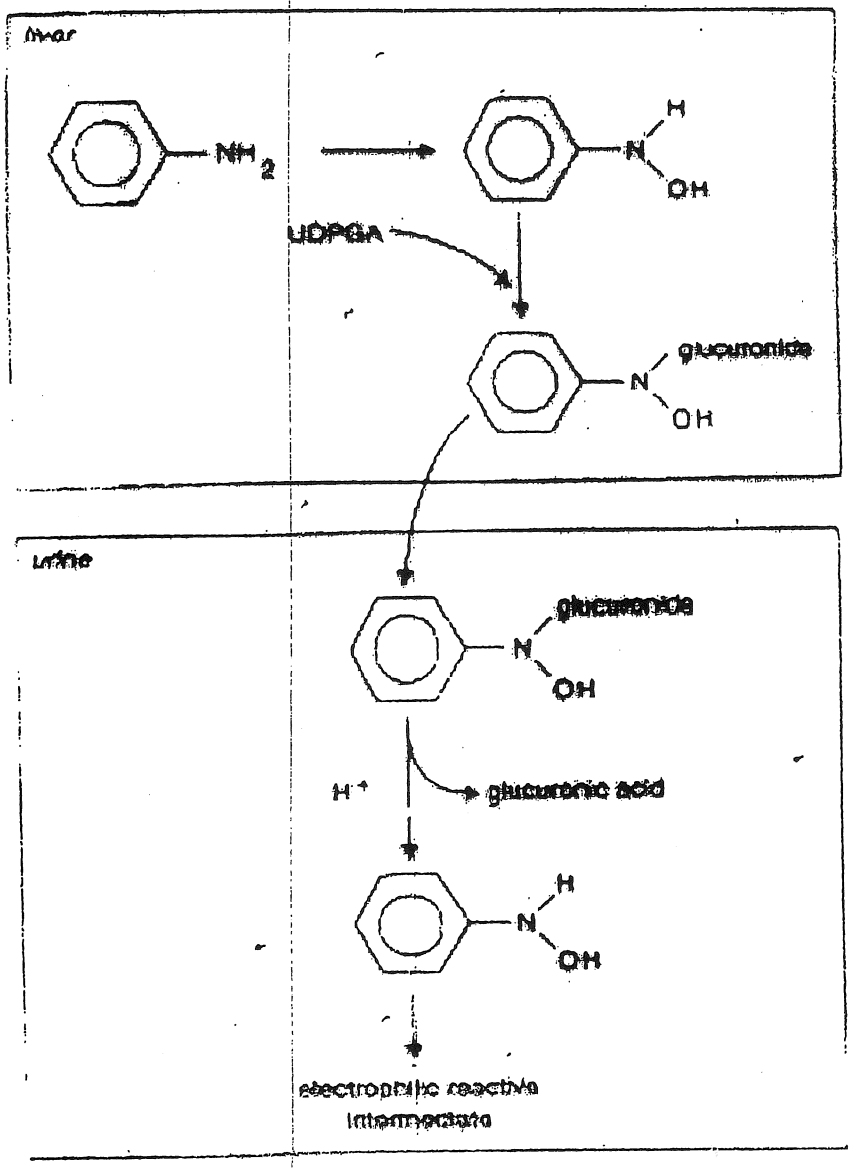
Example of (indirect) bioactivation via phase II reactions:



Glucuronides may be unstable under certain circumstances (eg some aromatic amines). Compounds may be 'bio-activated' in the liver to form N-hydoxyl derivatives, after which they can be 'bio-inactivated' by forming N-glucuronides. However, in an acid environment (i.e., urine), the glucuride is a good leaving group, allowing the substance to exert a possible carcinogenic effect on the bladder epithelium.

- Typically, we think of only phase I reactions being able to metabolically bioactivate a substrate.

- However, as there are exceptions to most rules, here is an example of bioactivation via a phase II pathway.

Organ and species differences in aromatic hydroxylation of benzo[a]pyrene

species	*liver*	*kidneys*	*lungs*
rat	5.8	0.37	0.13
mouse	11.26	0.03	1.02–0.2
rhesus monkey	2.5	0.38	0.2

[a]hydroxylase activity in pmol product min^{-1} mg^{-1} microsomal tissue

- There are many differences in metabolic capacity between species, some of which are indicated in the table above.
- As you are now well aware, there are also intra-specific differences associated with age,

  gender, nutrition, genetic predisposition and environmental factors including various exposures that may cause enzyme induction or inhibition.

