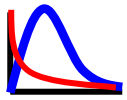
A Short Course in Pharmacokinetics

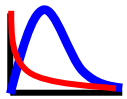
Chris Town

Research Pharmacokinetics



Outline

- Pharmacokinetics - Definition
- Ideal Pharmacokinetic Parameters of a New Drug
- How do we optimize PK for new compounds
- Why do Drug Candidates fail?
- Processes involved in PK
  - Absorption
    - PK study example
  - Distribution
    - Whole Body Autoradiography example
  - Metabolism
    - Discussion
  - Excretion
    - Discussion
- Allometric Scaling between species



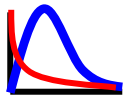
Definitions

Pharmacokinetics:

the activity or fate of drugs in the body over a period of time, including the processes of absorption, distribution, localization in tissues, biotransformation and excretion.

Pharmacodynamics:

the study of the biochemical and physiological effects of drugs and the mechanisms of their actions, including the correlation of action and effects of drugs with their chemical structure; also, the relationship between drug concentration and effect.



More Definitions

Exposure: A measure for the amount of drug that an organism has really "seen"

Bioavailability A measure for the proportion of the dose that reaches the systemic circulation (not the same as exposure)

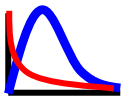
Clearance A measure of the elimination of a compound from the blood given as volume cleared/time

Volume of Distribution A measure of the theoretical volume that a compound distributes to.

Unbound Fraction The fraction of drug not bound to proteins:

$C_{unbound} = f_u \times C_{total}$

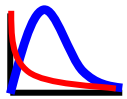
Half-Life A measure of the time it takes for the organism to decrease the concentration of the drug by 50%



Ideal PK Properties of a Drug

From a Marketing Perspective

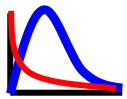
- Must be efficacious with once/day dosing
- One or two dose levels should be safe and efficacious in all individuals
- No dosing adjustments should be required with multiple dosing.



Ideal PK Properties of a Drug

From a Clinical Perspective

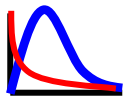
- Should give consistent plasma concentrations in all individuals (patients) from one dose.
  - No variability in metabolism
  - Excretion by both renal and hepatic mechanisms for those with liver or kidney problems
- Rapid, predictable onset of action
- Clearance high enough so compound is removed from body if any untoward side-effects are observed.
- No accumulation
- No interaction with co-administered drugs due to
  - High Protein Binding
  - Metabolism (induction or inhibition)
  - Interference with Excretion



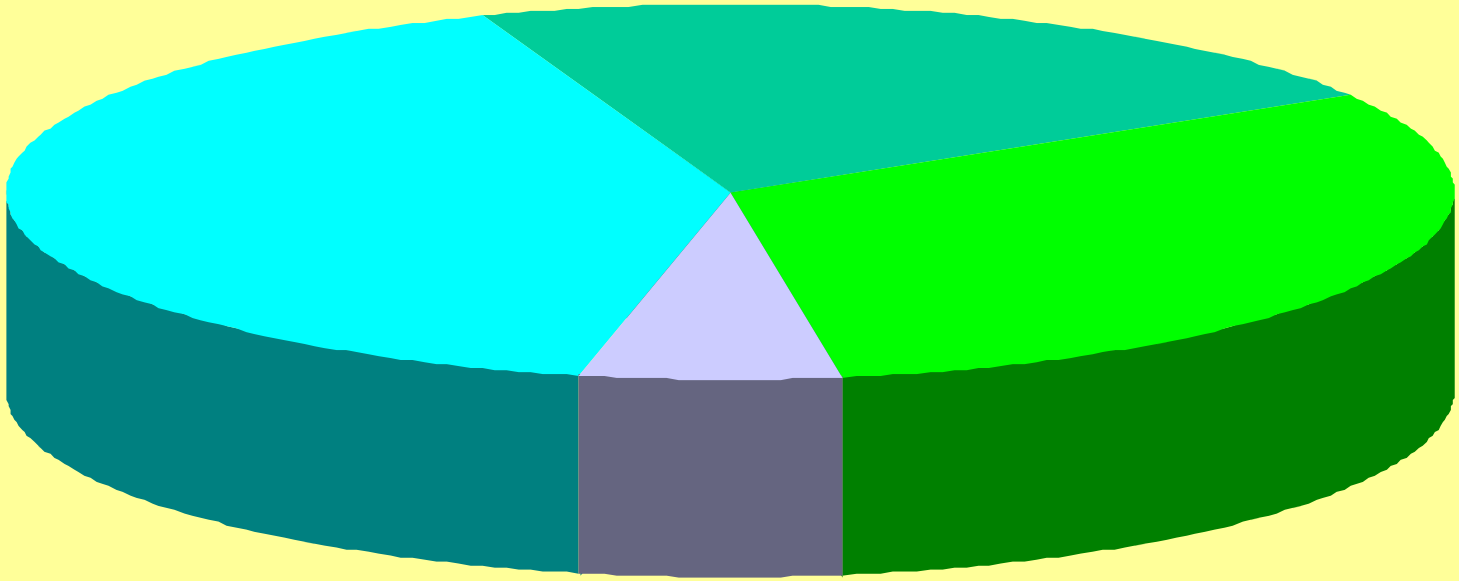
PK in Discovery

Do you optimize PK for the animal model or humans or both?

- We generally optimize for animal model to show POP and check for activity.
- Human in-vivo PK is estimated from animal in-vivo/in-vitro and human in-vitro data, after the DP-1 candidate is chosen.
- Human PK is one of the major determinants of Drug's success or failure in the clinic
  - BID or TID Dosing
  - Non-reproducible PK on multiple Dosing
  - Drug-Drug Interactions



Reasons for Failure in Development



- Toxicity (22%)
- Lack of Efficacy (31%)
- Market Reasons (6%)
- Poor Biopharmaceutical (PK) Properties (41%)

Pharmacokinetics

Absorption

Distribution

Metabolism

Excretion

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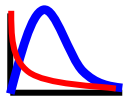

A Pharmacokinetic Study

Rats were dosed with BAY XX-XXXX and Blood samples were collected over 96 hours after oral and Intravenous dosing

(h)	(ug/l)		(h)	(ug/l)
0	0		0	--
0.166	2422.971		0.0833	37700
0.333	4435.444		0.166	28600
0.666	7552.264		0.333	25500
1	7421.424		0.666	18100
2	5572.851		1	15700
4	2784.17		2	12200
7	2270.989		4	4200
24	1046.388		7	2200
30	714.68		24	1630
48	445.44		30	932
72	108.63		48	108
96	5.046		72	130
			96	36

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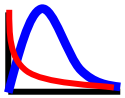
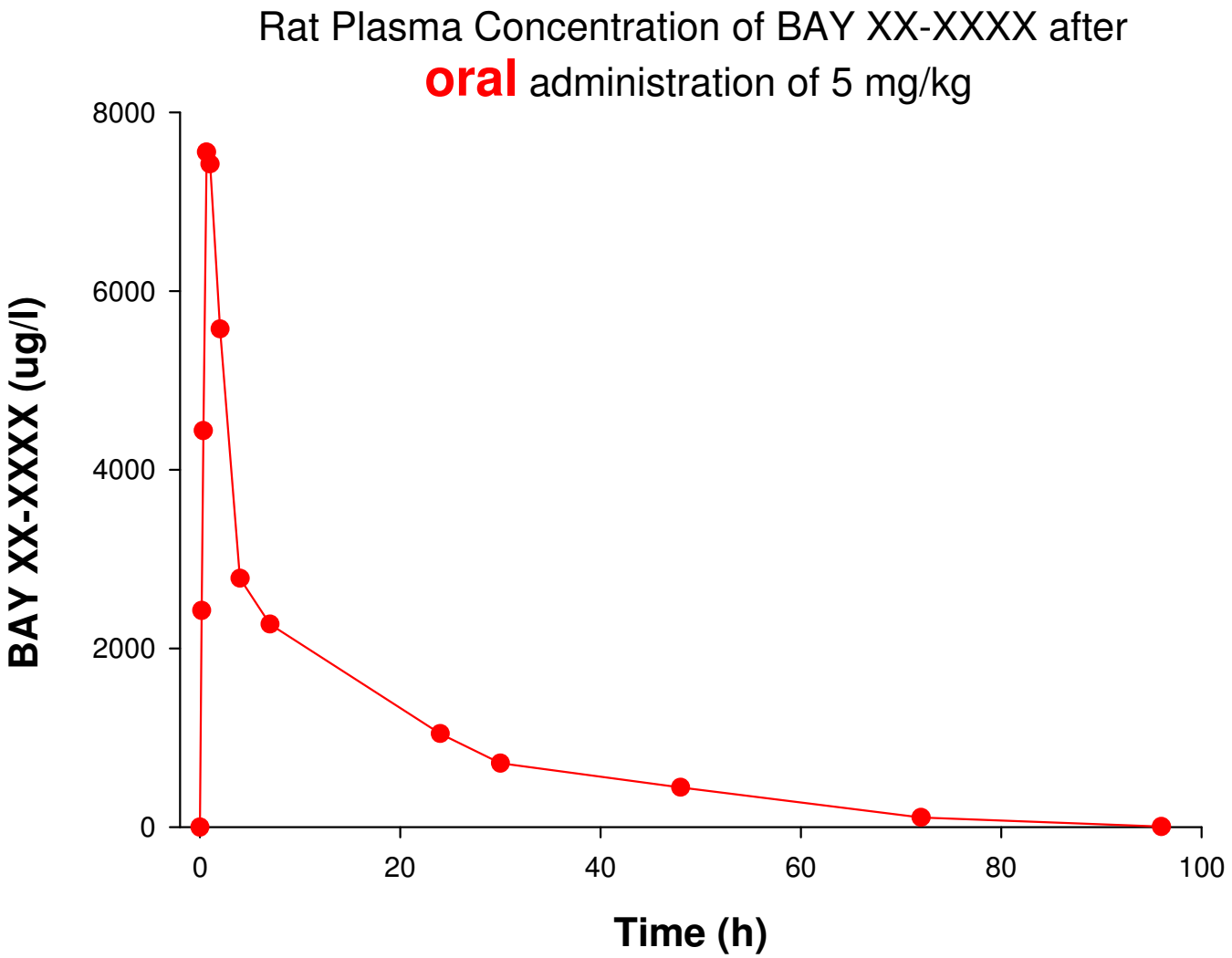


