

# PHARMACOKINETIC DRUG INTERACTIONS

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## DRUGS REMOVED FROM THE MARKET DURING THE 1990s

DRUG	CATEGORY	REASON
Astemizole	antihistamine	serious metabolic drug intxns
Bromfenac	analgesic	hepatotoxicity
Dexfenfluramine	anorectic	cardiovascular tox
Felbamate	anticonvulsant	aplastic anemia
Flosequinan	vasodilator	increased mortality
Grepafloxacin	antibiotic	proarrhythmic
Mibefradil	Ca channel blocker	serious drug intxns
Temafloxacin	antibiotic	severe ADR
Terfenadine	antihistamine	serious drug intxn
Travafloxacin	antibiotic	hepatotoxicity

Source: *J Clin Pharmacol* 40:1093, 2000

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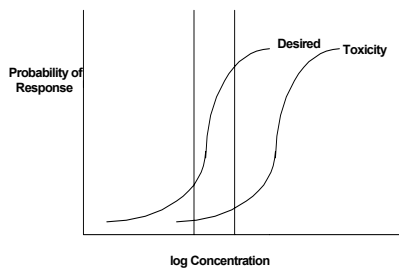
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## I. GENERAL CONSIDERATIONS

### A. CONCEPT OF A THERAPEUTIC WINDOW




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**B. EPIDEMIOLOGICAL CONSIDERATIONS**

**HOSPITALIZED PATIENTS EXPERIENCING AN ADVERSE REACTION**

<u>Drug Class</u>	<u>% Pts with Reaction</u>
Antihypertensives	12
Anticoagulants	11
Antimicrobials	6
Antiarrhythmics	4
Antiinflammatory	3
Diuretics	3
Analgesics	2

Data from: May FE et.al. Drug interactions and multiple drug administration. *Clin Pharmacol Ther* 22:323, 1977.

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**B. EPIDEMIOLOGICAL CONSIDERATIONS**

**Effect of the Number of Drugs a Patient Receives on the Frequency of Adverse Drug Reactions**

<u>Number</u>	<u>Antihypertensives</u>	<u>Anticoagulants</u>
0-5	9	7
6-10	9	8
11-15	18	15
16-20	23	18

Data from: May FE et.al. Drug interactions and multiple drug administration. *Clin Pharmacol Ther* 22:323, 1977.

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**B. EPIDEMIOLOGICAL CONSIDERATIONS**

**Prospective study of 237 patients treated with warfarin analyzed for determination of whether or not a drug interaction occurred with concurrent chloral hydrate**

All patients who received chloral hydrate during warfarin therapy	237
Those patients who received chloral hydrate for at least 3 consecutive days	69
Impossible to evaluate (unstable/change therapy)	28
Potentialiation of anticoagulant action	22
No observable interaction	19

Data from: Koch-Weser J. Hemorrhagic reactions and drug interactions in 500 warfarin treated patients. *Clin Pharmacol Ther* 14:139-146, 1973.

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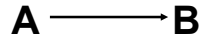
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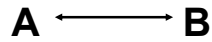
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**C. TYPE OF INTERACTION**

***Unidirectional***



***Bidirectional***



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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***

**Complexation/Chelation**

**Example: antacids + tetracycline**

**Impact: tetracycline complexes with divalent cations forming an insoluble complex**

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***

**Complexation/Chelation**

**Altered GI Transit**

**Example: anticholinergics + acetaminophen**

**Impact: delay in absorption of acetaminophen**

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***

**Complexation/Chelation**

**Altered GI Transit**

**Altered Gastric pH**

**Example: H-2 blockers + ketoconazole**

**Impact: dissolution of ketoconazole is decreased, resulting in reduced absorption**

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***

***ALTERATIONS IN HEPATIC METABOLISM***

**Induction of Metabolism**

**Example: phenobarbital + warfarin**

**Impact: phenobarbital increases the metabolism of warfarin, resulting in reduced anticoagulation**

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***

***ALTERATIONS IN HEPATIC METABOLISM***

**Induction of Metabolism**

**Inhibition of Metabolism**

**Example: cimetidine + theophylline**

**Impact: cimetidine reduces the clearance of theophylline causing an increase in adverse effects**

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***  
***ALTERATIONS IN HEPATIC METABOLISM***  
***ALTERATIONS IN RENAL CLEARANCE***

