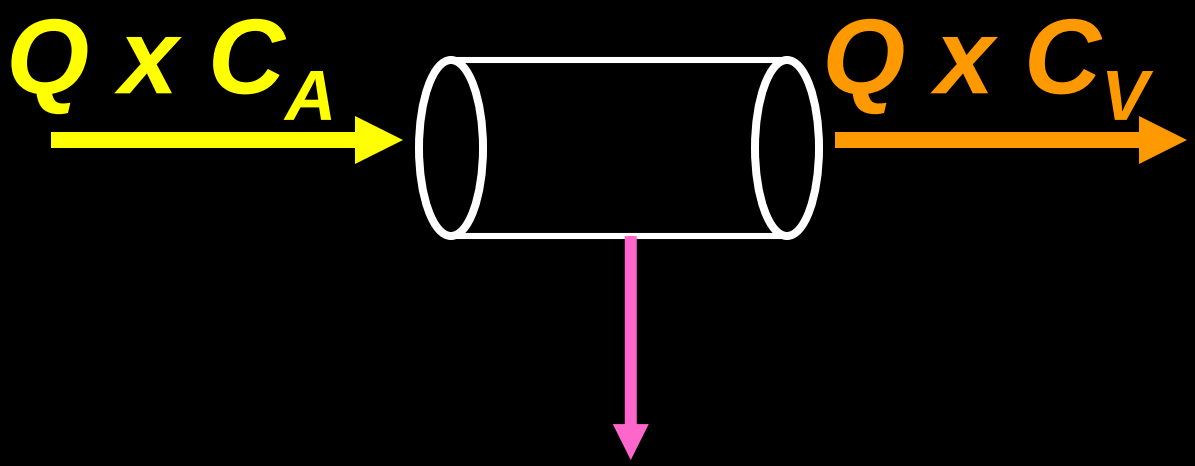
HEPATIC CLEARANCE

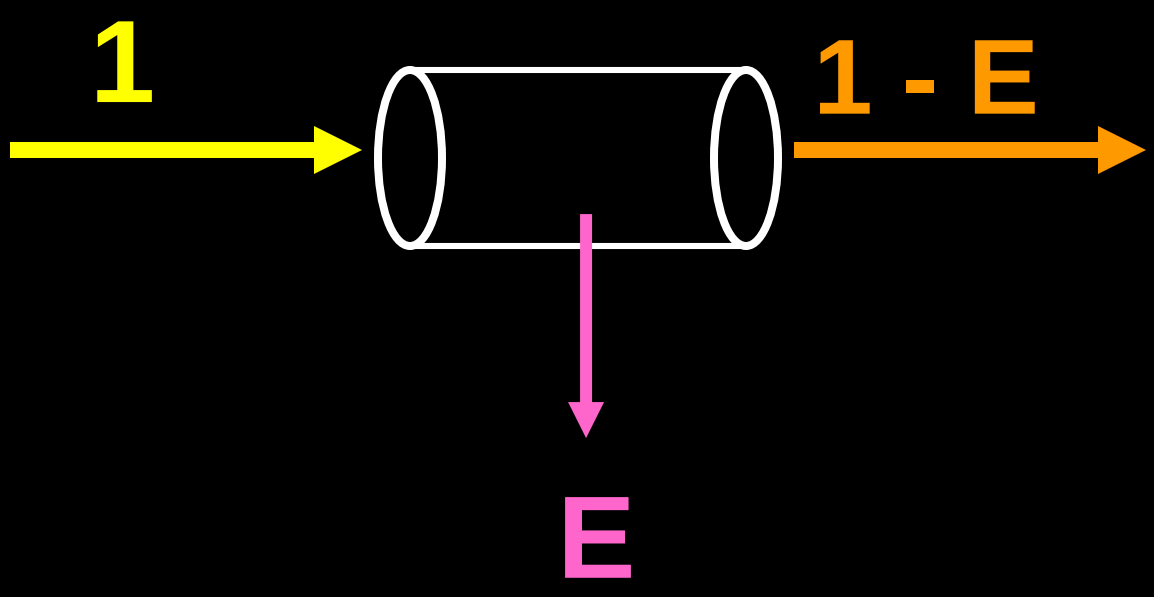
1. Mass Balance



Rate of Extraction

HEPATIC CLEARANCE

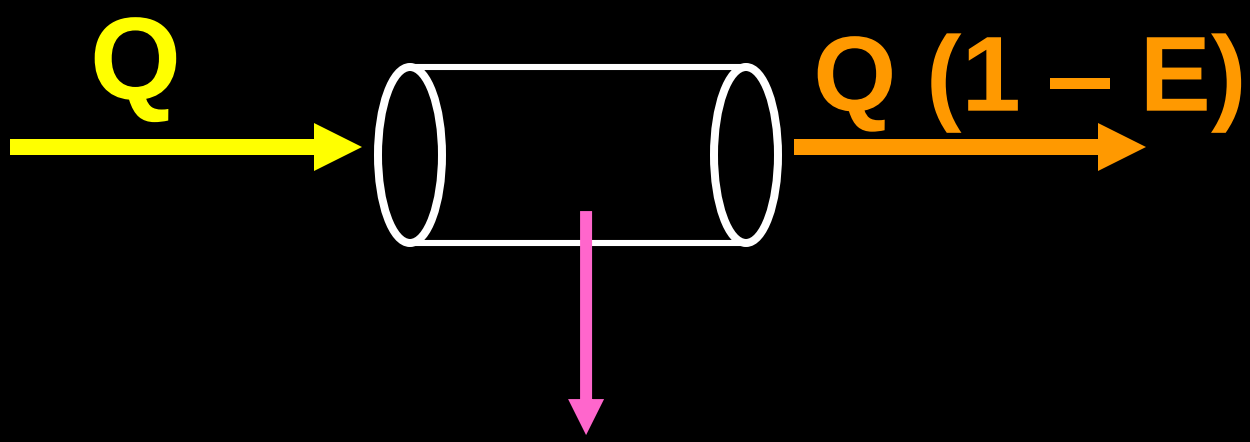
2. Mass Balance Normalized to Rate of Entry



Extraction Ratio

HEPATIC CLEARANCE

3. Mass Balance Normalized to C_A



Clearance

III. ALTERATIONS IN DRUG METABOLISM

A. Induction

$$E_H = \frac{f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$CL_H = \frac{Q_H\, f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$AUC = \frac{F \times Dose}{f_{ub} CL_{u\,\mathrm{int}}}$$

$$F = \frac{Q_H}{Q_H + f_{ub} CL_{\mathbf{uint}}}$$

$$CL_H = Q_H E$$

Suggests that

$$CL_H \sim Q_H$$

Actually

$$\uparrow Q_H = \downarrow E$$

HEPATIC EXTRACTION RATIO OF REPRESENTATIVE DRUGS

Low (<0.3)

- Antipyrine
- Diazepam
- Phenylbutazone
- Theophylline
- Tolbutamide
- Warfarin

High (>0.7)

- Lidocaine
- Meperidine
- Propoxyphene
- Propranolol
- Verapamil

Intermediate: Quinidine

$$CL_H = \frac{Q_H \times f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

When $Q_H >> f_{ub} CL_{u\,\mathrm{int}}$, then $CL_H \cong f_{ub} CL_{u\,\mathrm{int}}$

When $Q_H << f_{ub} CL_{u\,\mathrm{int}}$, then $CL_H \cong Q_H$

Consider a low clearance drug iv:

CL_{uint} = 0.25 L/min Q_H = 1.5 L/min

f_{ub} = 0.1 R_0 = 0.25 mg/min

$$CL_H = \frac{Q_H \times f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$CL_H = \frac{1.5\ \mathrm{L/min} \times 0.1 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.1 \times 0.25\ \mathrm{L/min})}$$

$$CL_H = 0.0246\ \mathrm{L/min}$$

What if f_{ub} = 0.2?

$$CL_H^* = \frac{Q_H \times f_{ub}^* CL_{u\,\mathrm{int}}}{Q_H + f_{ub}^* CL_{u\,\mathrm{int}}}$$

$$CL_H^* = \frac{1.5\ \mathrm{L/min} \times 0.2 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.2 \times 0.25\ \mathrm{L/min})}$$

$$CL_H^* = 0.0484\ \mathrm{L/min}$$

What about oral administration?

