JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Absorption, Distribution, and Excretion

Michael A. Trush, PhD
Bloomberg School of Public Health

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

Section A

The Toxicological Process

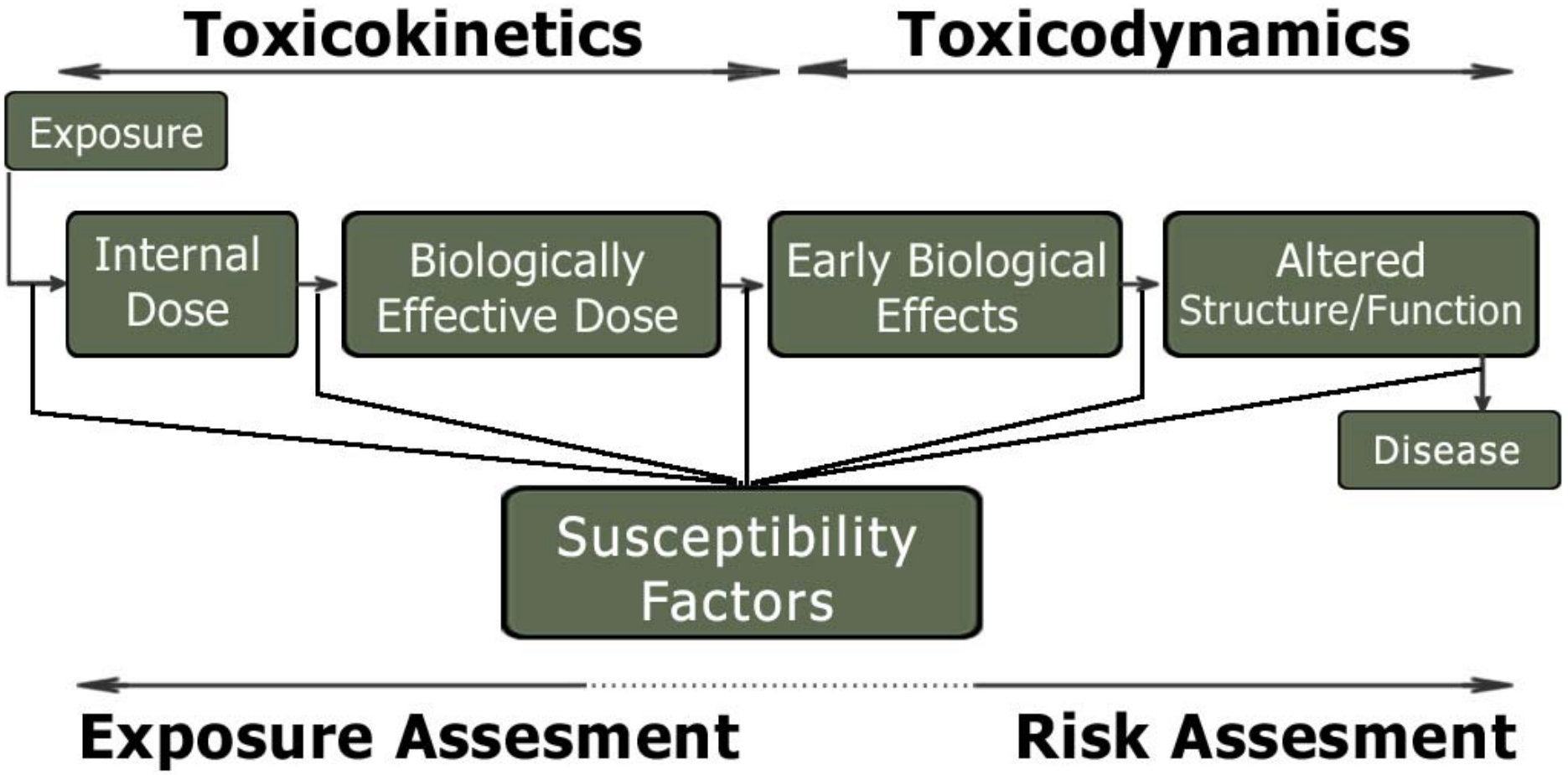
Definition

- Toxicology is the study of poisons
- Poisons are chemical/physical agents that produce adverse responses in biological organisms

"What is there that is not poison? All things are poison and nothing without poison. Solely, the dose determines that a thing is not a poison"

Paracelsus (1493-1541)

The Toxicological Paradigm



Toxicokinetics

- Toxicokinetics is the quantitation of the time course of toxicants in the body during the processes of **absorption**, **distribution**, **biotransformation**, and **excretion** or clearance of toxicants. In other words, toxicokinetics is a reflection of how the body handles toxicants as indicated by the plasma concentration of that xenobiotic at various time points
- The end result of these toxicokinetic processes is a **biologically effective dose** of the toxicant.

Toxicodynamics

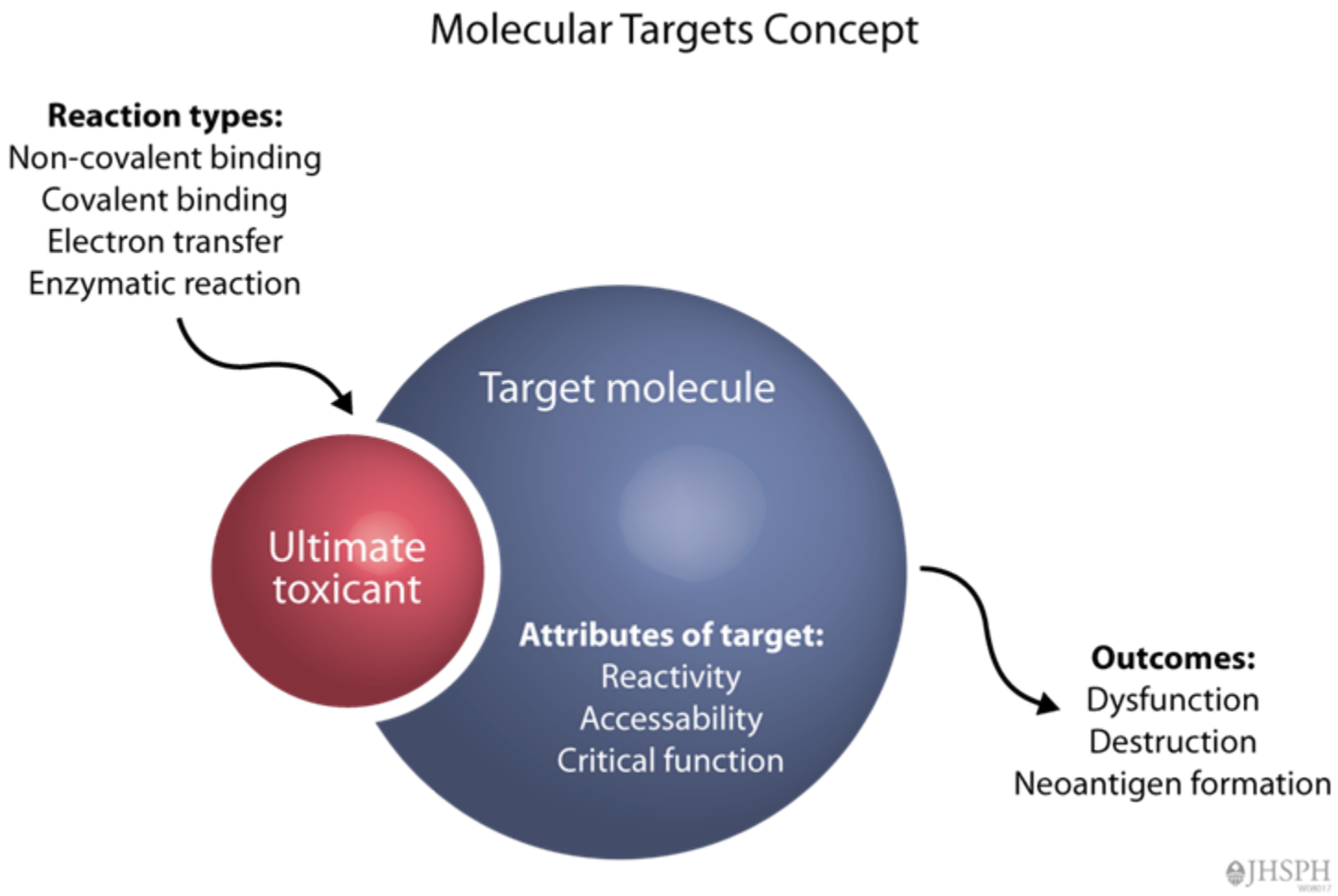
- Toxicodynamics refers to the molecular, biochemical, and physiological effects of toxicants or their metabolites in biological systems
- These effects are result of the interaction of the biologically effective dose of the ultimate (active) form of the toxicant with a molecular target