Increase in Renal Blood Flow

Example: hydralazine + digoxin

Impact: hydralazine increases the renal clearance of digoxin

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***  
***ALTERATIONS IN HEPATIC METABOLISM***  
***ALTERATIONS IN RENAL CLEARANCE***

Increase in Renal Blood Flow

Inhibition of Active Tubular Secretion

Example: probenecid + penicillin

Impact: probenecid prolongs the half-life of penicillin, allowing single dose therapy

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**D. CLASSIFICATION OF MECHANISM**

***ALTERATIONS IN ABSORPTION***  
***ALTERATIONS IN HEPATIC METABOLISM***  
***ALTERATIONS IN RENAL CLEARANCE***

Increase in Renal Blood Flow

Inhibition of Active Tubular Secretion

Alterations in Tubular Reabsorption

Example: antacids + aspirin

Impact: antacids reduce the tubular reabsorption of salicylate via an increase in urine pH

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## D. CLASSIFICATION OF MECHANISM

**ALTERATIONS IN ABSORPTION**  
**ALTERATIONS IN HEPATIC METABOLISM**  
**ALTERATIONS IN RENAL CLEARANCE**  
**ALTERATIONS IN PLASMA PROTEIN BINDING**

Example: phenytoin + valproic acid  
Impact: protein binding of valproic acid is reduced and total C<sub>ss</sub> decreased

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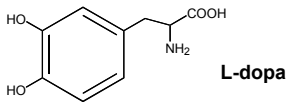
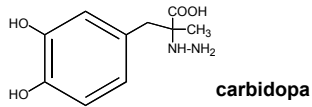
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## II. ALTERATIONS IN ABSORPTION

A. Mediated by binding or chelation of drug in the gastrointestinal tract



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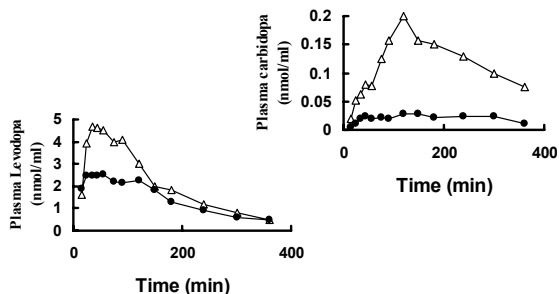
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Effect of ferrous sulfate (325 mg) on plasma levodopa and carbidopa concentrations after ingestion of Sinemet (100/25) in patients with Parkinson's disease. Concentrations shown are mean values without (triangles) and with (circles) ferrous sulfate administration simultaneously. Adapted from Campbell NRC et al: *Br J clin Pharmacol* 30:599-605, 1990

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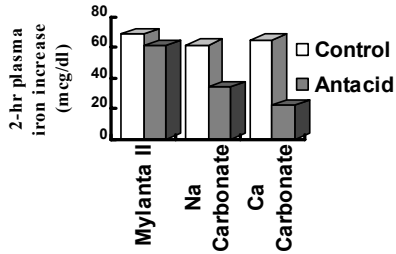
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**Effect of Antacids on Iron Absorption from a Multivitamin.** Antacid was ingested immediately after multivitamin ingestion. Data from: O'Neil-Cutting MA, Crosby WH. The effect of antacids on the absorption of simultaneously ingested iron. *JAMA* 255:1468- 1470, 1986.




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**COMPOUNDS DEMONSTRATED TO BIND WITH IRON**

- |               |                |
|---------------|----------------|
| ACETAMINOPHEN | MINOXIDIL      |
| AMPICILLIN    | NALIDIXI ACID  |
| CAPTOPRIL     | NORFLOXACIN    |
| CARBIDOPA     | PENICILLAMINE  |
| CIPROFLOXACIN | RIFAMPIN       |
| ETHAMBUTOL    | TETRACYCLINE   |
| FOLIC ACID    | THYROXINE      |
| INDOMETHACIN  | SALICYLIC ACID |
| LEVODOPA      |                |
| METHYLDOPA    |                |

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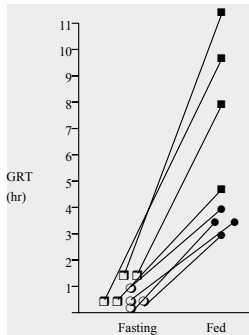
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**B. Mediated by alterations in gastric emptying or gastrointestinal transit**



**Effect of food on gastric residence time (GRT) of the Heidelberg capsule administered to healthy male (circles) and female (squares).** Reproduced from: Mojaverian P et al. Effect of food on the absorption of enteric coated aspirin: Correlation with gastric residence time. *Clin Pharmacol Ther* 41:11-17, 1987.