Plasma Concentration vs. Time



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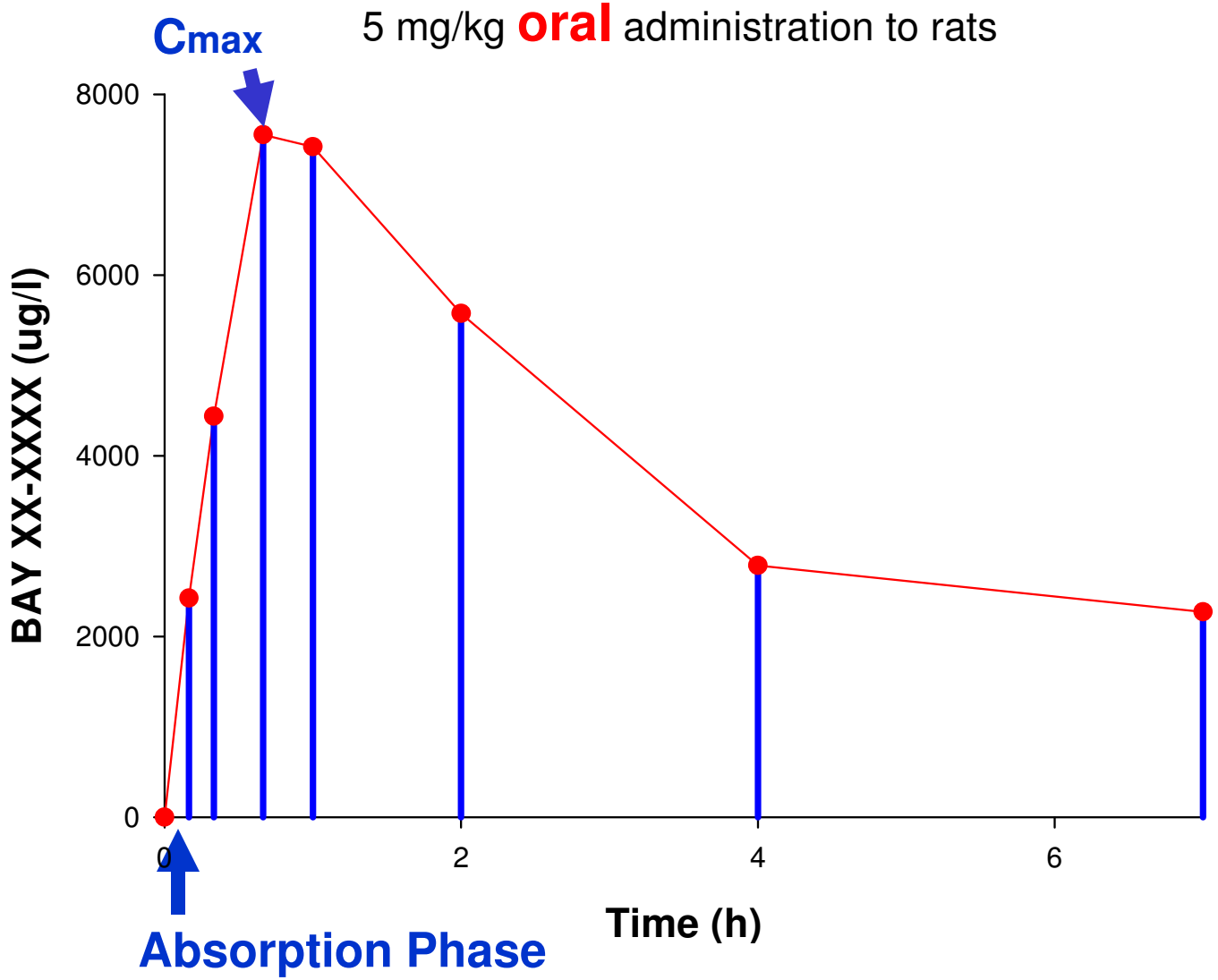
Area Under the Curve

Rat plasma Concentrations of BAY XX-XXXX after 5 mg/kg **oral** administration to rats



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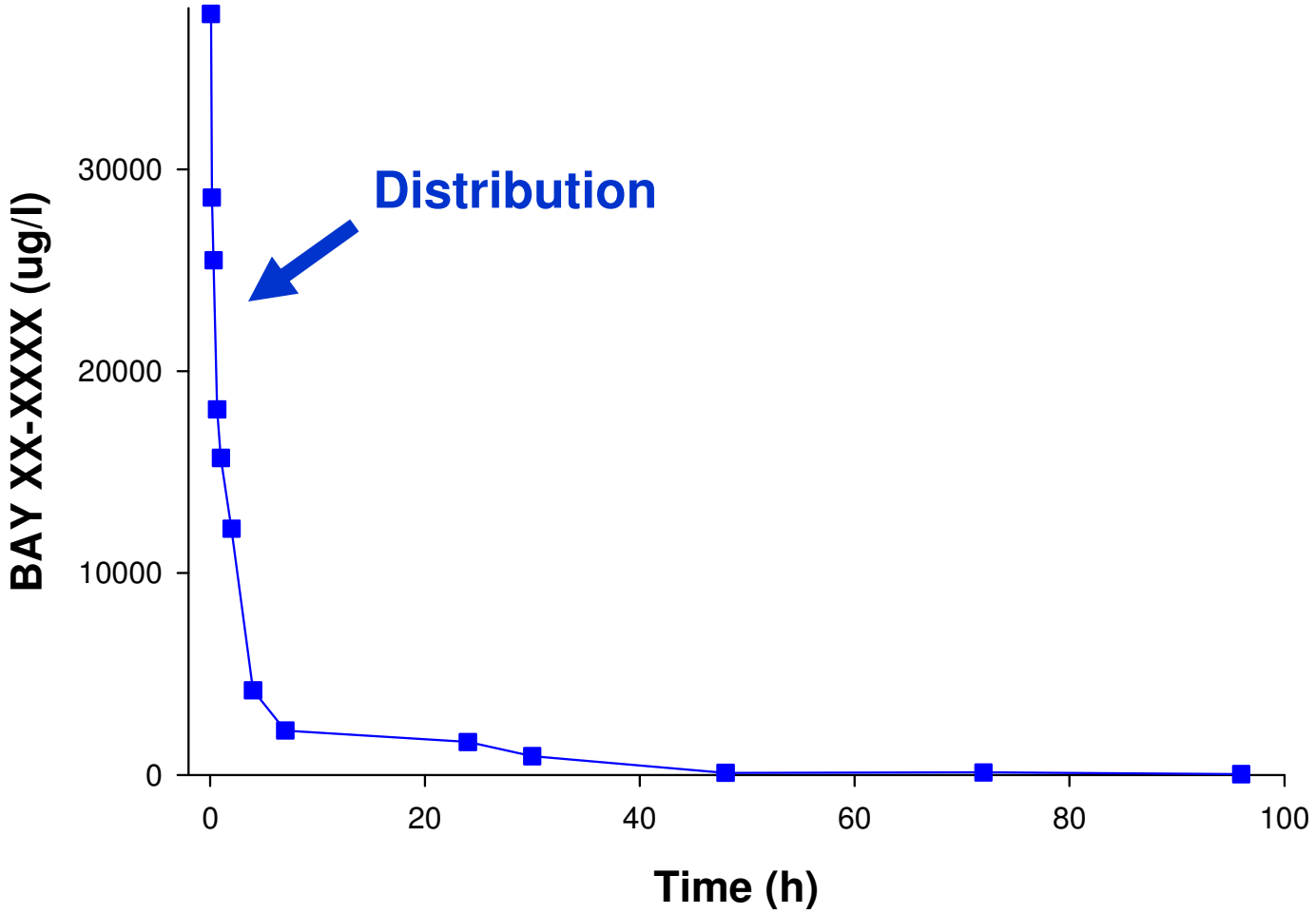
Plasma Concentration vs. Time

