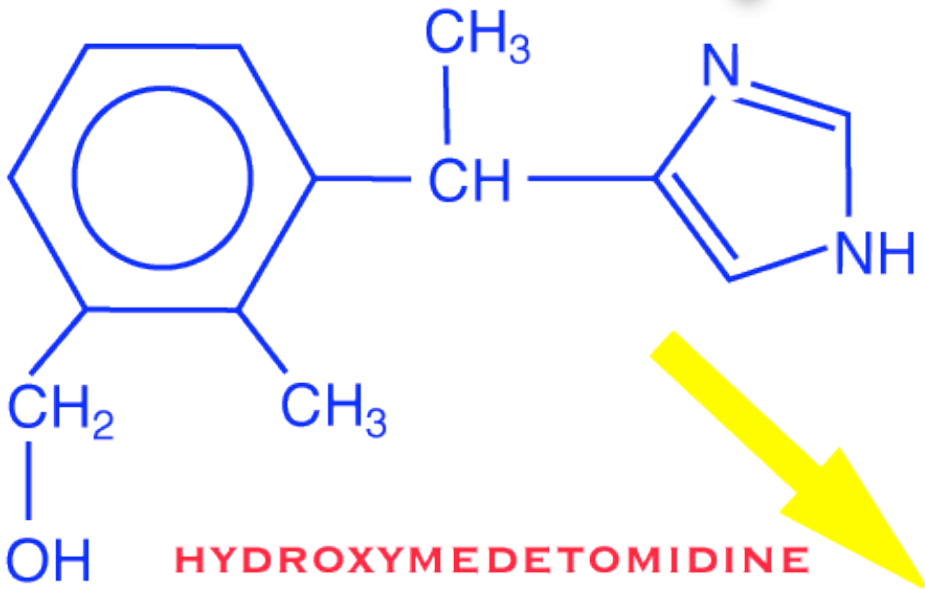
phase 2

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

conjugation

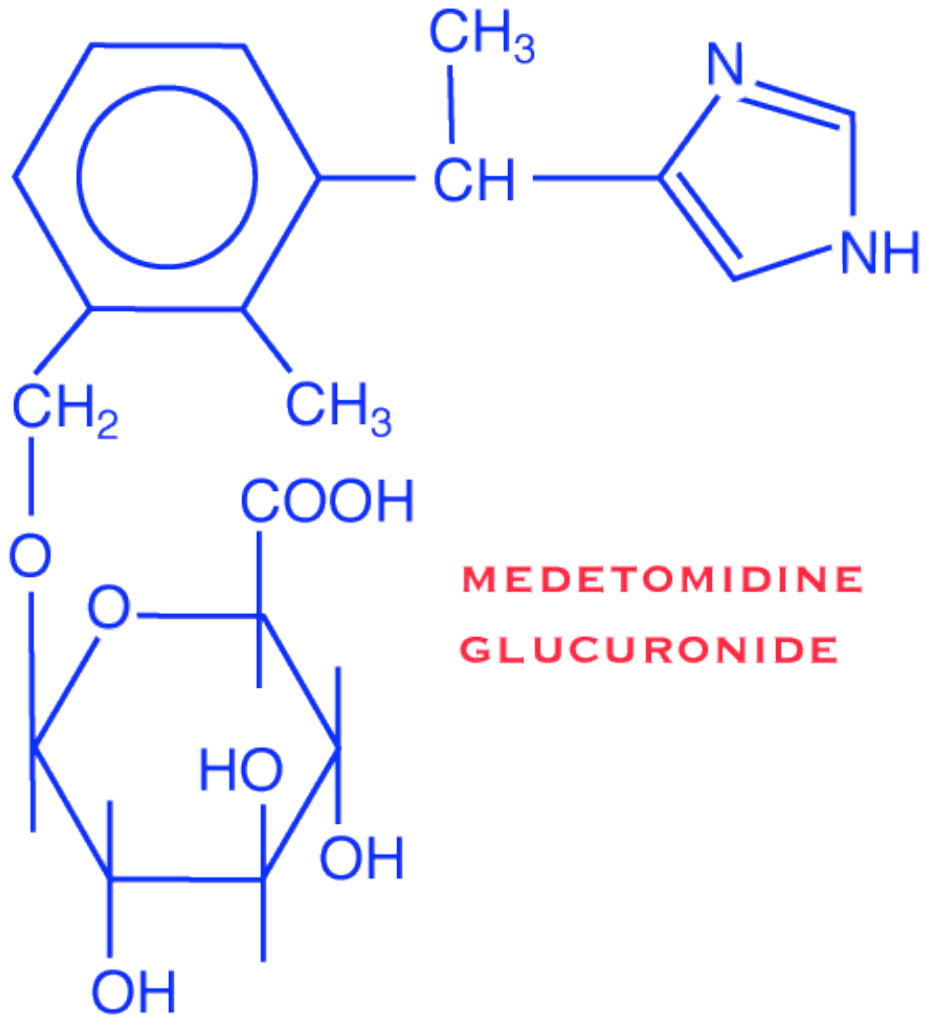
- glucuronide - not cats
- sulphate - not pigs
- acetyl - not cats & dogs
- methyl
- glycine
- ornithine - only birds