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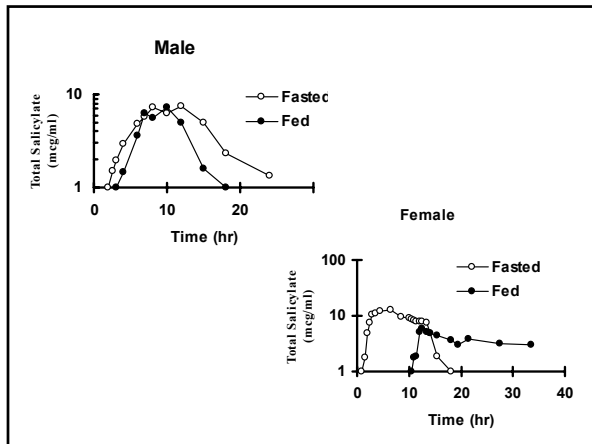
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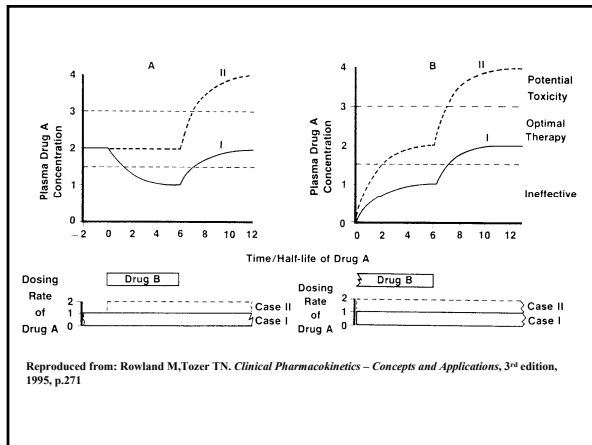
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**Effect of sumatriptan on acetaminophen absorption in patients with migraines**

Parameter	APAP alone	with Sumatriptan	p value
C <sub>max</sub> (mg/L)	36.3 (10.9)	18.3 (6.7)	0.001
t <sub>max</sub> (hr)	1.4 (0.4)	2.7 (1.0)	0.001
t <sub>1/2</sub> (hr)	2.3 (0.7)	3.0 (1.4)	NS
AUC <sub>0-1.5</sub>	26.9 (9.5)	11.8 (3.7)	0.001
AUC <sub>0-3</sub>	62.3 (14)	33.1 (12.9)	0.001
AUC <sub>0-8</sub>	109 (37)	78.8 (31.3)	NS

Data from: Rani PU, et al. Sumatriptan delays paracetamol absorption in migraine patients. *Clin Pharmacokinetics* 11:300-304, 1996.

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### III. ALTERATIONS IN DRUG METABOLISM