Molecular Targets Concept

- The toxic action of a chemical is a consequence of the physical/chemical interaction of the **active** form of that chemical with a molecular target within the living organism

Continued

Molecular Targets Concept



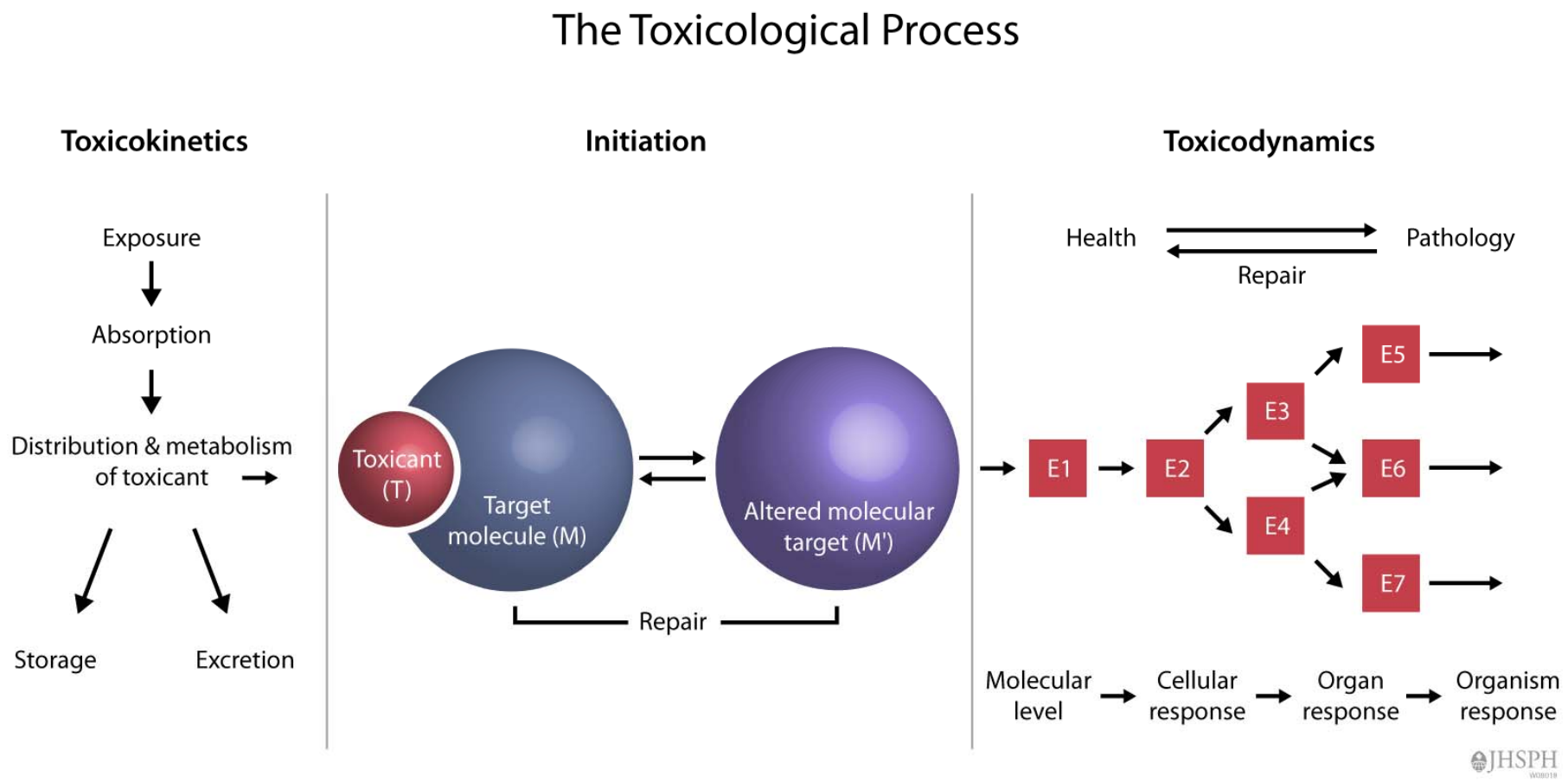
Examples of Molecular Targets

- Proteins
  - **A**ryl**h**ydrocarbon(Ah) receptor—Dioxin
  - Hemoglobin—CO
- Lipids—Carbon tetrachloride
- DNA—Aflatoxin

Dose-Response Concept

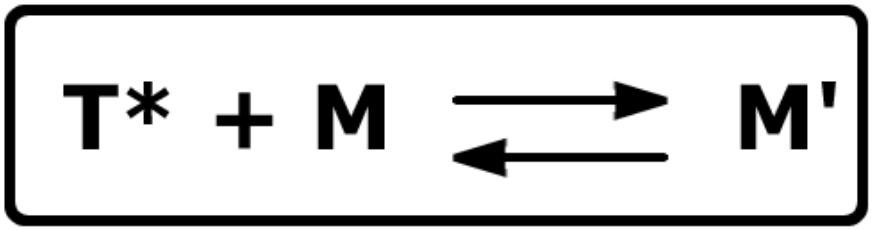
- The magnitude of the toxic effect will be a function of the concentration of altered molecular targets, which in turn is related to the concentration of the active form of the toxicant(biologically effective dose) at the site where the molecular targets are located.