phase 2



HYDROXYMEDETOMIDINE

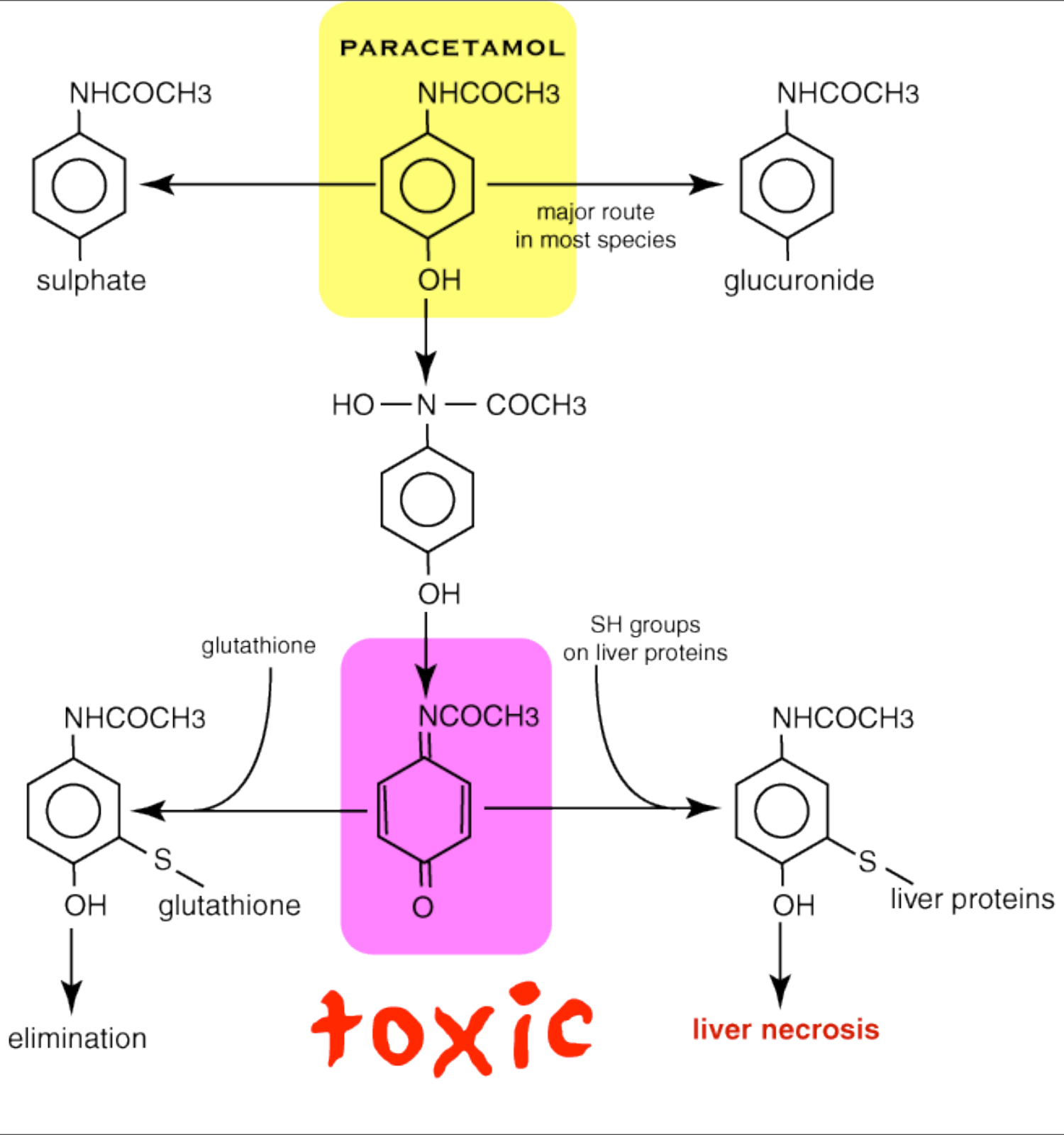
glucuronidation



MEDETOMIDINE GLUCURONIDE

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


PARACETAMOL
NHCOCH3
NHCOCH3
NHCOCH3
sulphate
OH
major route
in most species
glucuronide
HO — N — COCH3
OH
glutathione
SH groups