BAY XX-XXXX after 2 mg/kg **IV** administration to rats



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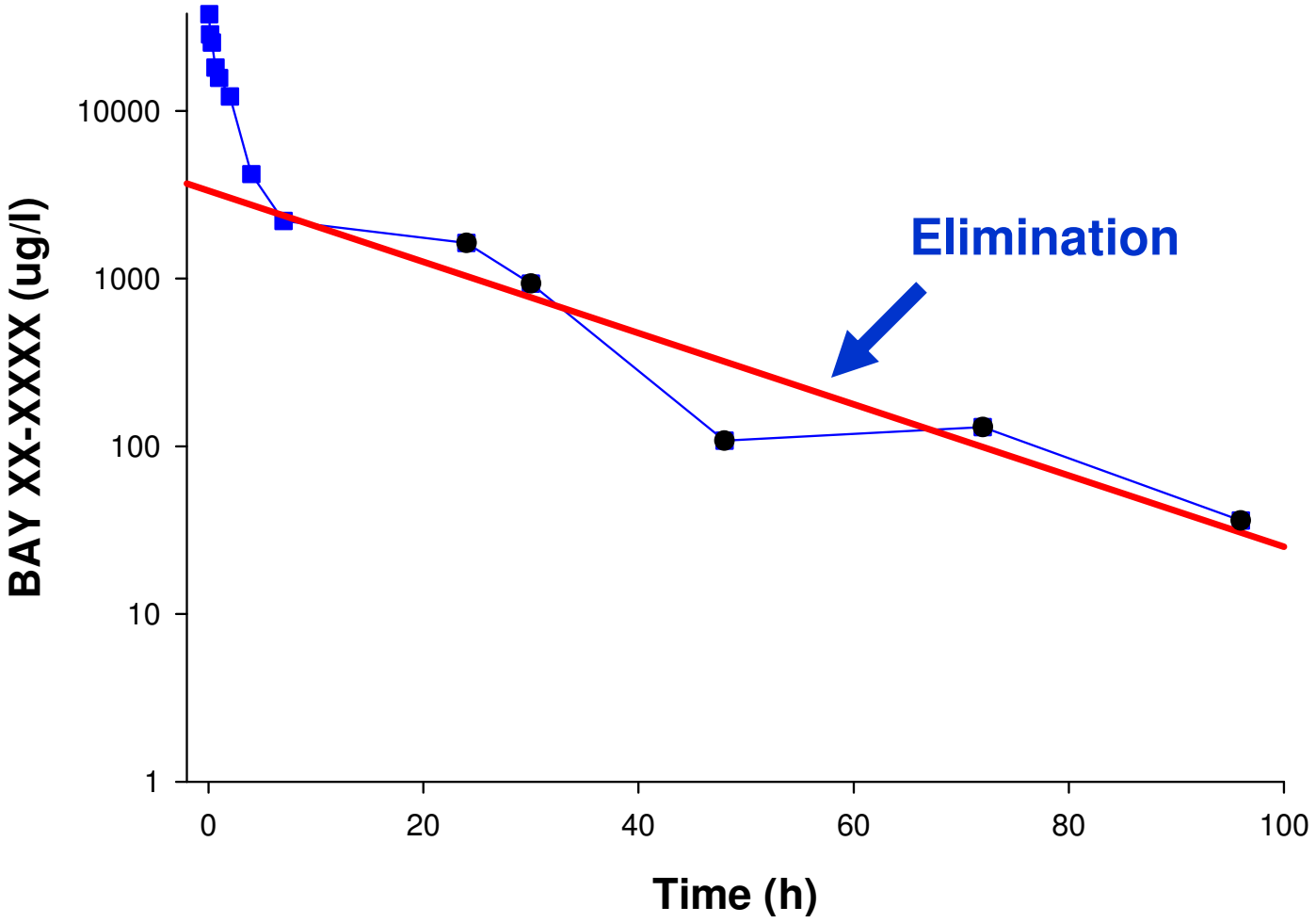
Semi-Log Plot

BAY XX-XXXX after 2 mg/kg **IV** administration to rats



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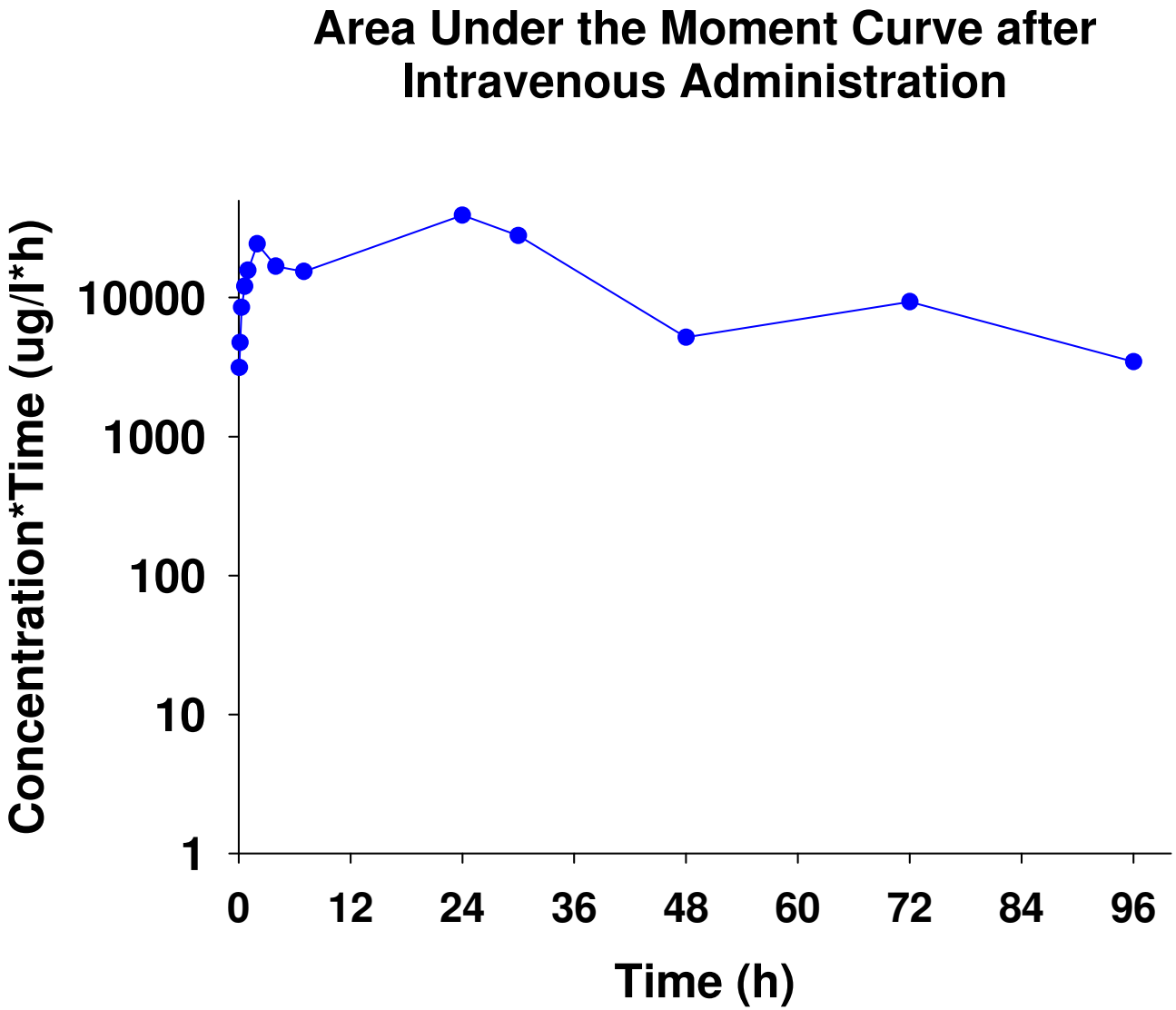
Plot of Concentration * Time vs Time



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Some Equations

$$AUC = \mu g * h / l$$

$$Vd = dose / C_0 = mg/kg/\mu g/l = l/kg$$

$$Cl = Dose/AUC = (\mu g / kg)/(\mu g * h)/l = l/h/kg$$

$$AUMC(ti\text{-}ti+1) = 0.5[C(i)ti + C(i+1)(ti+1)][ti+1\text{-}ti] = ((\mu g/l + \mu g/l) * h) + h = (\mu g * h^2)/l$$

$$MRT = AUMC/AUC = \mu g * h^2/l / \mu g * h/l = h$$

$$Vss = (dose/AUC)(MRT) = ((\mu g/kg)/(\mu g * h/l))/h = l/kg$$

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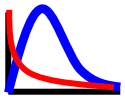
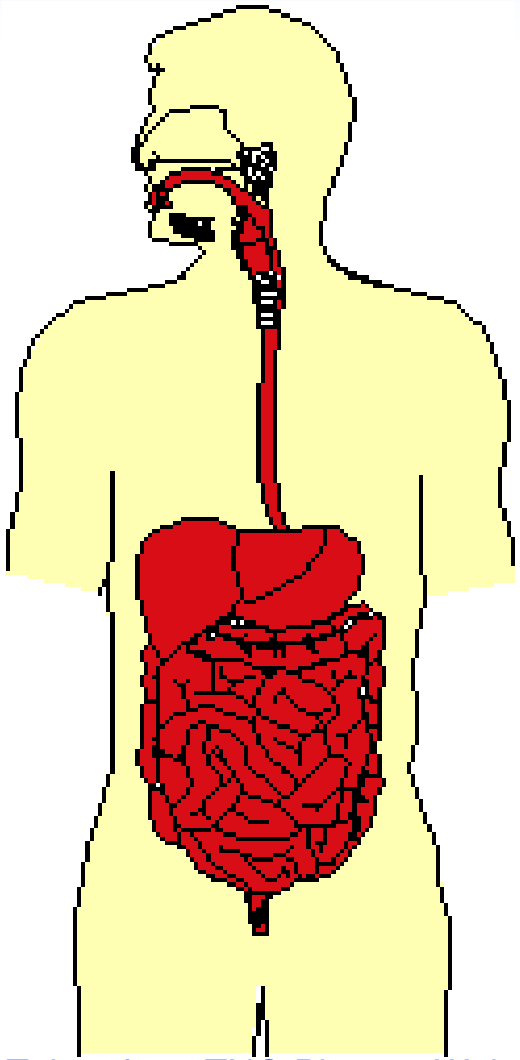