#### A. Induction

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

$$AUC_O = \frac{F \times \text{Dose}}{f_{ub} CL_{u\text{int}}}$$

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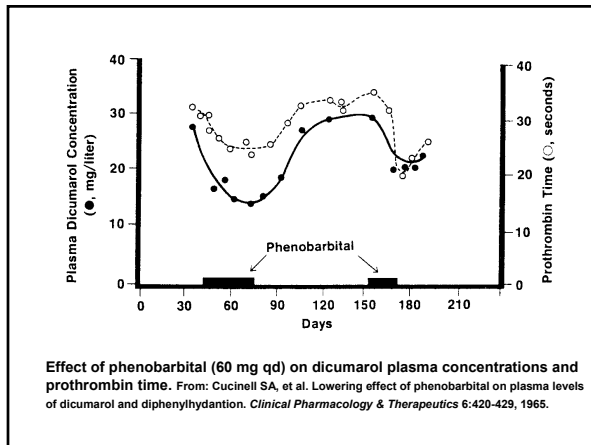
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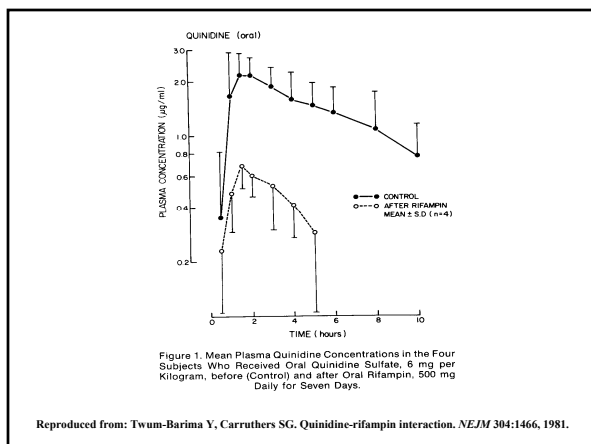
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Reproduced from: Twum-Barima Y, Carruthers SG. Quinidine-rifampin interaction. *NEJM* 304:1466, 1981.

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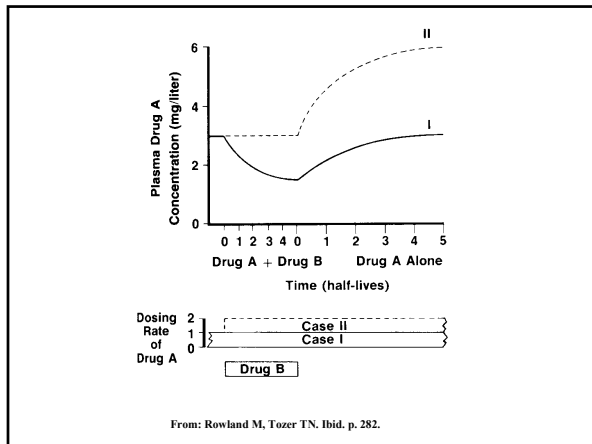
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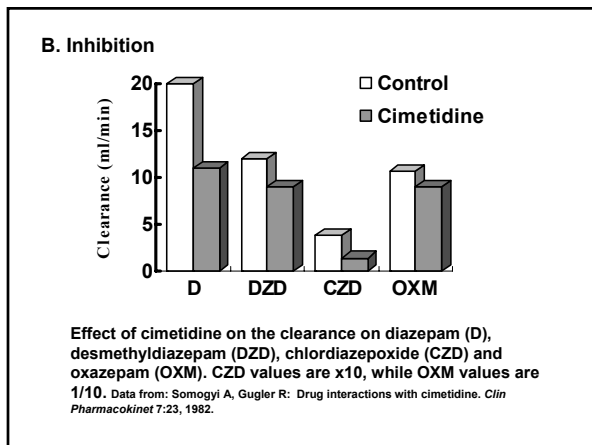
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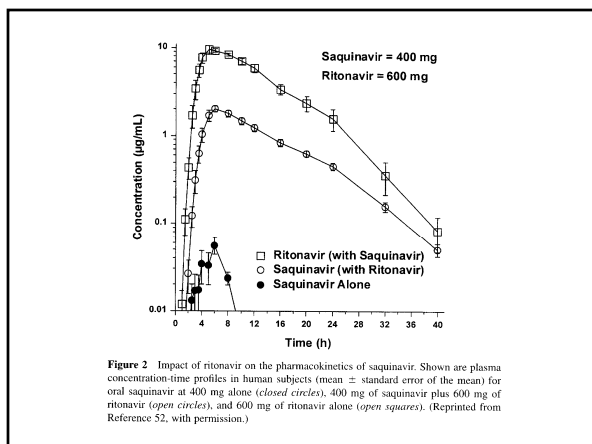
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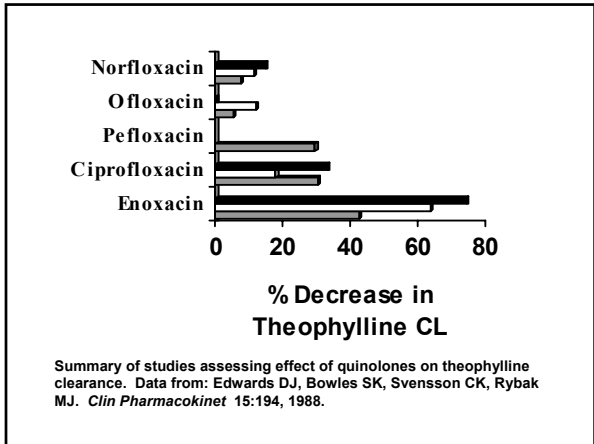
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- FACTORS WHICH ALTER HEPATIC BLOOD FLOW**
- |                              |                              |
|------------------------------|------------------------------|
| <u><i>Increased Flow</i></u> | <u><i>Decreased Flow</i></u> |
| •Glucagon                    | •Propranolol                 |
| •Isoproterenol               | •Norepinephrine              |
| •Phentolamine                | •Anesthetics                 |
| •Phenobarbital               | •Labetalol                   |
| •PGE                         | •Upright posture             |
| •Supine posture              | •Hypovolemia                 |
| •High-protein meal           | •CHF                         |
| •Viral hepatitis             | •cirrhosis                   |

