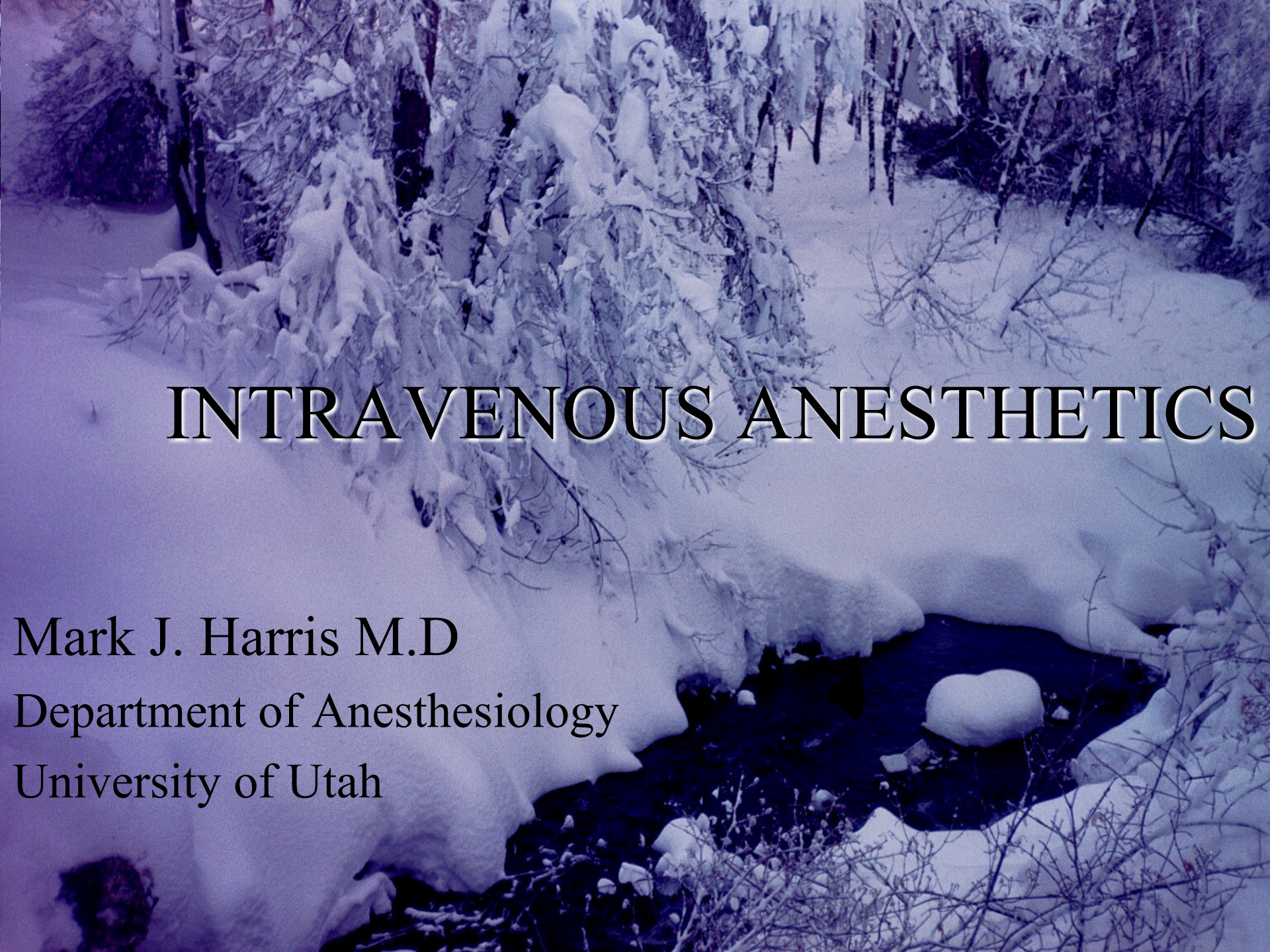

INTRAVENOUS ANESTHETICS

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Pharmacokinetics

= the quantitative study of the absorption, distribution, biotransformation, & excretion of injected drugs and their metabolites.

i.e. ***what the body does to a drug***.

- determines intensity of the drug's effects with time.
- determines variability in responses

Problems with Pharmacokinetics

- Study healthy lean adults
- **But**, drugs administered to patients with chronic diseases at various extremes of age, hydration, & nutrition.
- GA / surgery alters PK because alters:
  - renal / hepatic blood flow
  - hepatic enzyme activity.

Drug Distribution

	Body Mass (% of 70-kg adult)	Blood Flow (% of cardiac output)
Vessel-rich group (heart, brain, kidneys, liver)	10	75
Muscle group	50	19
Fat group	20	6
Vessel-poor group (bone, skin)	20	<1

Rate & Capacity of Tissue Uptake

DETERMINANTS OF TISSUE UPTAKE	DETERMINANTS OF STORAGE CAPACITY
Blood flow	Solubility
Concentration gradient	Tissue Mass
Blood-brain barrier	Binding to macromolecules
Drug physico-chemical properties	pH
Ionization	
Lipid solubility	
Protein binding	

Volume of Distribution (V_d)

= a mathematical expression of the sum of the apparent volumes of the compartments that constitute the compartmental model.

$$= \frac{\text{iv dose}}{\text{resulting plasma concentration (before elimination)}}$$

Volume of Distribution

V_d is influenced by physicochemical characteristics of the drug, including :

1. lipid solubility
2. binding to plasma proteins
3. molecular size.