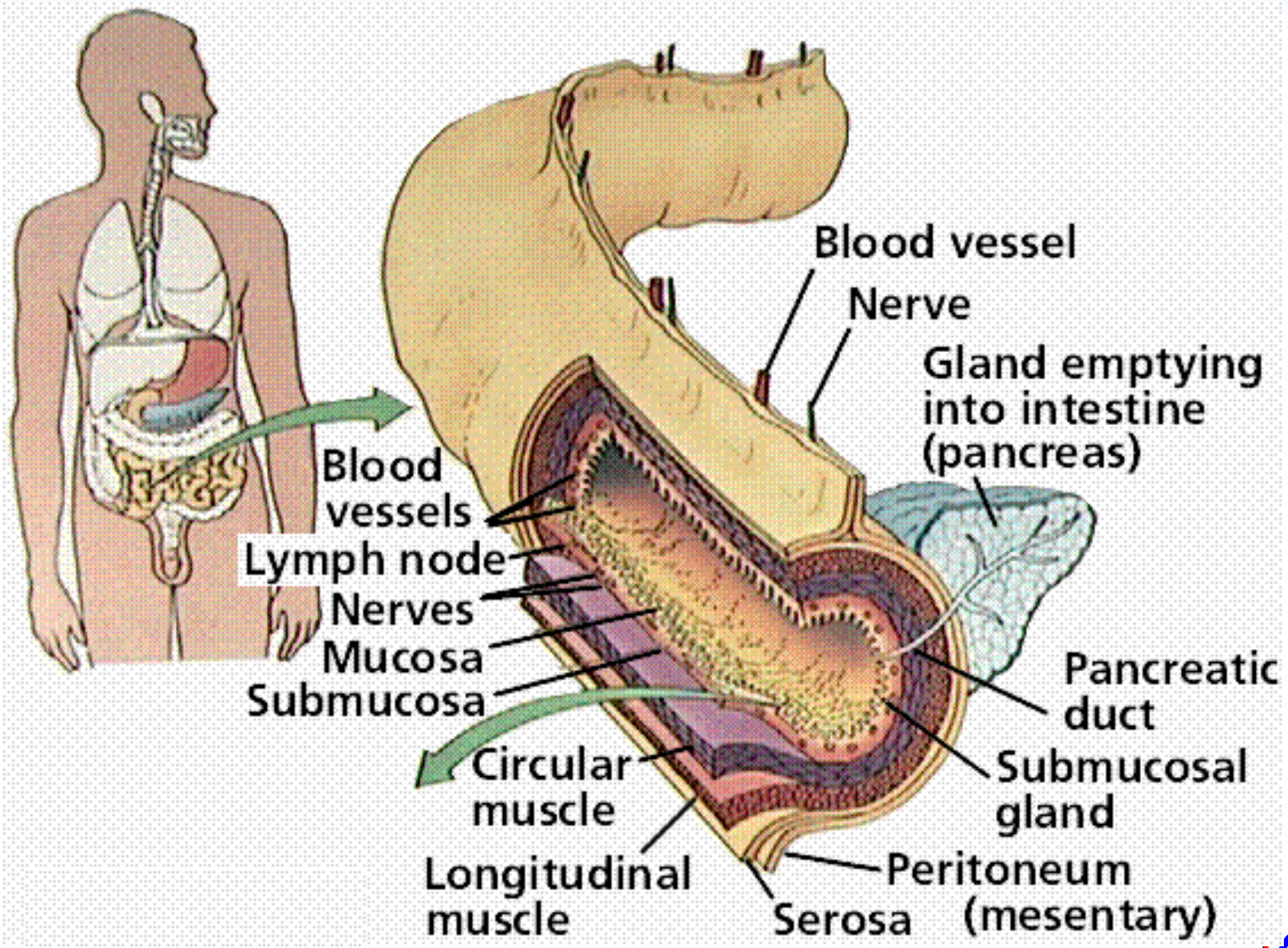
Absorption



Taken from TNO Pharma Web

- Most Drugs administered orally as pills
- Absorbed largely from small intestine
  - Some Sublinqual absorption
  - Rectal Absorption (suppository)
  - Some Absorption from stomach (rare)
- Molecules need to be near the intestinal mucosa to be absorbed
  - Compound should be soluble in gut contents or in vehicle
- Crystals are not well absorbed
- Gummy stuff is not well absorbed

Anatomy of the intestines



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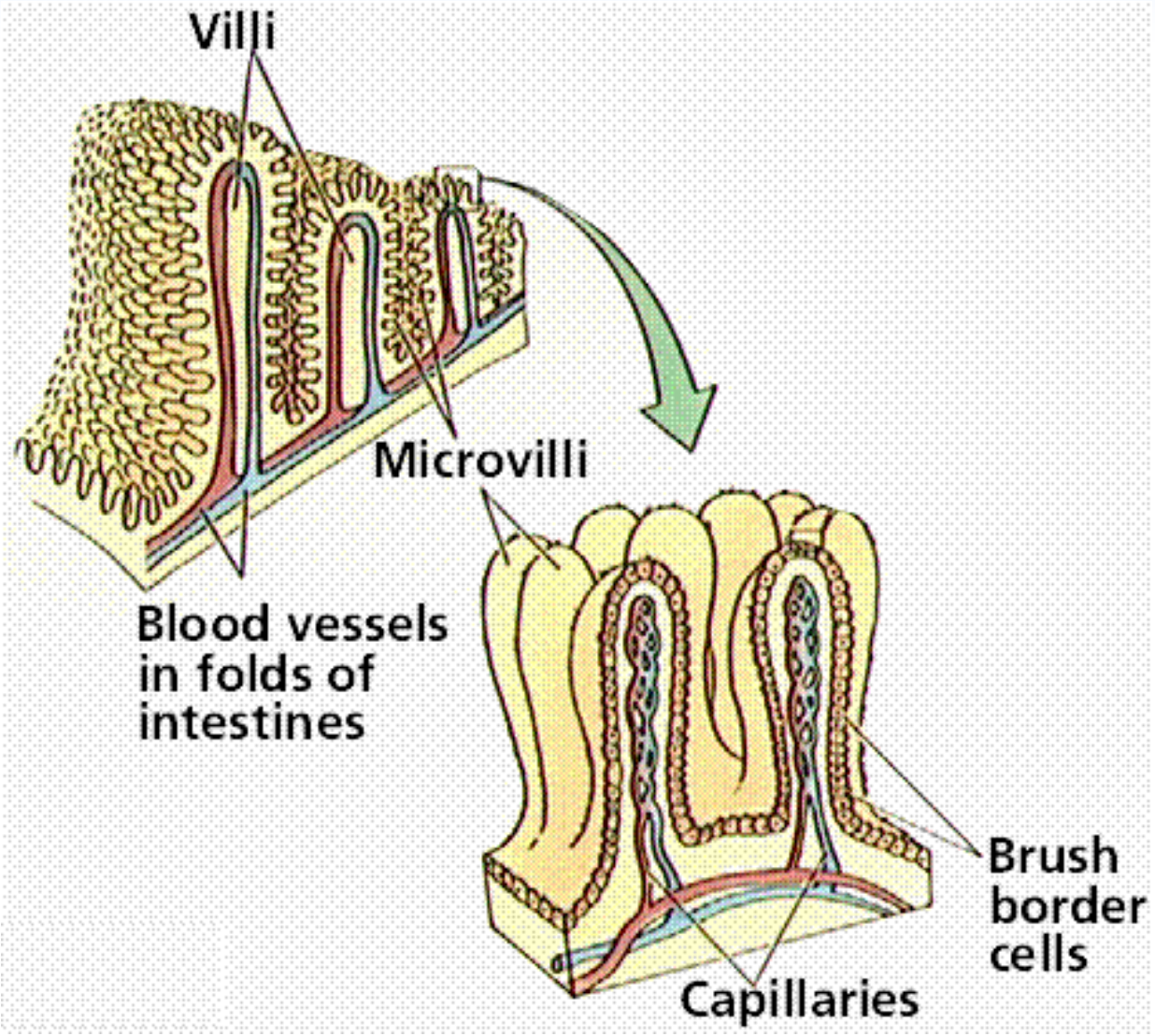
Anatomy of the intestines



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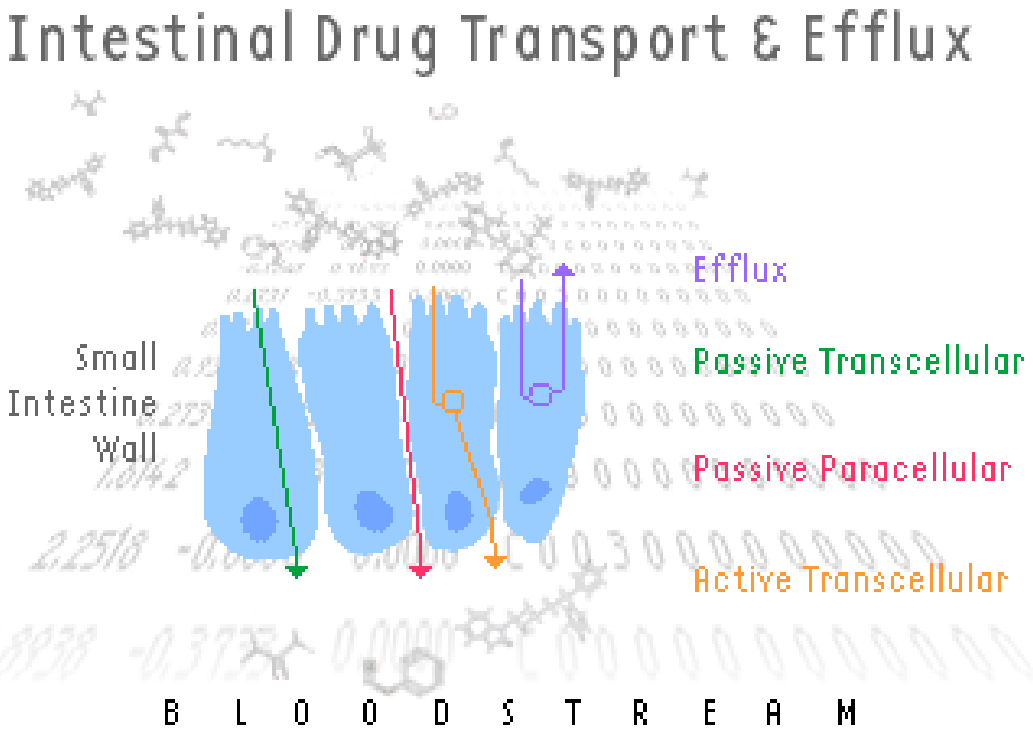
Absorption at brush border cells



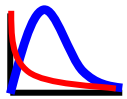
Taken from Camitro Web Site

- **Passive transcellular thought to be major route**
  - **Non-charged compounds diffuse best**

Distribution

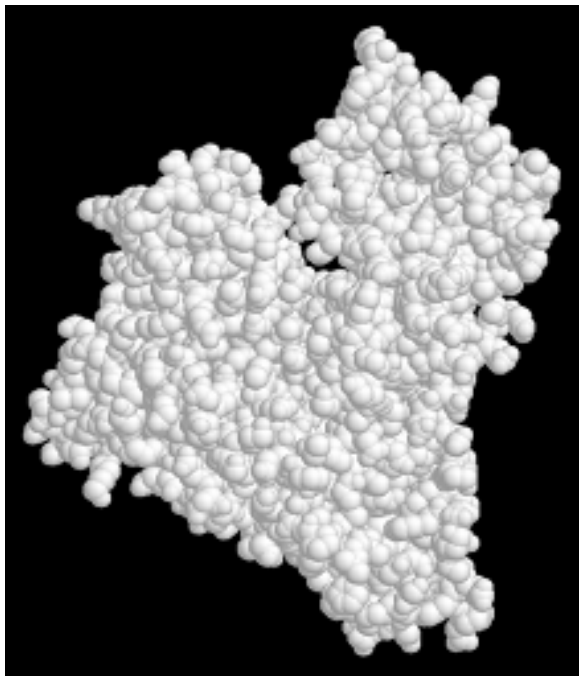
Site of action of most compounds can be related back to the concentration of the compound in the plasma, though the relationship is not always clear.