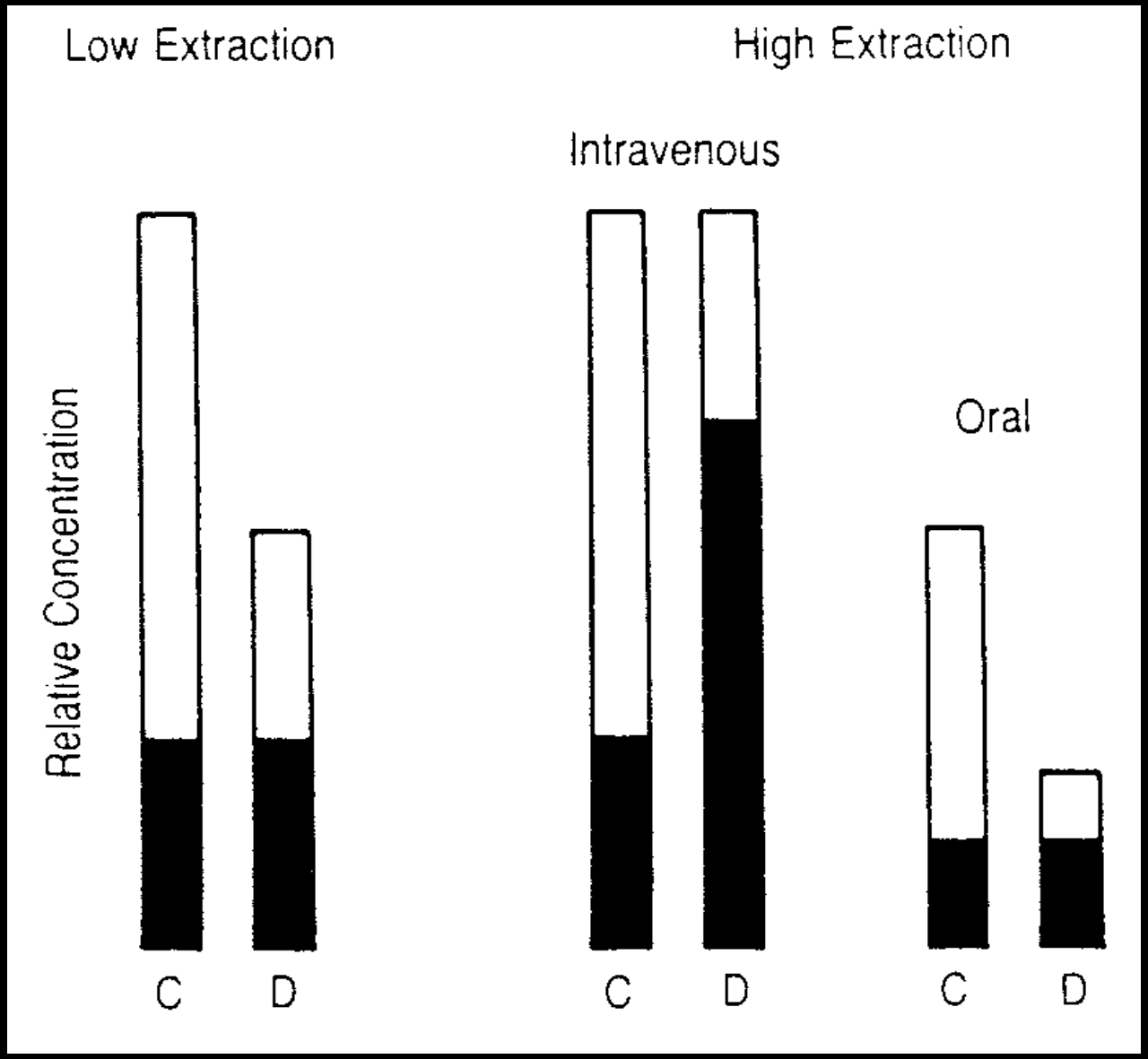
$$F = 1 - \frac{f_{ub} CL_{u\,\mathrm{int}}}{Q_H + f_{ub} CL_{u\,\mathrm{int}}}$$

$$F = 1 - \frac{0.1 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.1 \times 0.25\ \mathrm{L/min})}$$

$$F = 0.98$$

$$F^* = 1 - \frac{0.2 \times 0.25\ \mathrm{L/min}}{1.5\ \mathrm{L/min} + (0.2 \times 0.25\ \mathrm{L/min})}$$

$$F^* = 0.97$$



From: Rowland M, Tozer TN. *Clinical Pharmacokinetics – Concepts and Applications*, 3rd edition

	E	Q_H	f_{ub}	f_{ut}	CL_T	V_{ss}	$t_{1/2}$	F
High		↑		⇔		⇔		
Low		↑		⇔		⇔		

CL = 420 ml/in, Fu = 0.5, Fe = 0.7

Administration with competitive inhibitor renal secration

Cl = V= T1/2=

Fe = F=