The Toxicological Process



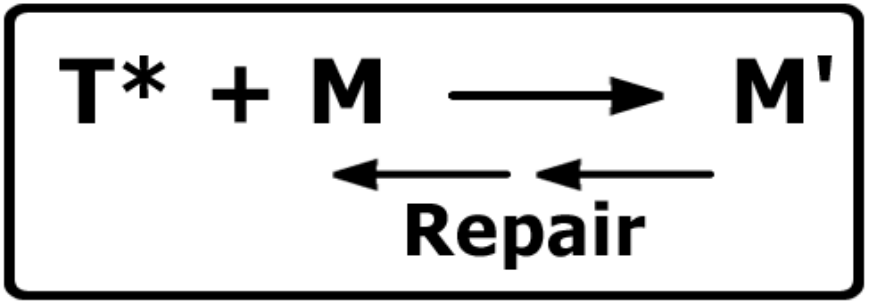
The Toxicological Process

Reversible



Irreversible

Irreversible with repair



T= toxicant; M= molecular target
M'= altered molecular target

JOHNS HOPKINS
BLOOMBERG
SCHOOL of PUBLIC HEALTH

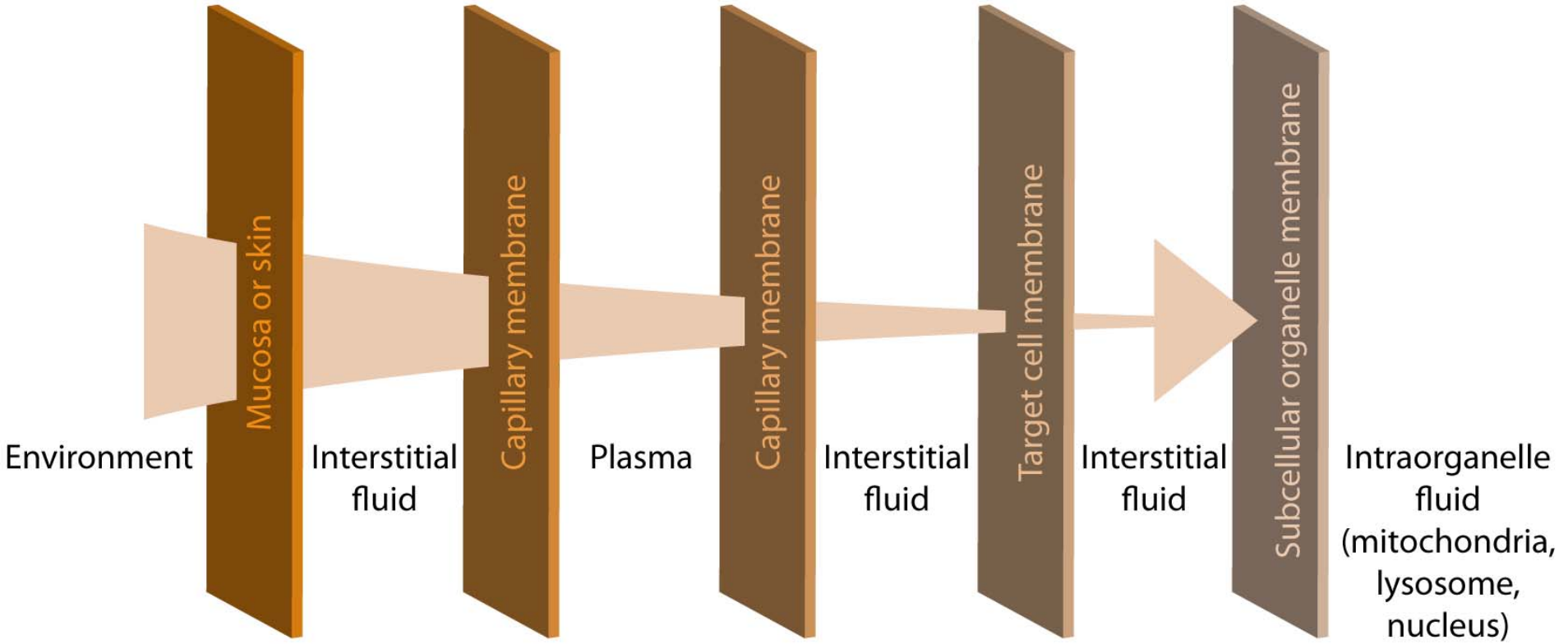
Section B

Transport Process Mechanisms

Membrane Transport of Xenobiotics

- The absorption, distribution, and excretion of xenobiotics involves passing through various cell and organ membranes.
- This occurs through various transport mechanisms

Membrane Transport of Xenobiotics



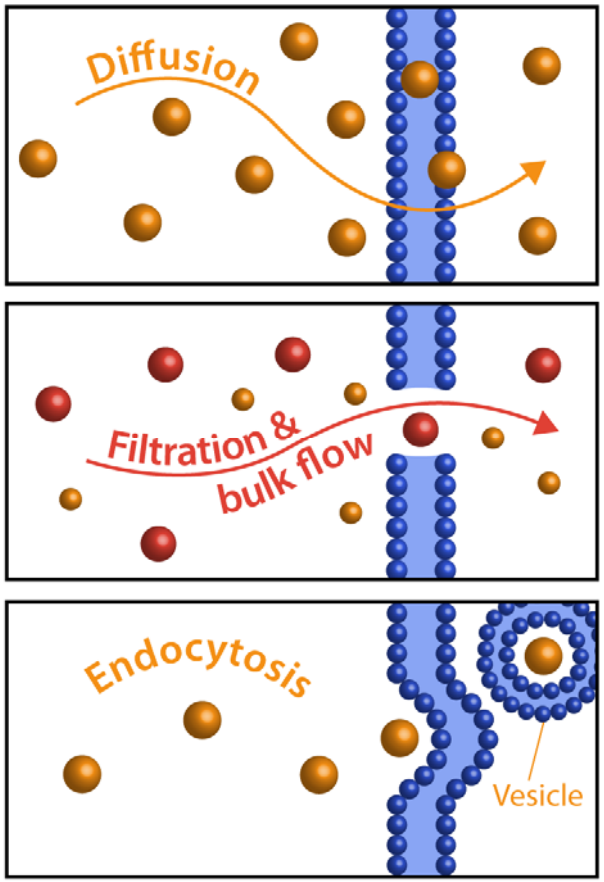
Xenobiotics: Transport Mechanisms

- Factors affecting membrane transport of chemicals:
  - Molecular weight/shape
  - Charge
  - Lipid solubility
  - Membrane composition
  - Membrane thickness

Types of Transport

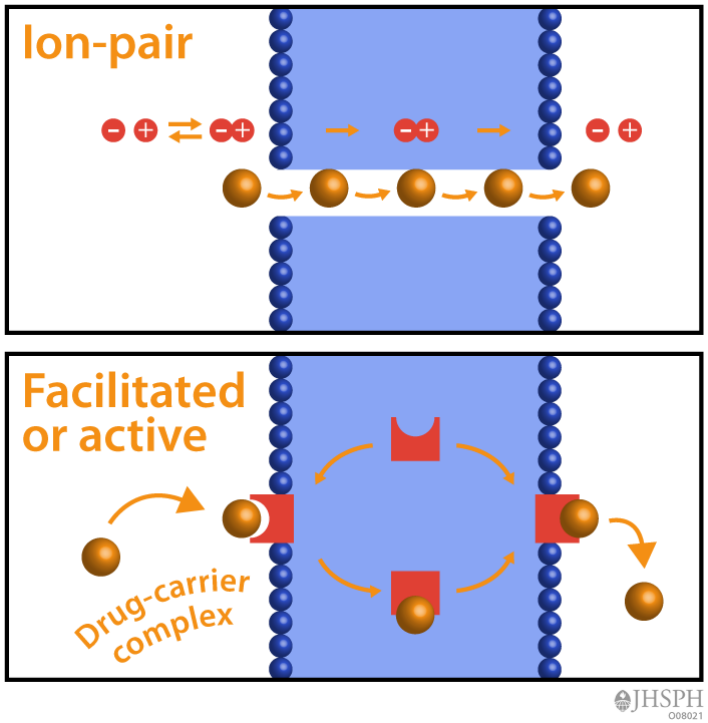
- Simple diffusion
- Facilitated diffusion
- Active transport
- Pinocytosis/receptor-mediated uptake
- Filtration