Alterations in Protein Binding

Usually important only for drugs that are *highly* protein bound (e.g. warfarin, diazepam).

Determinants of Protein Binding

1. Lipid solubility of drug
2. Drug's plasma concentration
3. # available binding sites on protein
4. Competition from other substances
   (e.g sulfonamides *vs* bilirubin)
5. Disease states
   (e.g. renal, hepatic failure, surgery, MI)

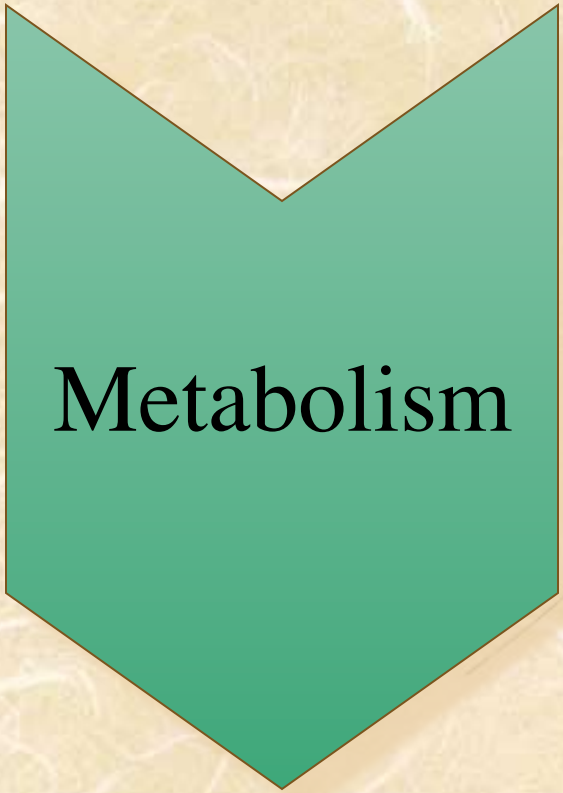
Clearance

= volume of plasma cleared of drug by excretion and/or metabolism.

Metabolism

- **Liver**
- Plasma
- Lungs
- Kidneys
- GI tract

Pharmacologically active, lipid-soluble drugs



H_2O-soluble metabolites

pharmacologically inactive?

Renal Excretion

- Kidney = most important organ for elimination of unchanged drugs or metabolites.
- H_2O-soluble excreted > lipid soluble.
- Drug elimination correlates with:
  - endogenous creatinine clearance
  - serum creatinine concentration.

Elimination Half-Life

= time necessary for the plasma concentration of drug to decline 50% during the elimination phase.

- $\propto V_d$
- $\propto {}^{1}/_{\text{clearance}}$
- independent of drug dosage.

Pharmacodynamics

= the study of the intrinsic sensitivity or responsiveness of receptors to a drug and the mechanisms by which these effects occur

i.e. ***what a drug does to the body***.

- Structure-activity relationships link the actions of drugs to their chemical structure.
- Variability exists in the intrinsic sensitivity of receptors among patients.

Receptors

- Receptors are identified & classified primarily by :
  1. the effects of specific antagonists
  2. the relative potencies of known agonists.

- Multiple subtypes exist for many receptors.

Receptor concentration is dynamic

Potency

- Influenced by:
  1. absorption
  2. distribution
  3. metabolism
  4. excretion
  5. receptor affinity

- Clinically, potency is irrelevant if drug's effective dose can be administered conveniently.

Efficacy

- Efficacy = concentration → maximal effect
- Undesirable effects may limit dosage

- Therapeutic index = margin of safety
  difference between:
  - dose → desired effect
  - dose → undesirable effects.

Individual Responses

1. Pharmacokinetics
2. Bioavailability
3. Renal function
4. Liver function
5. Cardiac function
6. Patient age - elderly vulnerable to cumulative drug effects.
7. Pharmacodynamics
8. Enzyme activity (e.g. smoking / alcohol)
9. Genetic differences (e.g. atypical cholinesterase activity)
10. Drug interactions

Age Effects

Aging does not → changes in receptor responsiveness

Variations in drug response reflect :

1. ⬇ cardiac output
2. ⬆ fat compartment
3. ⬇ protein binding
4. ⬇ renal function.

Idiosyncrasy

is present when an unusual effect of a drug occurs in a small % of patients *regardless of the dose of drug*.

Tolerance

= hyporeactivity from chronic exposure.

- ***Cross-tolerance*** develops between drugs of different classes that produce similar pharmacologic effects (*e.g ETOH / inhaled agent*).
- ***Tachyphylaxis*** = tolerance that develops acutely within only a few doses of a drug (*e.g. thiopental*).