- **Compounds distribute differentially within body.**
- **Plasma protein binding may limit distribution**
- **Lipophillic compounds may accumulate in fatty tissues**
- **Liver, kidneys and other excretory organs often show high concentrations of compounds.**
- **Concentrations in brain are often very different from plasma concentrations**
- **Distribution can be studied using ^{14}C-labeled compounds**



Protein Binding

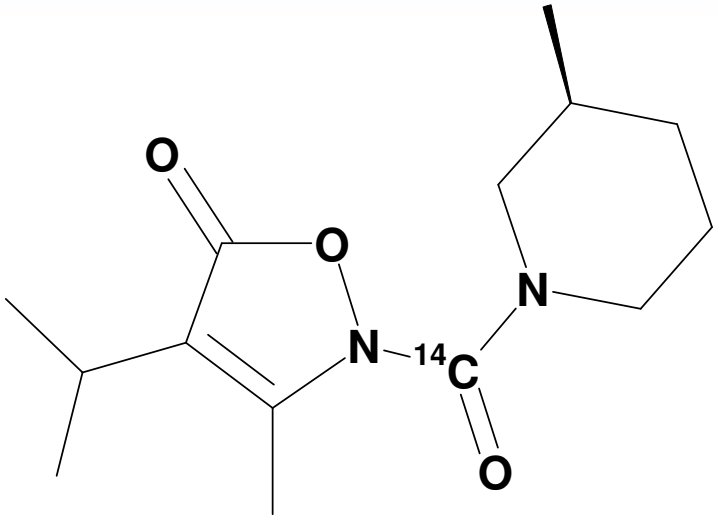
Human Serum Albumin



HSA and other plasma proteins Bind drugs

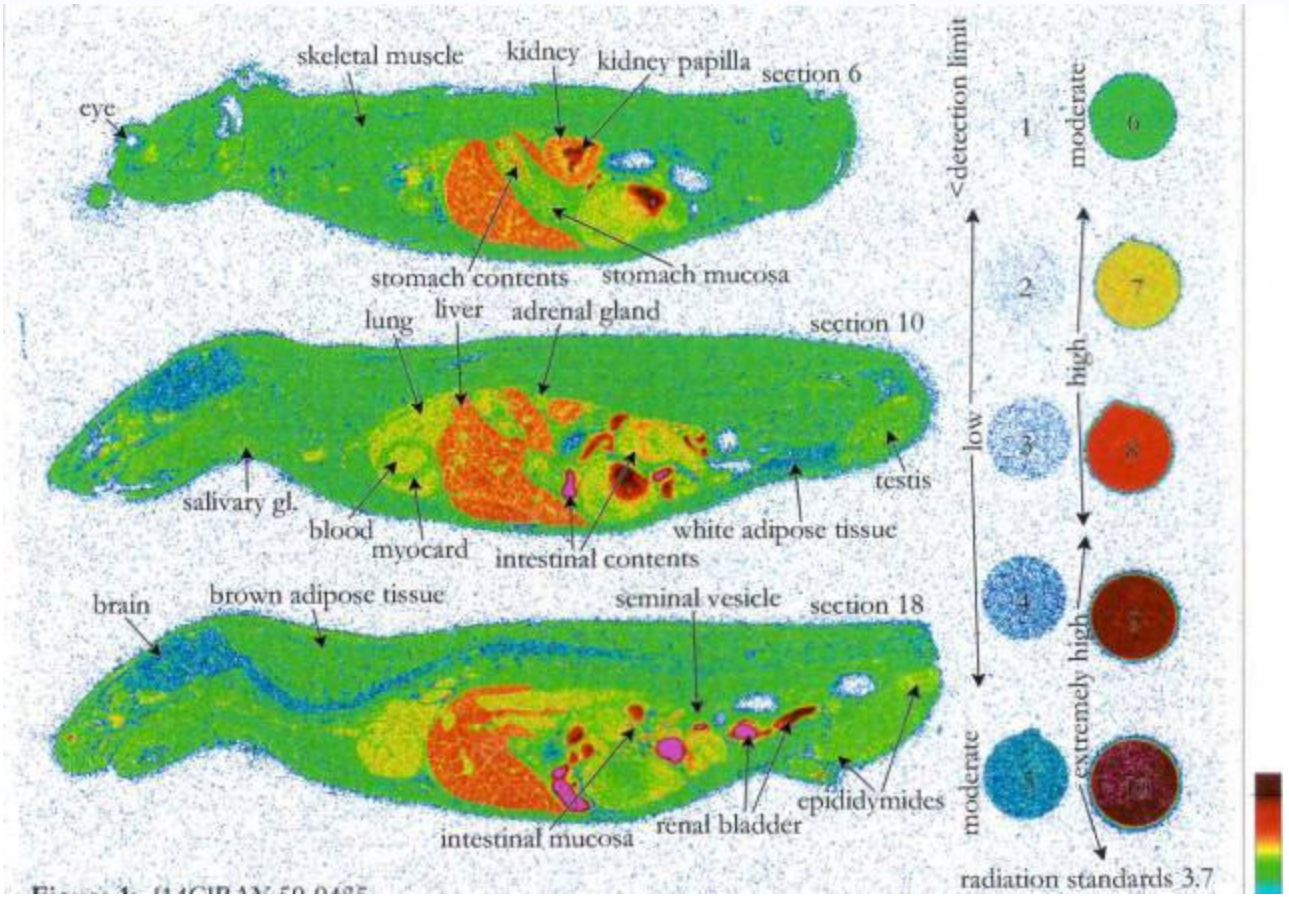
- **Only unbound fraction can interact with enzymes or receptors**
- **Only unbound fraction is excreted by kidney**
- **Compounds can compete for binding sites on HSA and tightly bound compounds can have suddenly high free fraction when displaced by other compounds**

Whole Body Autoradiograhy



[^{14}C]-BAY yy-yyyy was administered at a single oral dose of 10 mg/kg to male Wistar rats. The rats were sacrificed at 2, 4, 8, and 24 h post-dose. The animal bodies were deep frozen and whole-body cryo-sections of 50 mm thickness were prepared and freeze-dried. The distribution of total radioactivity, i.e., the sum of parent compound and/or labeled metabolites, in the sections was determined by radioluminography.

Distribution - Rat WBA



[^{14}C]-BAY yy-yyyy: Distribution of radioactivity in a male Wistar rat 2 h after oral administration of 10 mg/kg.

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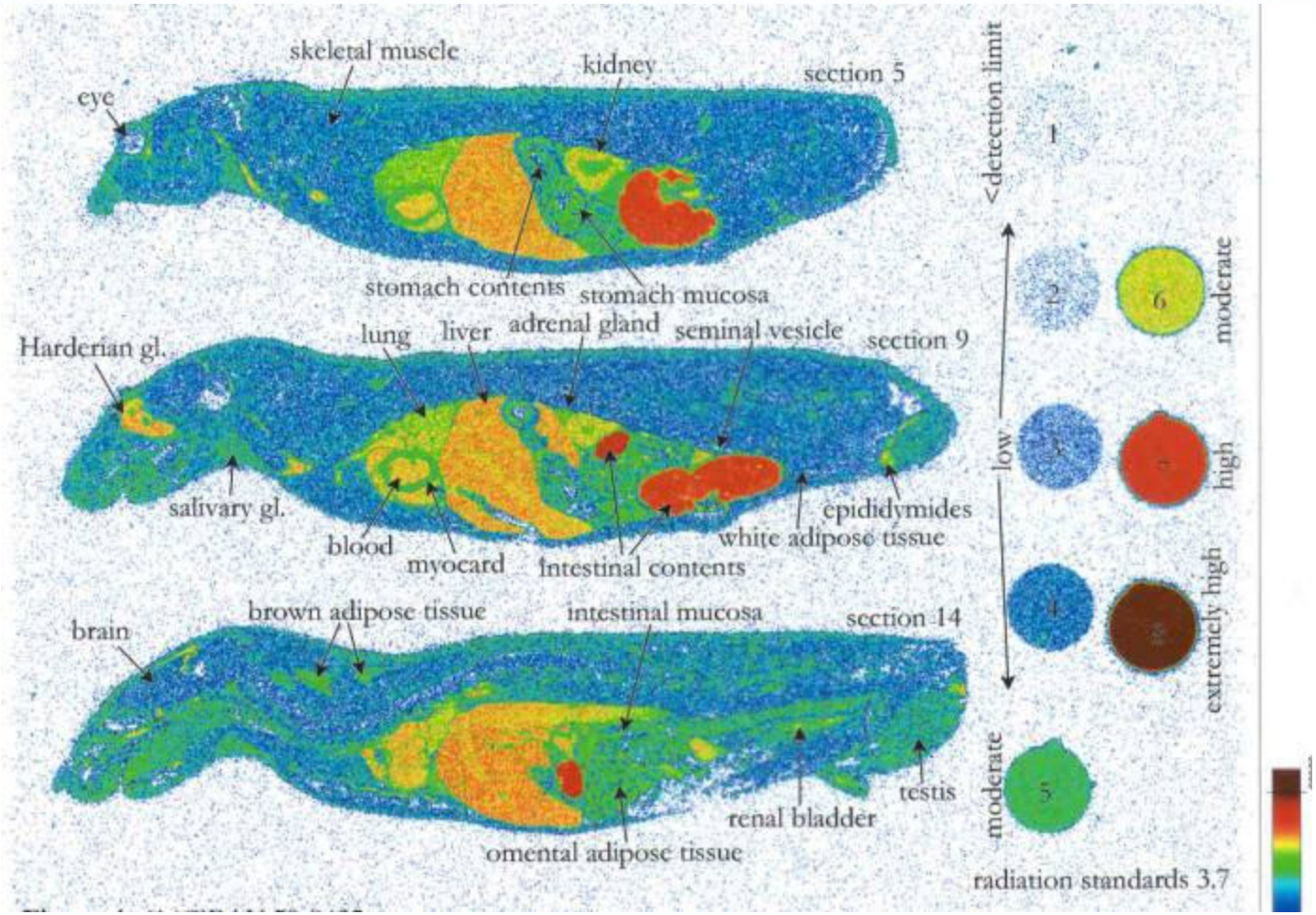
Distribution - Rat WBA