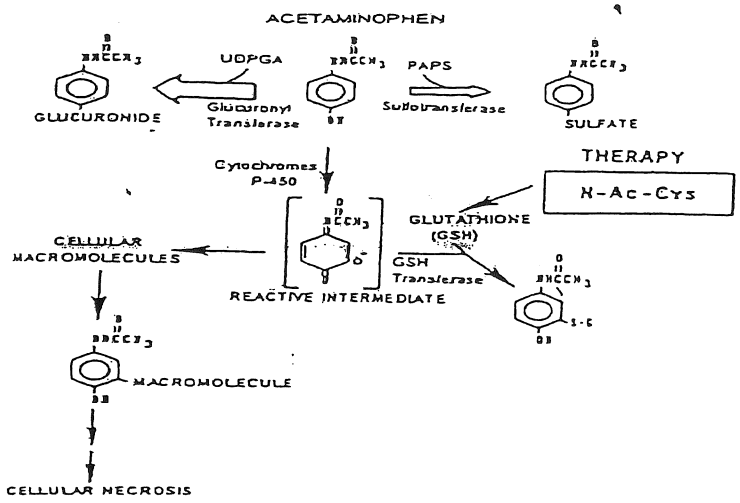


Figure 13–6. Biotransformation of acetaminophen.

As indicated by the larger arrows, the dominant pathways lead to glucuronide and sulfate conjugates, while the pathway leading to adducts with macromolecules is a minor pathway. Therapy with the glutathione precursor *N*-acetyl-cysteine (N-Ac-Cys) facilitates detoxification of the reactive intermediate. (Modified from To EAC, Wells PG: Biochemical changes associated with potentiation of acetaminophen hepatotoxicity by brief anesthesia with diethyl ether. *Biochem Pharmacol* 35:4139–4152, 1986.)

- Example of therapy to reduce acetaminophen toxicity by fostering GST conjugation of a reactive intermediate.

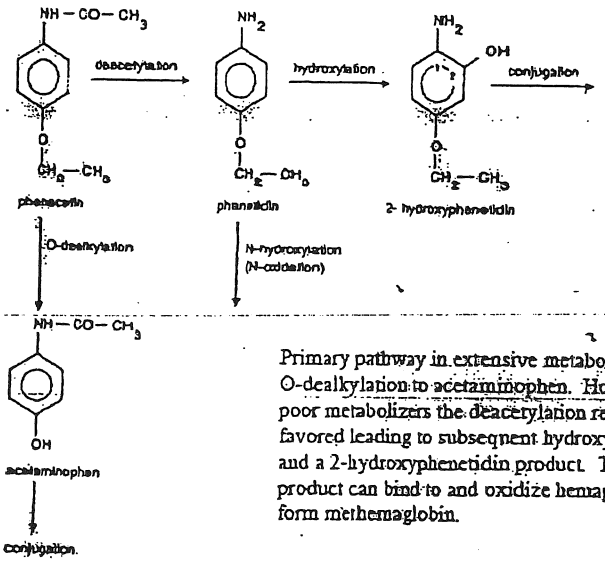
❖**Species Differences**

- Dogs do not acetylate aromatic amines.
- Cats are deficient in N-actyltransferase & glucuronyltransferase.
- Guinea pigs do not form mercapturic acid conjugates.
- Pigs are deficient in sulfate conjugation.

❖**Inter-individual Differences**

- Genetic differences (extensive vs poor metabolizers).
- Sex differences.
- Age differences.
- Other 'environmental stressors'.