Types of Transport



Non-electrolytes and un-ionized form of weak acids and weak bases

Molecules of varying sizes



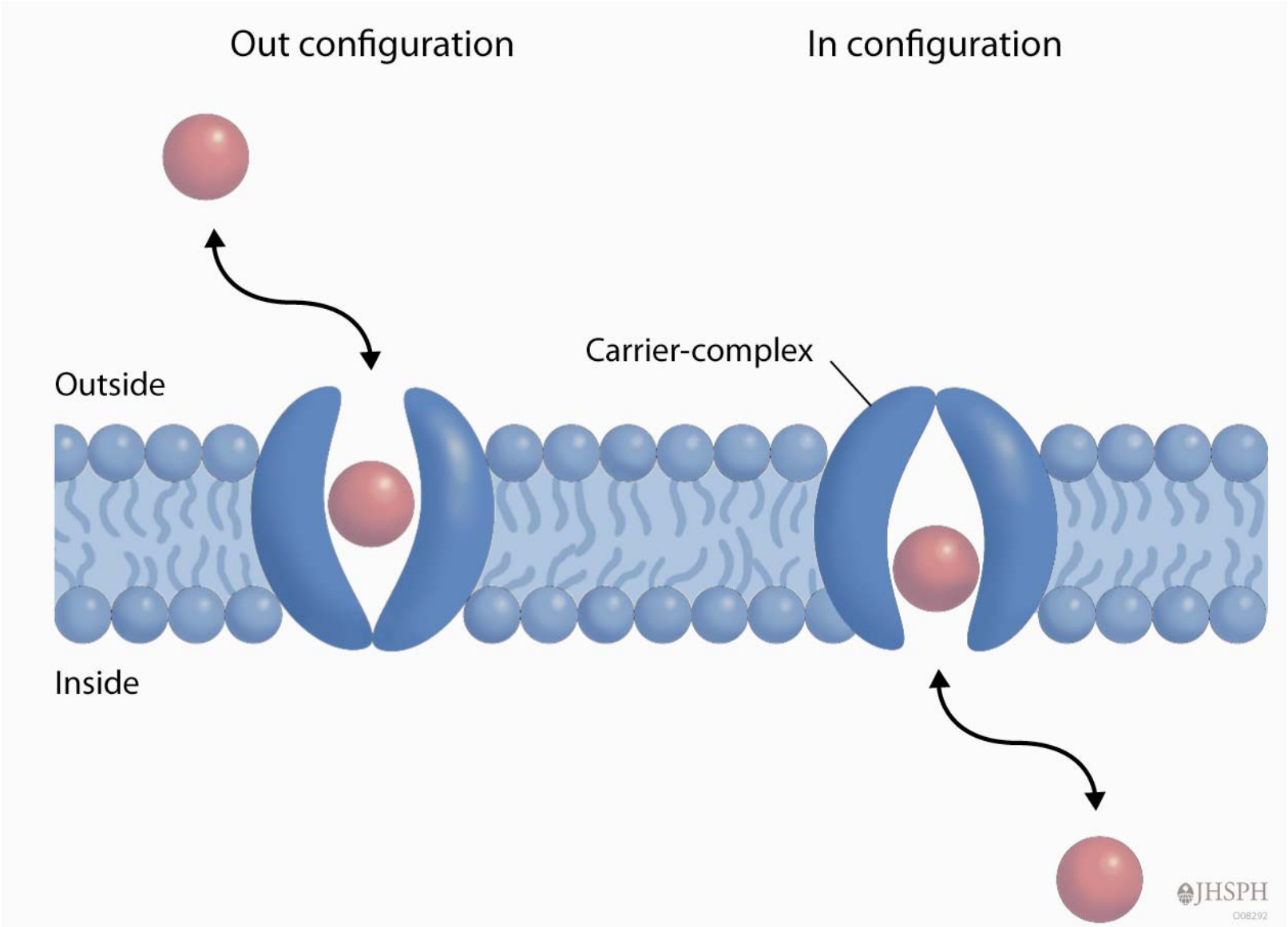
JHSPH
O08020

Characteristics of Simple Diffusion

- Transport proceeds in the direction of the electrochemical potential (concentration) gradient
- Transport is not saturable at high concentration gradients
- No structural specificity
- No energy requirement
- Inherently symmetrical transport

BOTH PASSIVE MEDIATED and ACTIVE MEDIATED TRANSPORT INVOLVE the USE of CARRIER PROTEINS

Carrier-Mediated Transport



Characteristics of Passive Mediated Transport

- Transport proceeds in the direction of the electrochemical potential (concentration) gradient
- The process is saturable at high concentration gradients, i.e., there is a maximum rate of transport

Continued

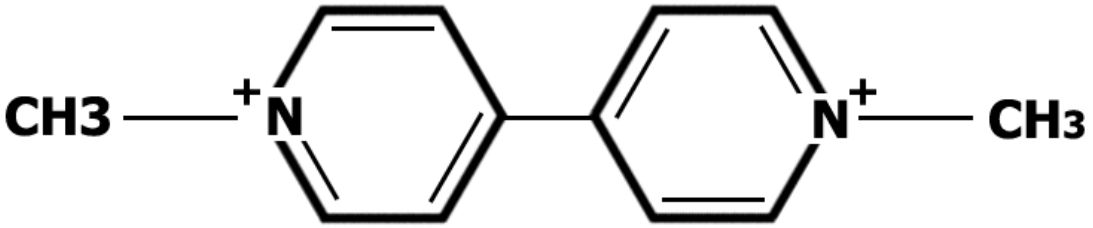
Characteristics of Passive Mediated Transport

- Structural specificity (specific inhibitors)
- No energy requirements
- Inherently symmetrical transport

Characteristics of Active Mediated Transport

- Transport can proceed against an electrochemical potential (concentration) gradient
- The process is saturable at high concentration gradients
- Structural specificity
- Requires cellular energy
- Asymmetrical transport

Active Mediated Transport



A.

$H_2N-(CH_2)_4-NH_2$

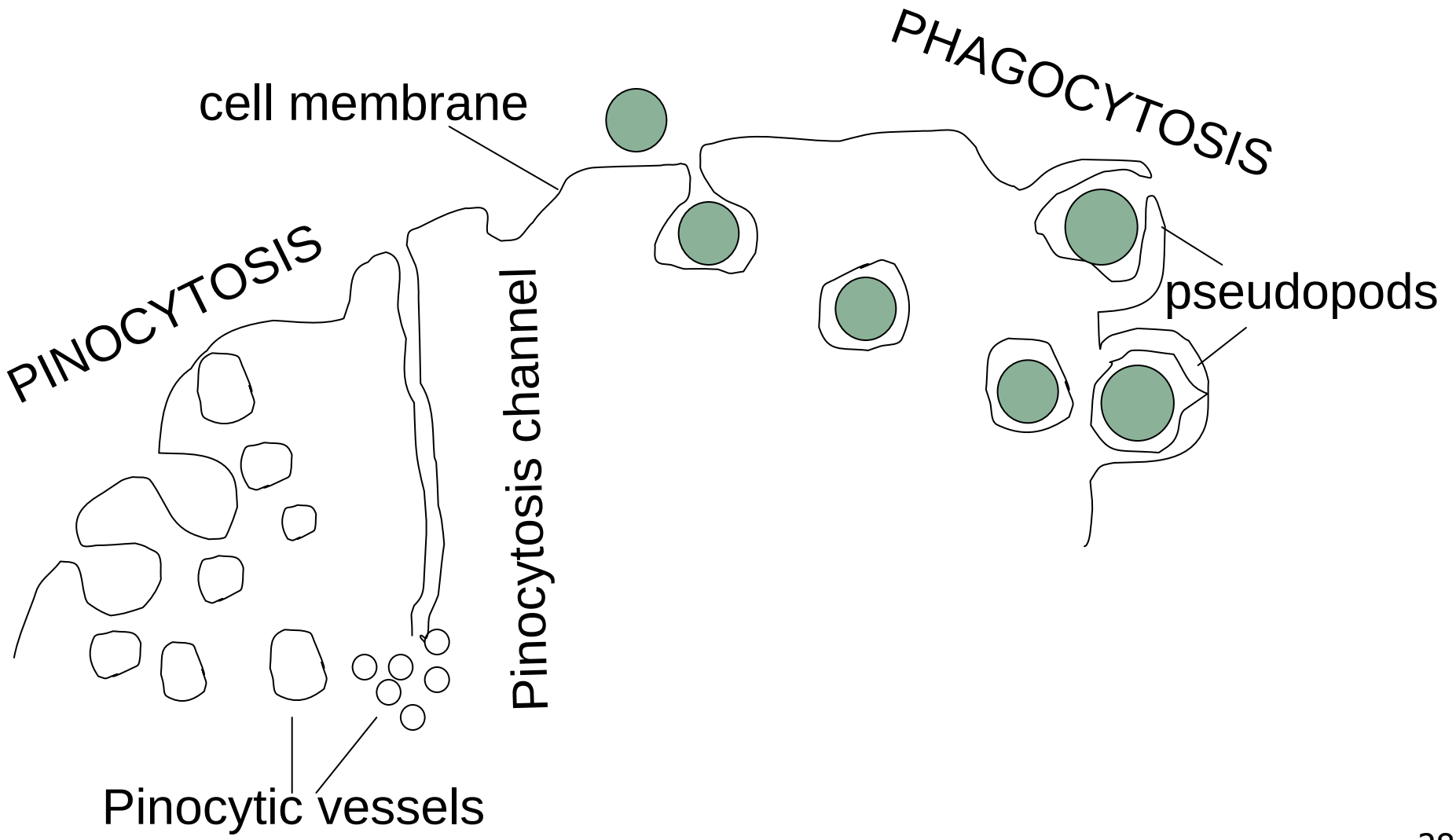
B.