[^{14}C]-BAY yy-yyyy: Distribution of radioactivity in a male Wistar rat 24 h after oral administration of 10 mg/kg.

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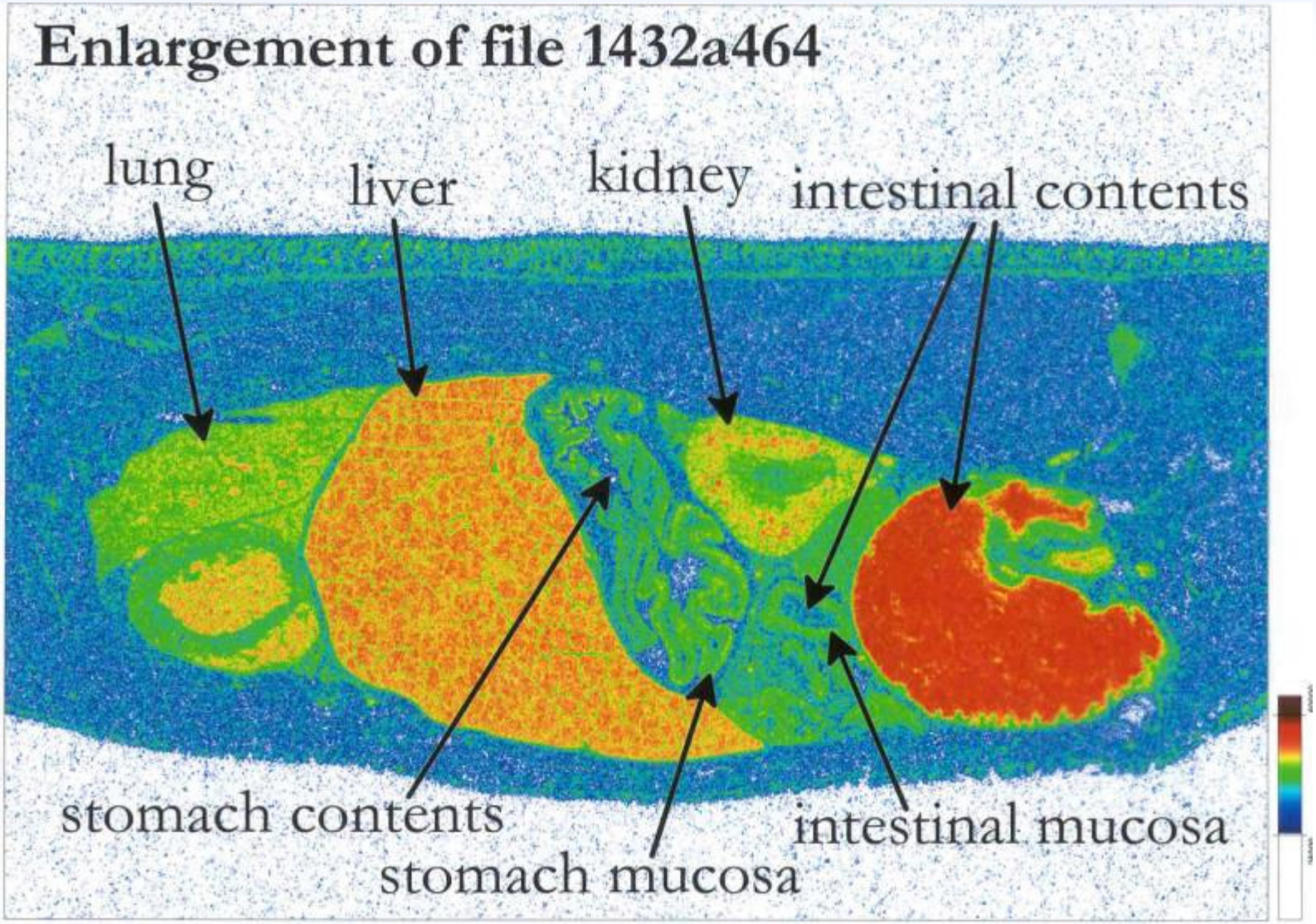
Distribution - Rat WBA



Metabolism

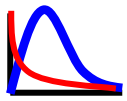
Metabolism occurs in liver, gut wall, lungs, kidneys and other organs:

Phase I:

- **Hydroxylation**
- **Dealkylation**
- **Sulfoxide and Nitroxide formation**
- **etc.**

Phase 2 (Conjugation)

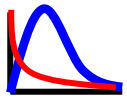
- **Glucuronide formation**
- **Sulfation**
- **Glutathione Conjugation**
- **Cysteine Conjugation**
- **Acetylation**
- **etc.**



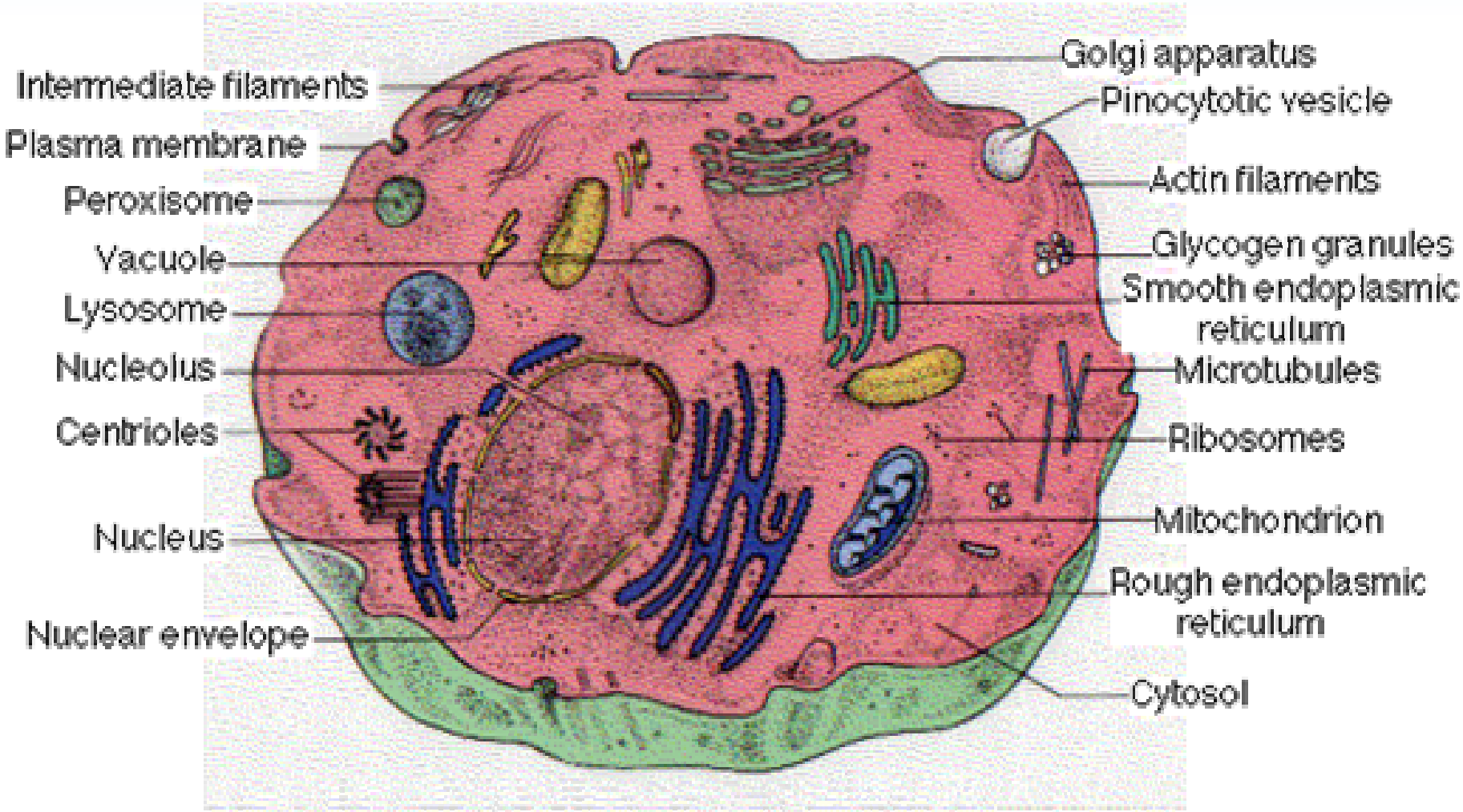
Metabolism

Liver is the major metabolizing organ in the body:

- **Sits between Gut and rest of the circulation**
- **Removes toxic substances and drugs from the blood.**
- **Hepatic clearance of some drugs approaches or exceeds liver blood flow (First Pass Effect).**
- **Cytochrome P450s are the major drug metabolizing enzymes, they are found in every organ in the body.**
- **The body generally makes compounds more polar so they are more readily excreted in the kidney.**



Hepatocyte Structure



www.ultranet.com/~jkimball/BiologyPages/A/AnimalCells.html

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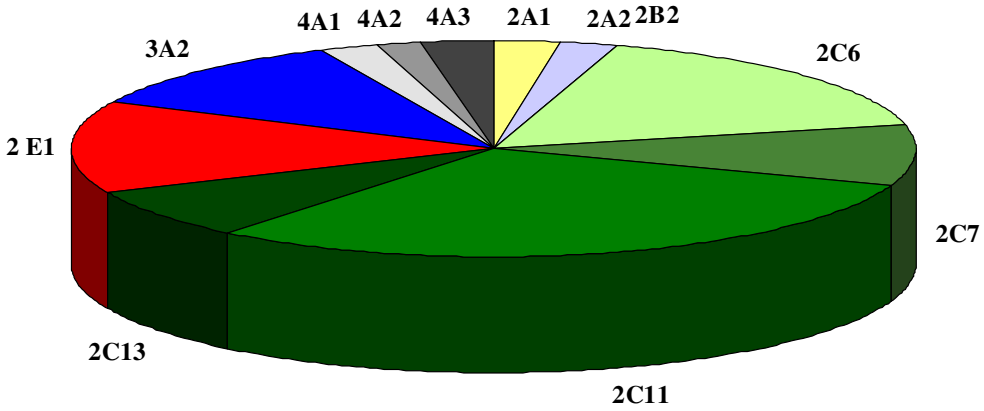
Cytochrome P450 in Rat and Man: Species Differences

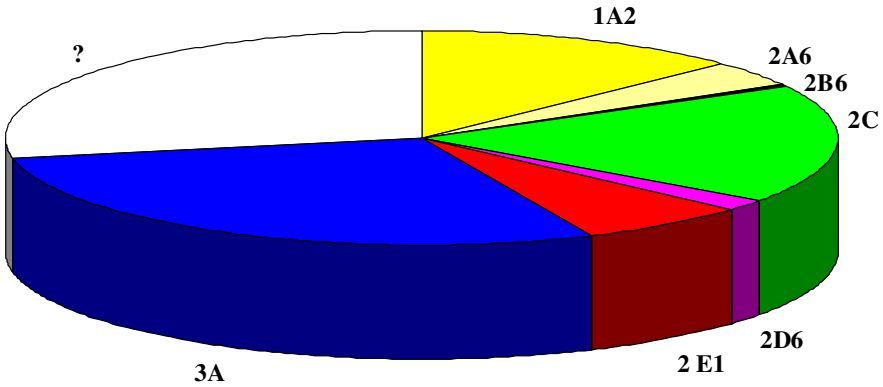
P450 isozymes in male rat liver

N. Ohishi et al., Xenobiotica **24**, 873-880 (1994)



P450 isozymes in human liver

Shimada et al., J. Pharmacol. Exp. Ther. **270**, 414-423 (1994)



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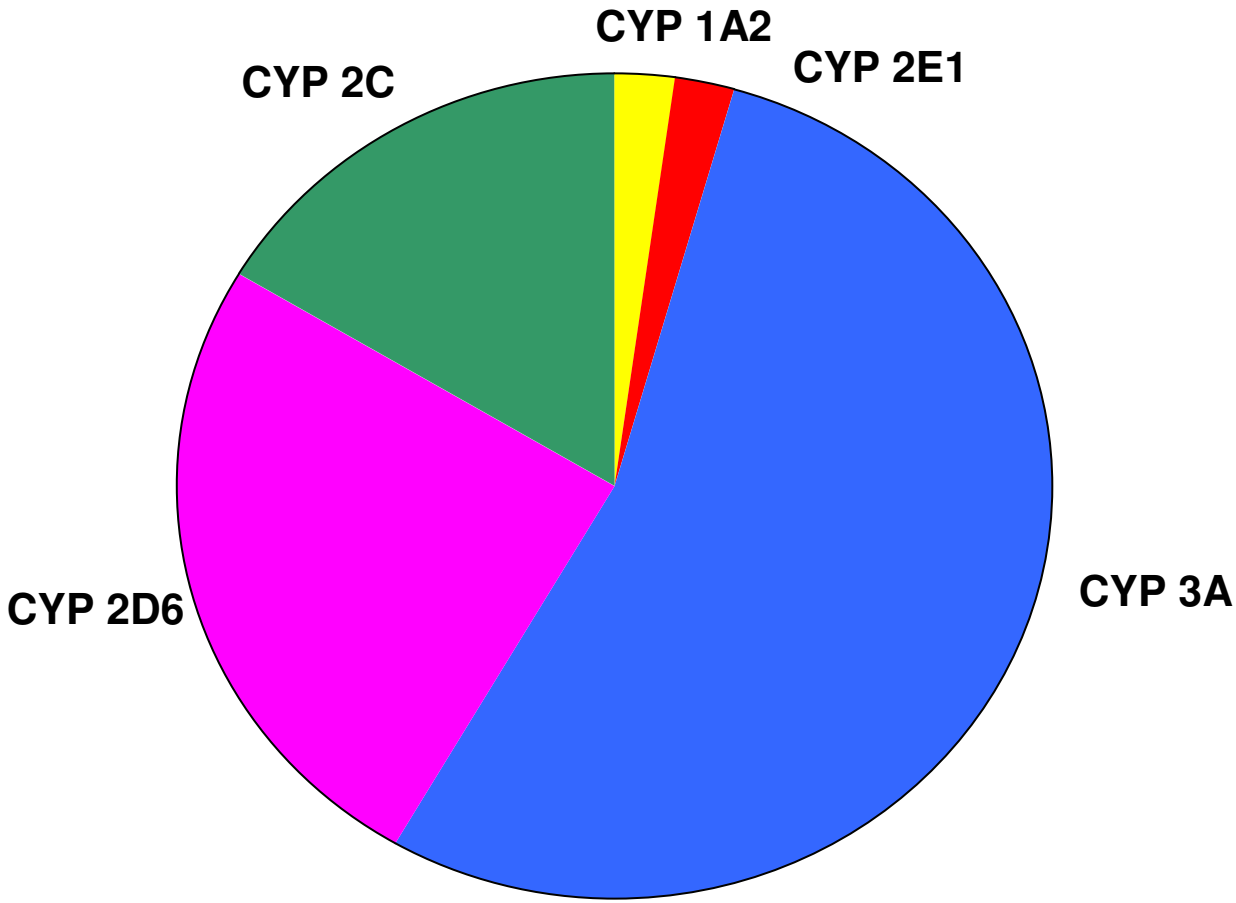
Proportion of Drugs Metabolized by the Major CYPs