Pathway shift in poor vs extensive metabolizers

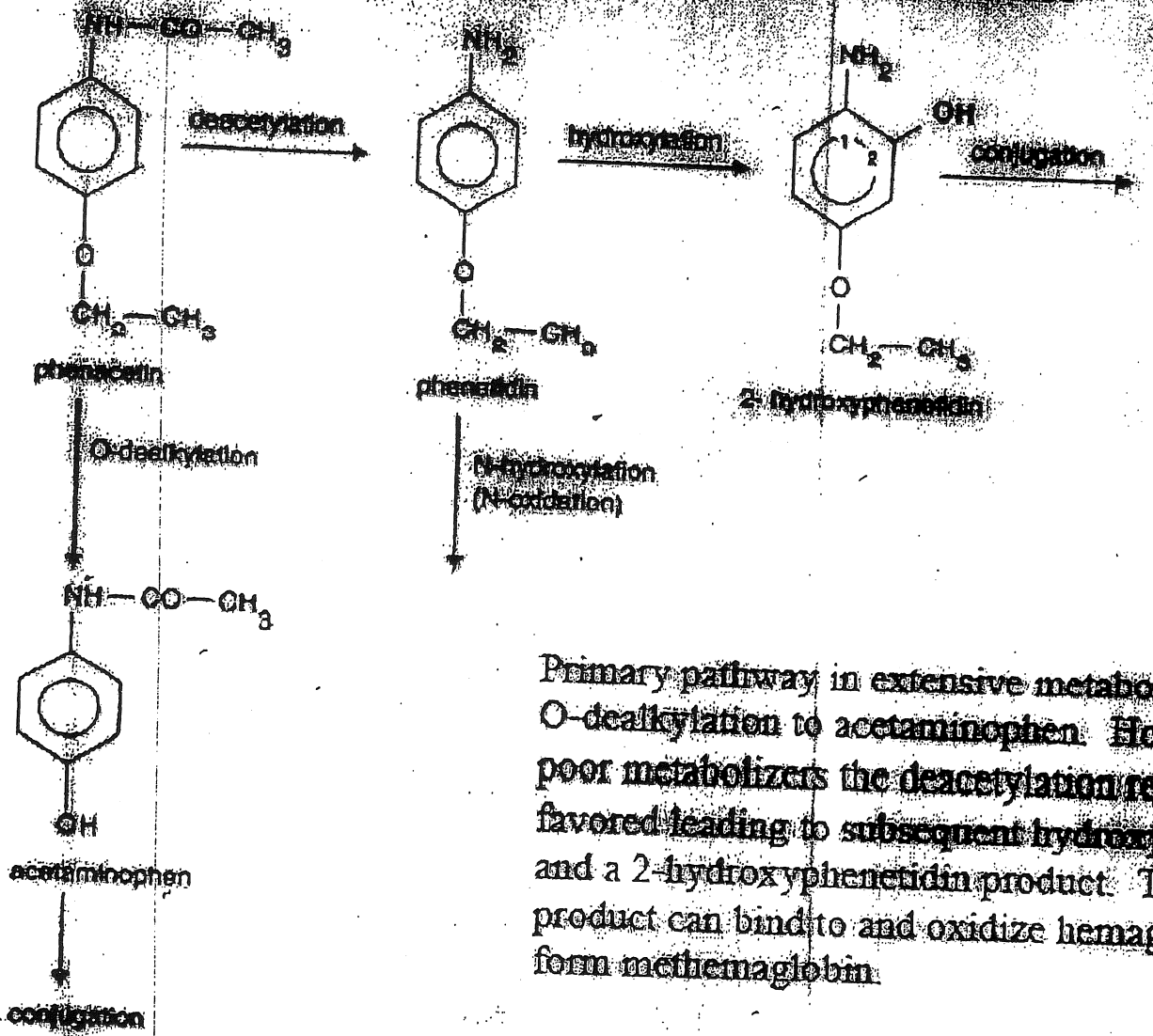


Primary pathway in extensive metabolizers is O-dealkylation to acetaminophen. However in poor metabolizers the deacetylation reaction is favored leading to subseqnent hydroxylation and a 2-hydroxyphenetidin product. This product can bind to and oxidize hemaglobin to form methemaglobin.

Dietary Metabolic Alterations

- ✓ IN MOUSE HEPATIC MICROSOMES, DIETARY BUTYLATED HYDROXYANISOLE (BHA) ENHANCED THE TOTAL METABOLISM OF BENZO(A)PYRENE (BP) BUT DECREASED THE MICROSOMAL METABOLISM OF (BP)-7,8-DIOL, ESPECIALLY THE FORMATION OF (BP)-TRANS-7,8-DIOL-ANTI-9,10-OXIDE.
- ✓ THE ALTERED METABOLISM OF BENZO(A)PYRENE IS BELIEVED TO BE DUE TO THE INDUCTION OF NEW CYTOCHROME P450 SPECIES BY DIETARY BHA.