$H_2N(CH_2)_3NH(CH_2)_4NH_2$

C.

- The structure of the herbicide paraquat (A) and the polyamines putrescine (B) and spermine (C)

Pinocytosis / Phagocytosis / Receptor Mediated Endocytosis



Filtration

- Transport of solutes as a consequence of bulk flow of fluid (aqueous) phase
- Glomerulus of kidney is a good example of site where filtration occurs

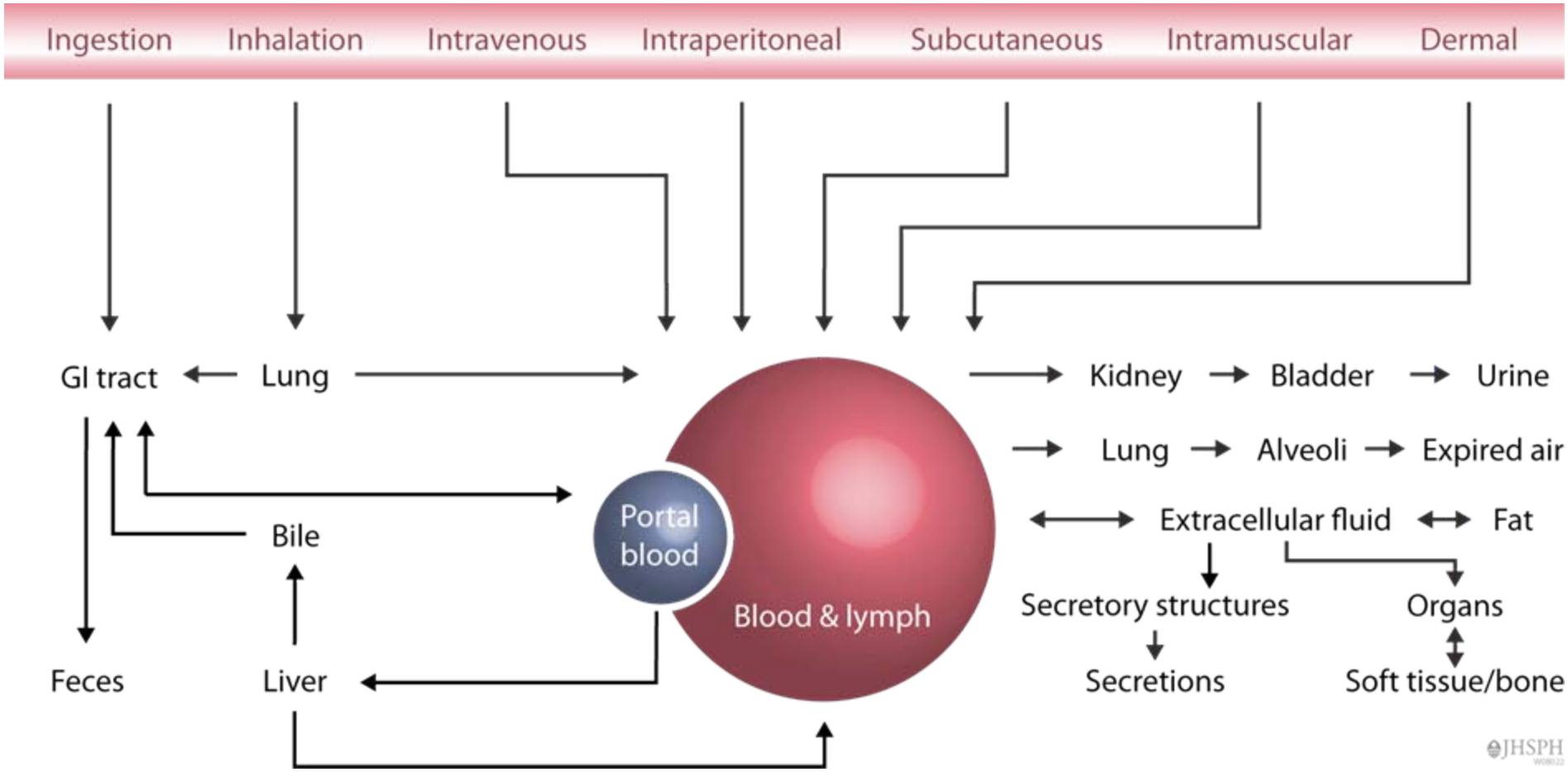
JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Section C

Toxicokinetics

Systemic Kinetics: Outline

- Physiological basis of toxicokinetics
- Biliary excretion route for foreign compounds
- Barriers
- Major difference between a general (non-neural) and brain capillary
- Excretion pathways


Ingestion
Inhalation
Intravenous
Intraperitoneal
Subcutaneous
Intramuscular
Dermal
GI tract
Lung
Kidney
Bladder
Urine
Lung
Alveoli
Expired air
Extracellular fluid
Fat
Portal blood
Bile
Blood & lymph
Secretory structures
Organs
Feces
Liver
Secretions
Soft tissue/bone
JHSPH