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Drug - Drug Interactions

Risks associated with CYP enzyme inhibition or induction

Inhibition of CYP enzymes

⮟

Decreased degradation
of comedicated drugs

⮟

Increased drug plasma
concentrations

⮟

Risk of severe
adverse events

Induction of CYP enzymes

⮟

Increased degradation
of comedicated drugs

⮟

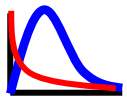
Decreased drug plasma
concentrations

⮟

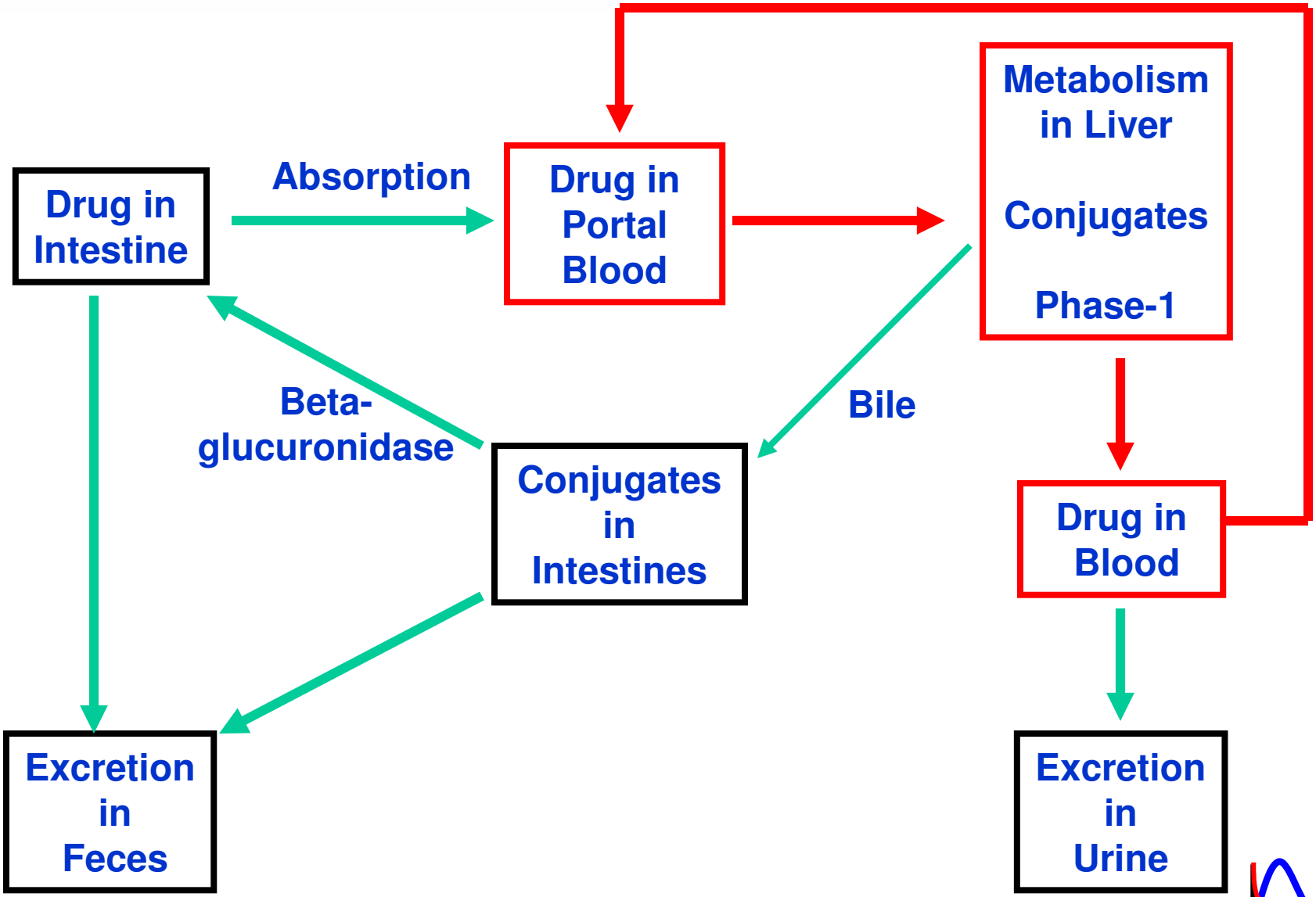
Loss of pharmacological
effect

⮟

Risk of severe
secondary effects



Routes of Excretion



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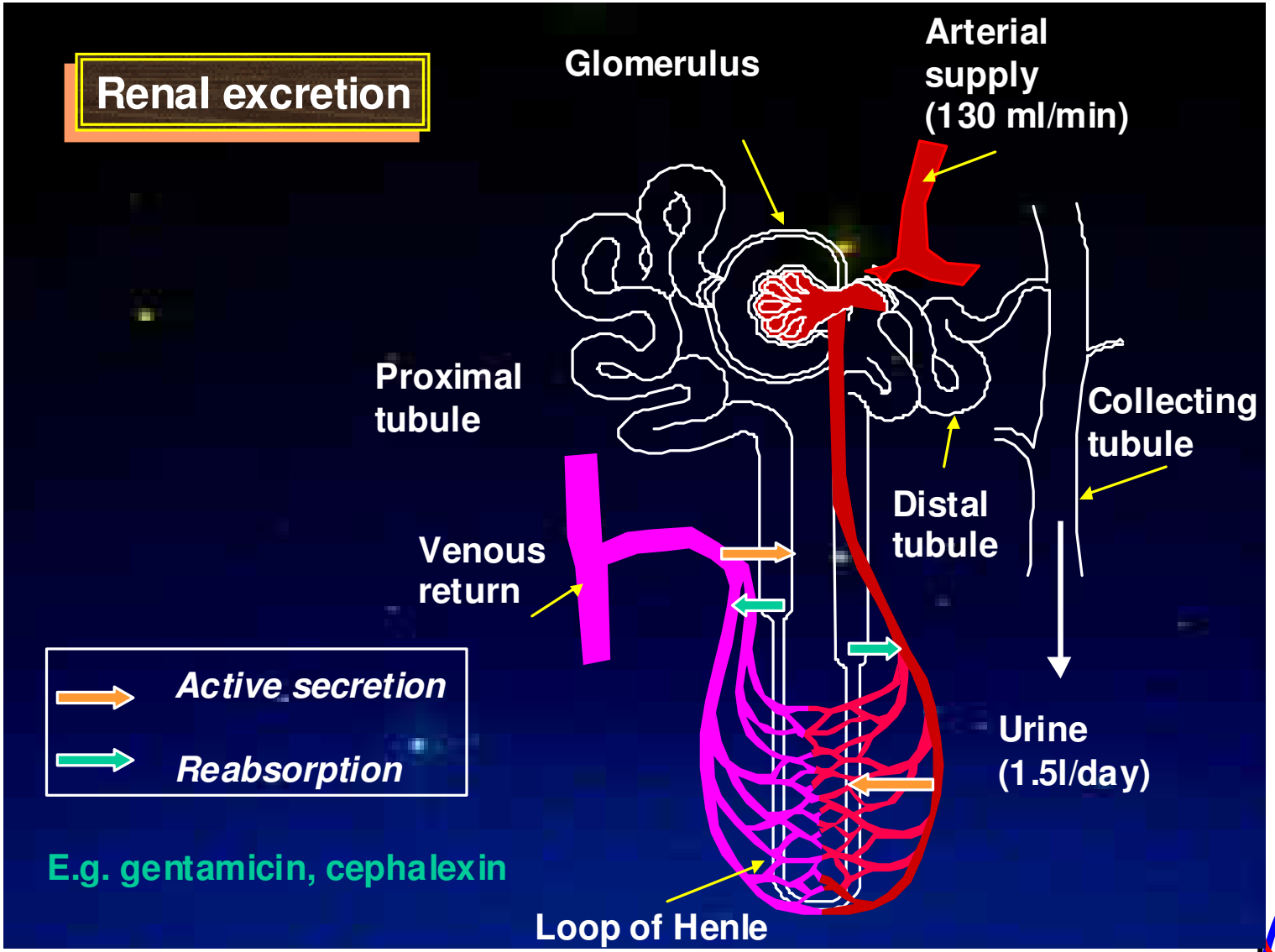
Renal Excretion

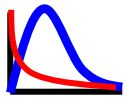
www.wits.ac.za/fac/med/pharmacy/bio-elim.ppt



Excretion

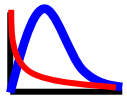
Most compounds are excreted in the urine or feces.
- **parent and metabolites**
- **difficult to quantitate without radiolabel**

Some excretion through lungs, in saliva or in sweat,
- **residues may remain in tissues for extended periods**



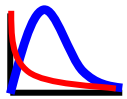
Moving from Animals to Man

- Humans and model animals have different biochemistry, physiology and anatomy
- Predictions of a drug's PK profile in humans using animal PK data must account for these differences
- For example, P450's
  - Isoform distribution varies from species to species
  - Orthologous proteins in different species may not be identical and may have different structures and substrate specificities
- Allometric scaling is used to predict differences based only on size.



Allometric Scaling

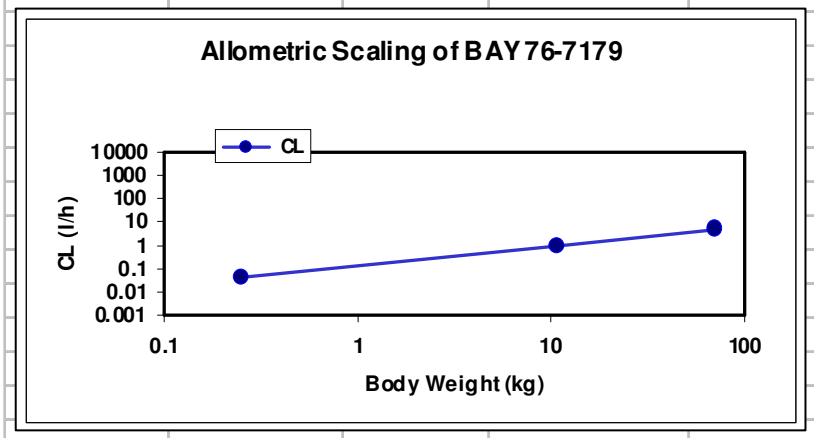
- The relationship of some pharmacokinetic parameters across species can be correlated with body weight.
- One can determine an empirical relationship of the log of the Clearance vs. the log of body weight and log of the volume of distribution vs. the log of body weight.
- These parameters can be used to extrapolate PK parameters in humans when parameters have been determined in lower species (mouse, rat, dog, monkey, etc.)
- The relationship is not always predictive, but it can often give a good estimate.

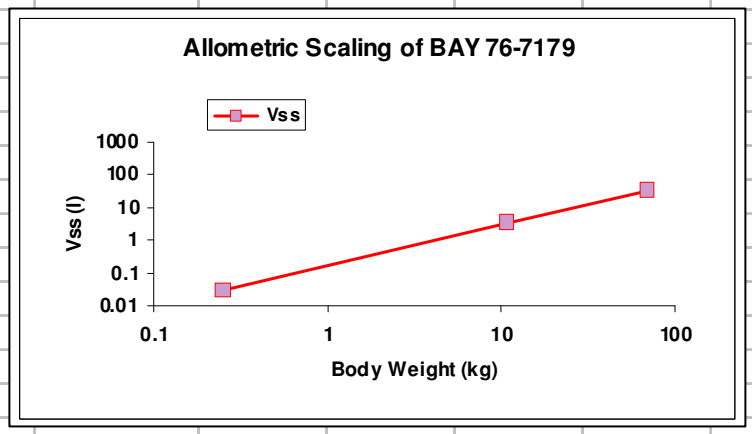


Allometric scaling of rat and dog extrapolate human

	CL,norm	CL	Vss,norm	Vss	B.W.
Rat	0.18	0.045	0.12	0.03	0.25
Dog	0.09	0.972	0.3	3.24	10.8
Human	**0.06**	**4.47**	**0.47**	**33.09**	70

		CL		Vss	B.W.
Log Value		-1.347		-1.523	-0.602
		-0.012		0.511	1.033
		0.650		1.520	1.845





Christopher Town, Ph.D.

Acknowledgements

Matthew Prevost
Sandhya Rahematpura
Wolfram Steinke (WBA)
Matthew Bryant
Anita Shah
Paul Adams
Derek Lowe
Michael Boberg

Many web sites where I downloaded images