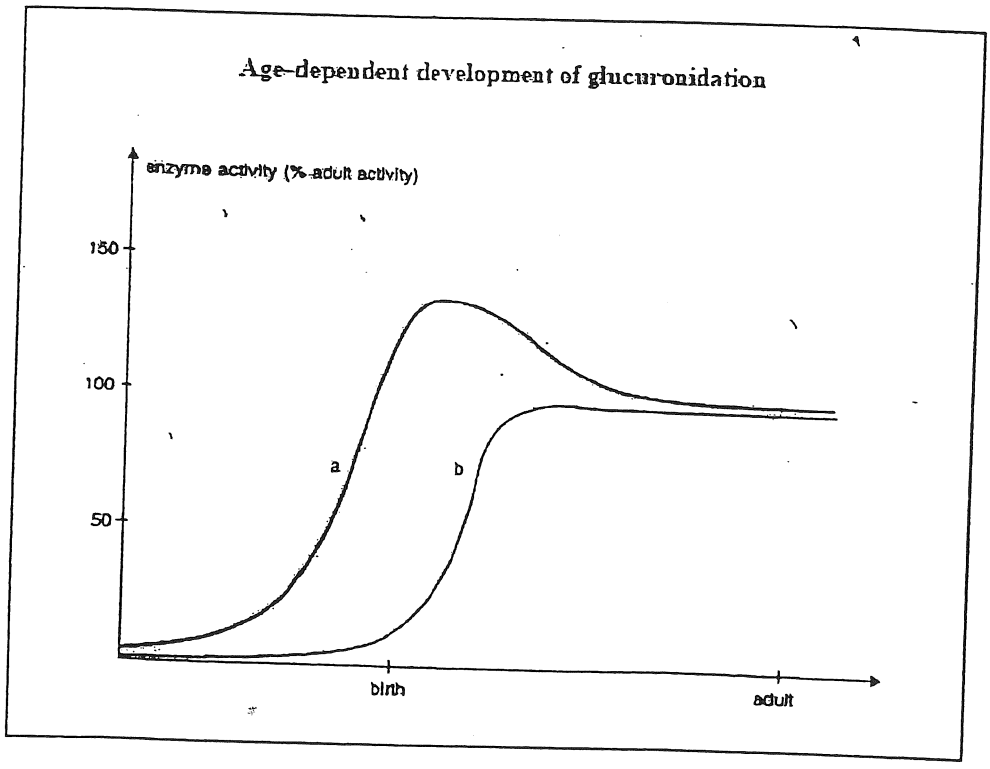
Pathway shift in poor vs extensive metabolizers



Primary pathway in extensive metabolizers is O-dealkylation to acetaminophen. However in poor metabolizers the deacetylation reaction is favored leading to subsequent hydroxylation and a 2-hydroxyphenetidin product. This product can bind to and oxidize hemaglobin to form methemaglobin.

✓THUS, BHA CAN AFFECT BENZO(A)PYRENE METABOLISM BY EXERTING ITS INHIBITORY EFFECT DIRECTLY & BY ALTERING THE COMPOSITION OF MICROSOMAL MONOOXYGENASE ENZYMES AFTER A FEW DAYS OF EXPOSURE.

➢ ***Diet is just one factor that can alter metabolic kinetics.***



- Another example of inter-individual differences in metabolic capacity.
- Line "a" refers to normal neonates and their glucuronysyl transferase

activity.

- There is an increase in activity up until birth, whereupon it peaks and then levels off.
- Line "b" refers to a subset of the population where GT activity does not peak until weeks after birth.

- These neonates are subject to jaundice (failure to conjugate bilirubin) and require the use of "bili lights."
- Using "bili lights" is a therapeutic procedure performed on newborn or premature infants to reduce elevated levels of bilirubin.
- If blood levels of bilirubin become too high, the bilirubin begins to dissolve in the body tissues, producing the characteristic yellow eyes and skin of jaundice.
- Bilirubin also has an affinity for brain tissue, where it can accumulate and cause permanent brain damage.

Preferred route of excretion of xenobiotic conjugates

Glucuronides	<250 M.W.—kidney >350 M.W.—bile
Sulfates	Kidney
Glutathione conjugates	Bile
Acetylated conjugates	None
Amino acid conjugates	Kidney
Mercapturic acids	Kidney

The route of excretion may vary with the type(s) of conjugation reaction favored and the molecular weight of the metabolite(s).

Routes of Elimination

Expired Air	Volatile Compounds
Urine	Major route for low molecular weight polar compounds
Bile	High molecular weight, conjugated compounds
Feces	Compounds not absorbed in gut or compounds excreted in the bile
Saliva	Very low molecular weight compounds
Milk	Both water and lipid soluble compounds
Hair	Quantitatively unimportant