on liver proteins
NHCOCH3
NCOCH3
NHCOCH3
S
OH
glutathione
O
S
OH
liver proteins
elimination
toxic
liver necrosis

stereoisomers

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

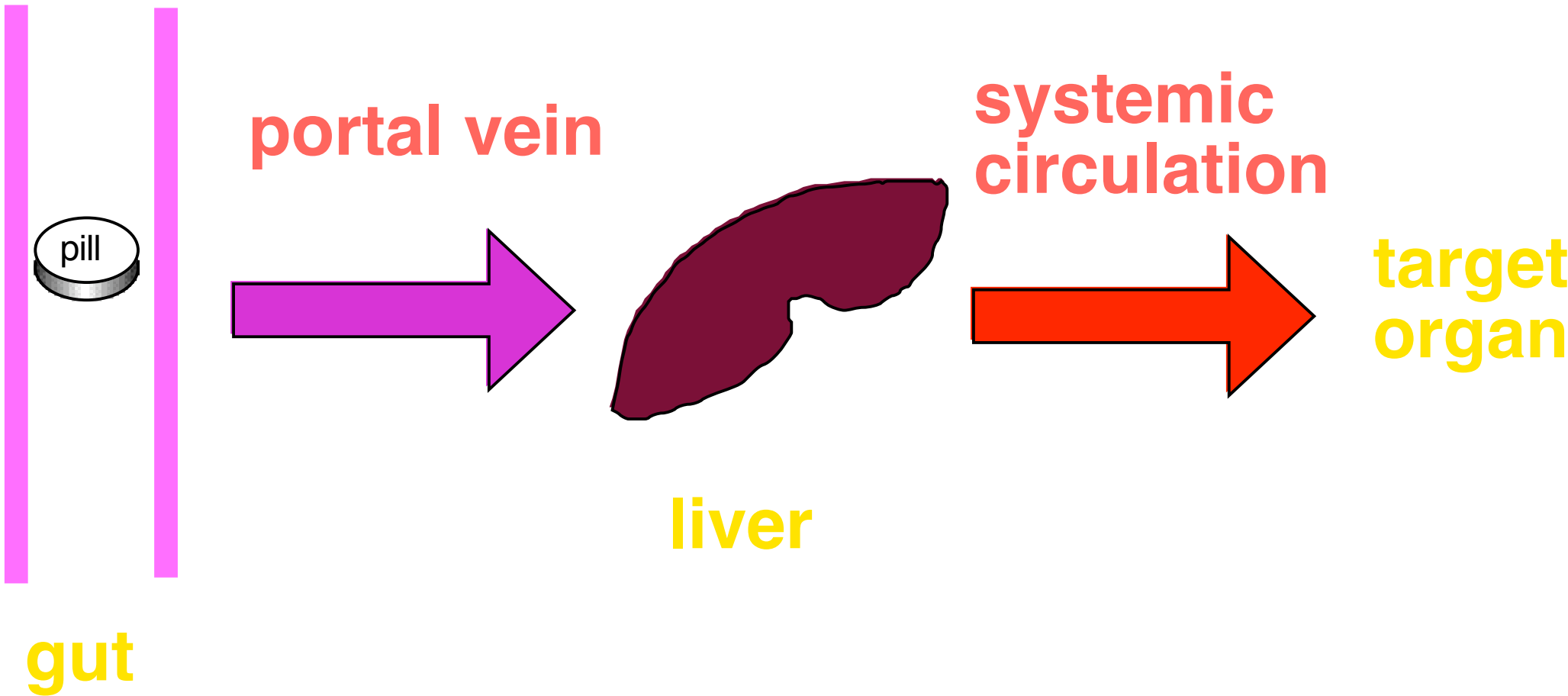
abnormal metabolism

- 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