Biliary Excretion Route For Foreign Compounds

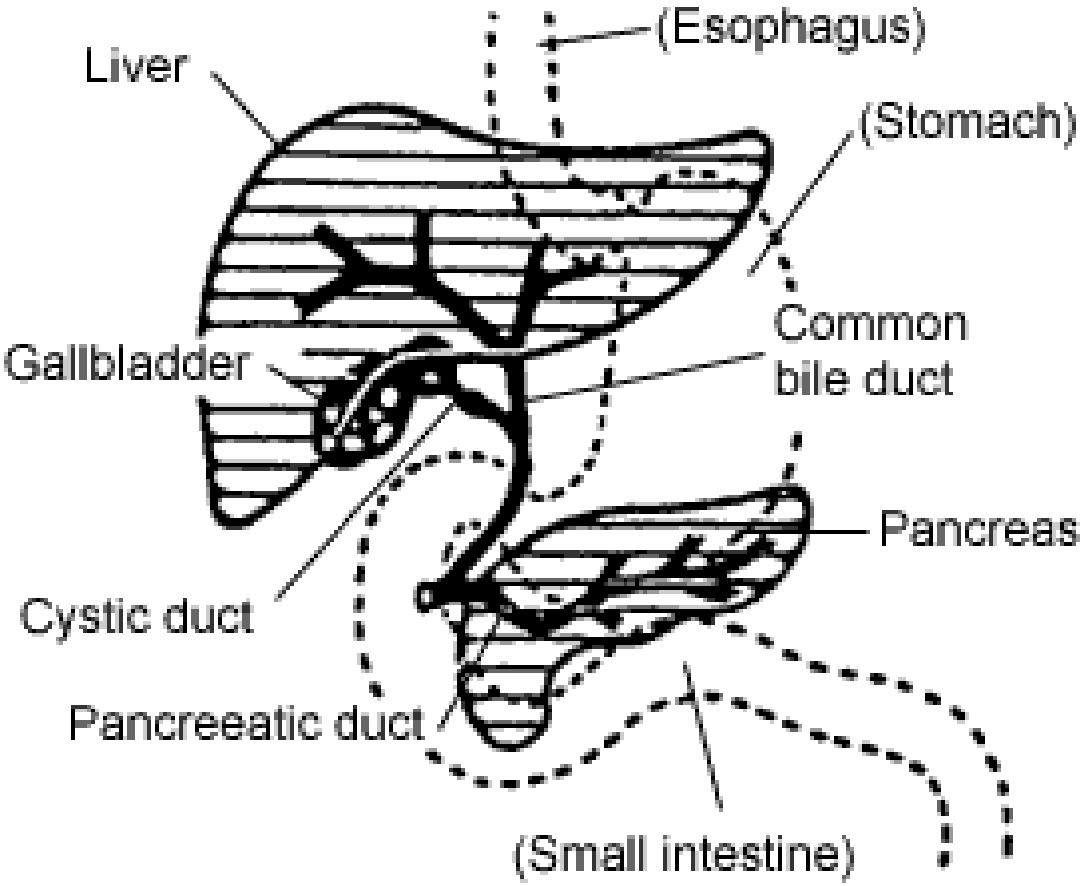
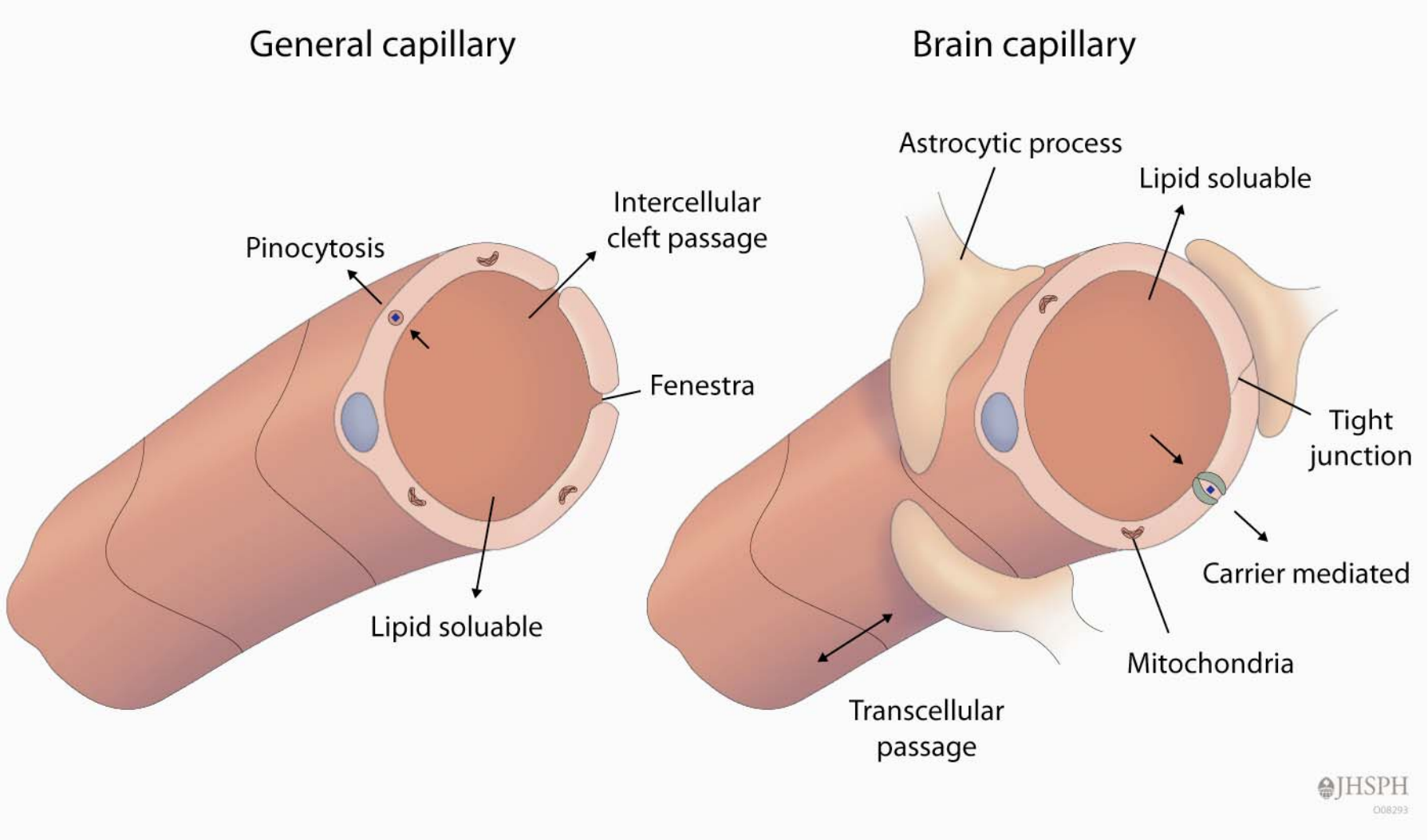


Image source: NIH/NIDDK. Public Domain.

Systemic Kinetics: Barriers

- Blood-brain barrier
- Placenta
- Blood-testicular barrier

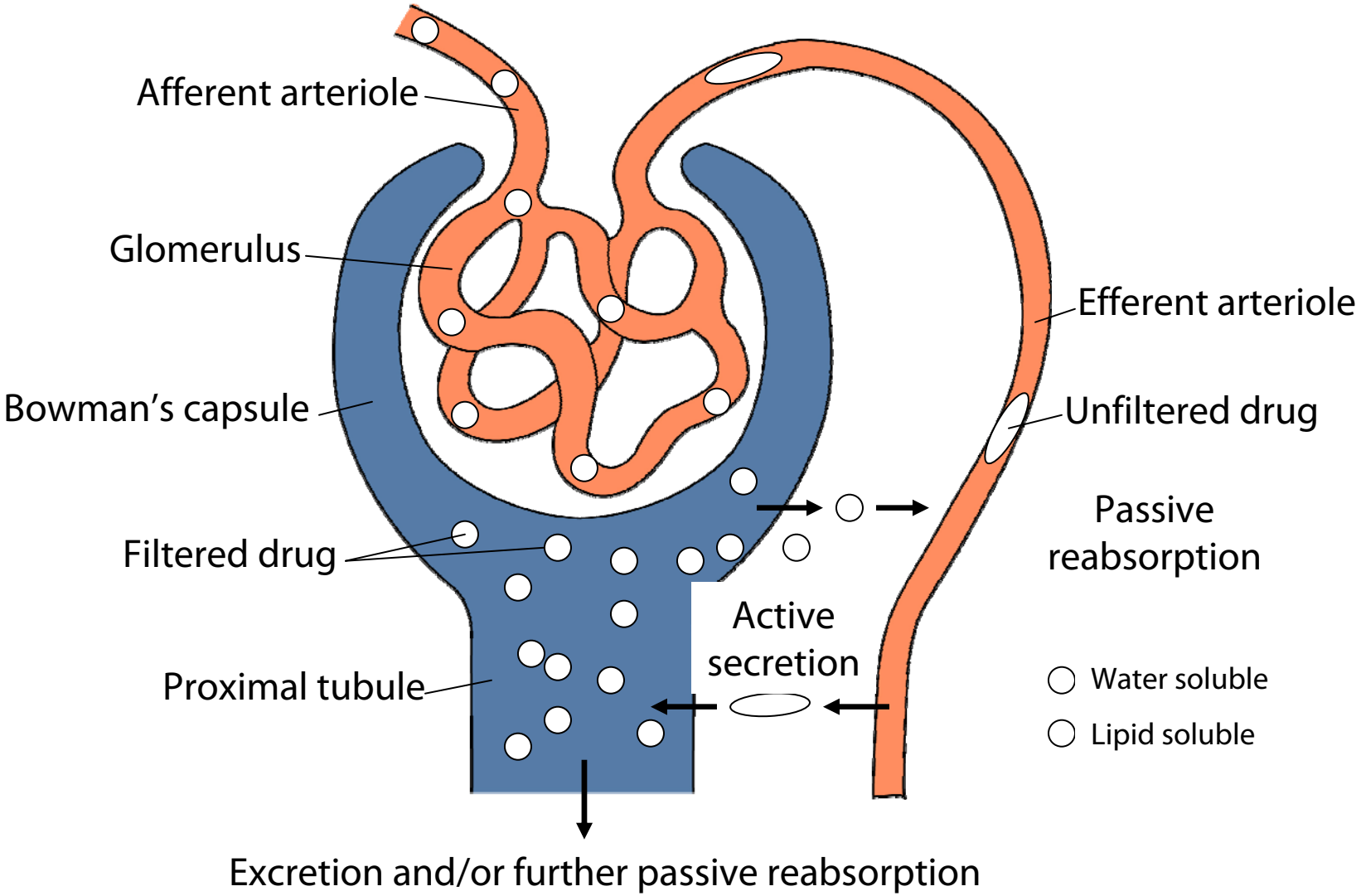
Major Difference between a General (Non-Neural) and a Brain Capillary



Excretion Pathways

- **Respiratory excretion**
  - Mucocilliary clearance
- **Gastrointestinal excretion**
  - Biliary excretion
  - Entero-hepatic circulation
- **Urinary excretion**
  - Glomerular filtration
  - Trans-tubular secretion

Renal Excretion of Chemicals



Other Routes of Excretion

- Milk
- Sweat
- Hair
- Nails
- Saliva

Biological Half Life

- The *biological half-life* (T1/2) is the time required for some measure of the amount of a chemical in the body (for example, body burden, tissue concentration) to decrease to 1/2 its value at the beginning of the observational interval

Continued

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH

Section D

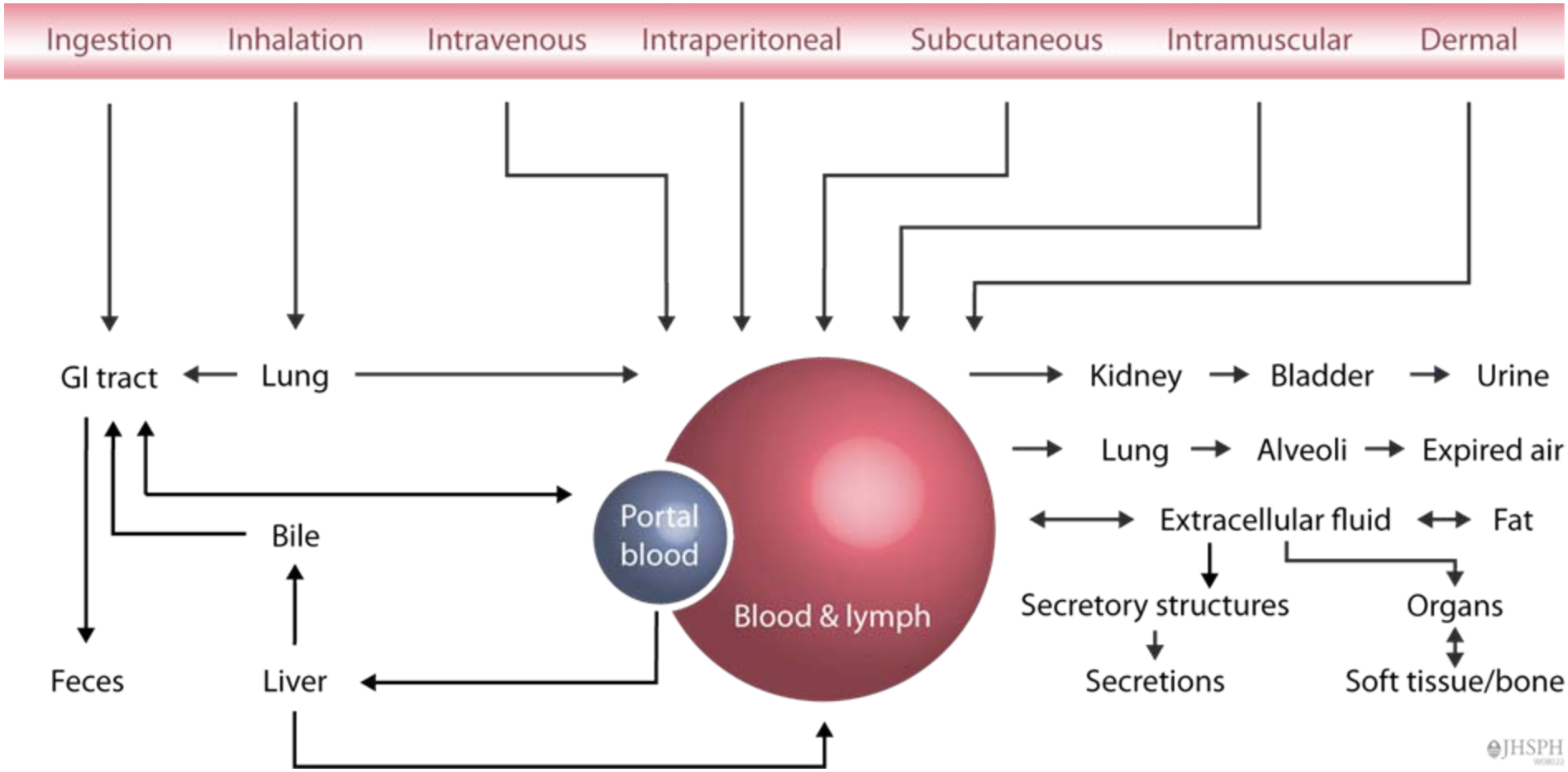
Toxicokinetics and PBK Modeling

PBPK Modeling

Physiologically Based Pharmacokinetic (Toxicokinetic)

- Purpose
  - To mathematically model how a substance is absorbed, distributed, and metabolized in the body to reduce uncertainties in determining the estimated dose

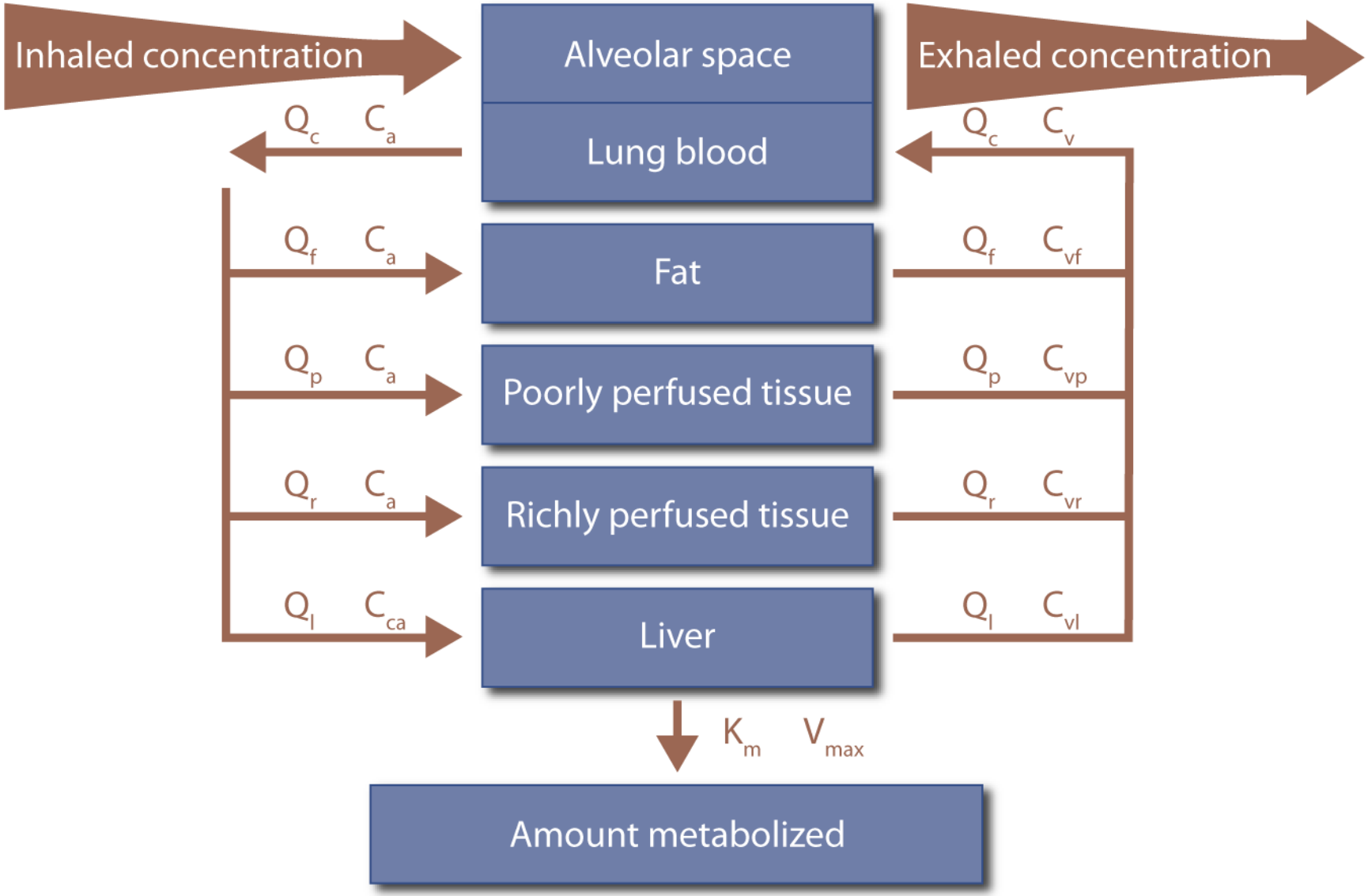
PBPK Modeling



Source: Casarett & Doull, Chaps. 5 and 7, 1996

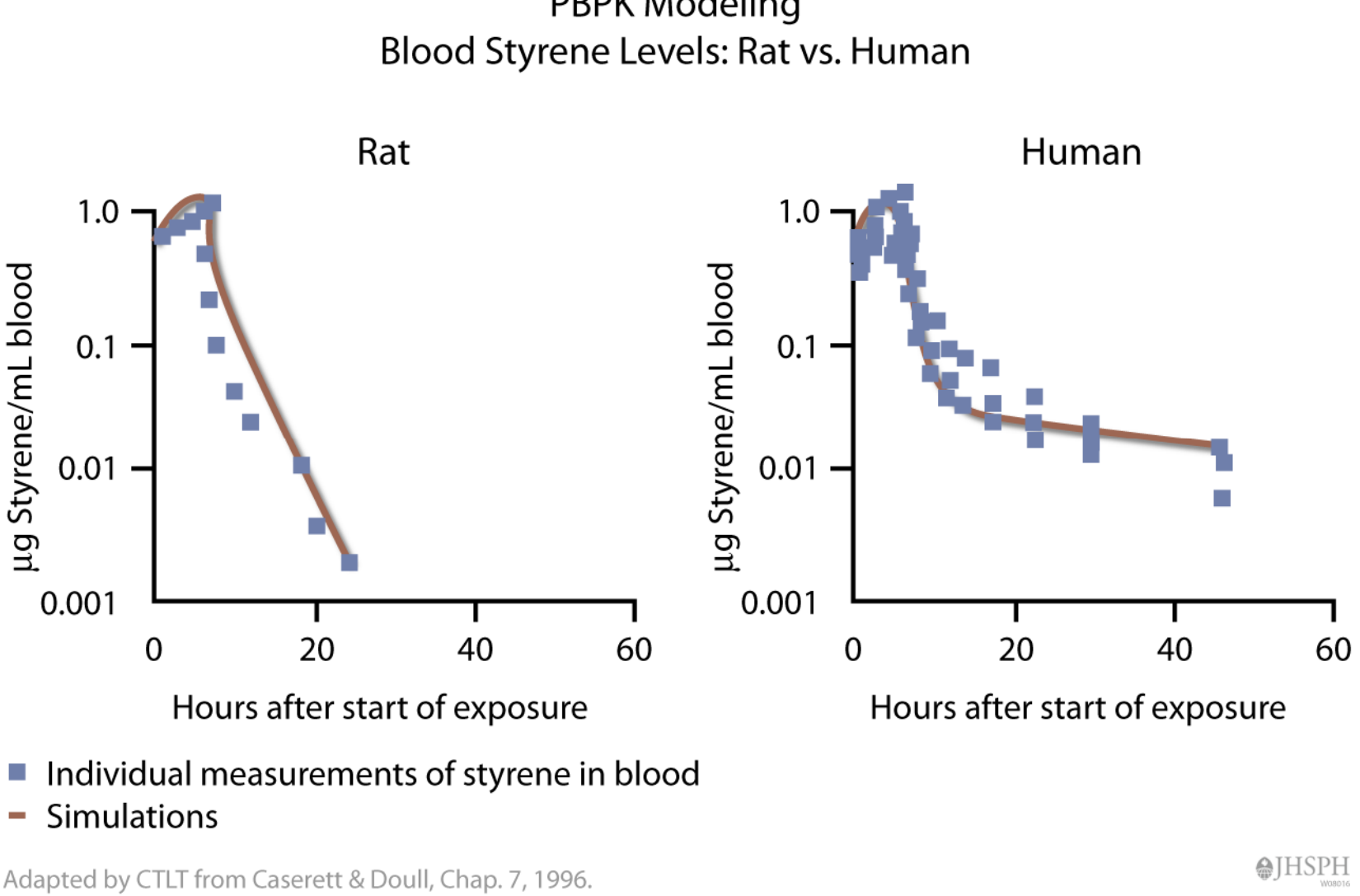
Continued

PBPK Modeling: Complex Models



Adapted by CTLT from Casarett & Doull, Chap. 7, 1996.

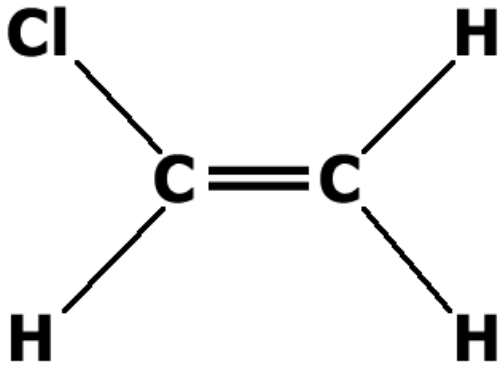
PBPK Modeling



Adapted by CTLT from Caserett & Doull, Chap. 7, 1996.

JHSPH

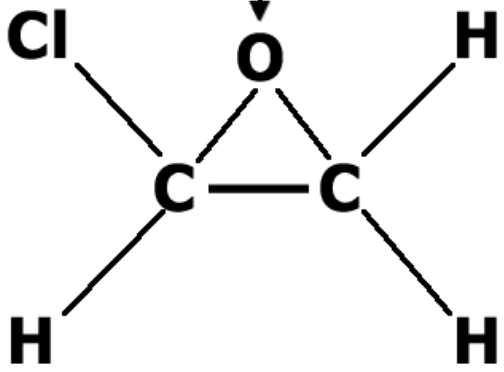
Vinyl Chloride Metabolism



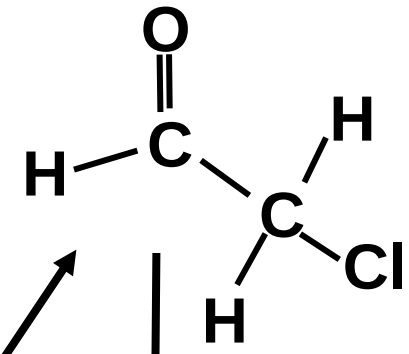
Vinyl Chloride

P450

Metabolism



Vinyl Chloride Epoxide



Chloroacetaldehyde

GSH conjugation

Covalent binding to proteins

Vinyl Chloride – Exposure, Metabolism in Rats & the Incidence of Hepatic Angiosarcoma

Exposure	µg of VC per L of air	µg of VC metabolized/4 hr	Incidence %
50	128	739	2
250	640	2435	7
500	1,280	3413	12
2,500	6,400	5030	22
6,000	15,360	5003	22
10,000	25,600	5521	15

Data source: Gehring et al. *Toxicol Appl Pharmacol.* 1978;44:581-591