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**Effect of changing posture on liver blood flow and lidocaine clearance**

Parameter	Supine	Sitting/tilted
Q <sub>H</sub> (mL/min)	1100 (167)	765 (106)
CL (mL/min)	602 (101)	475 (109)

Data presented as mean (SD)  
 From: Feely J, et al. Effect of hypotension on liver blood flow and lidocaine disposition. *N Engl J Med* 307:866-869, 1982.

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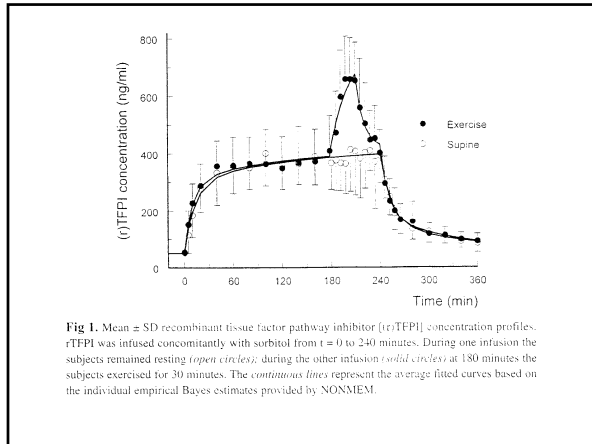
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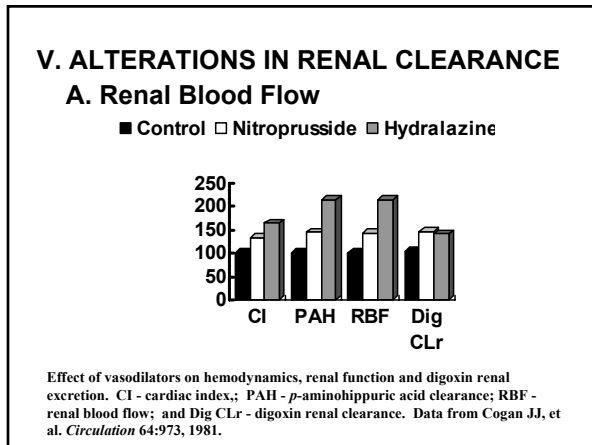
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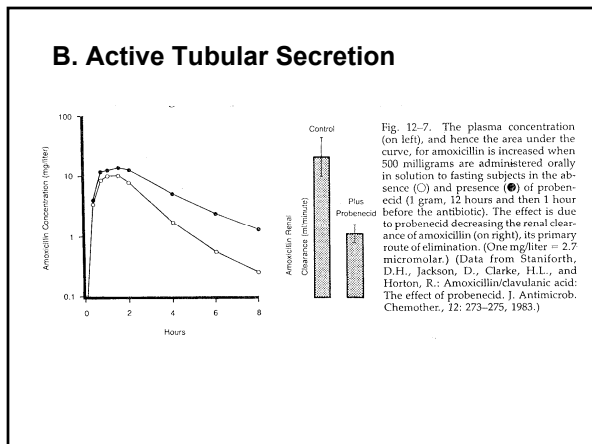
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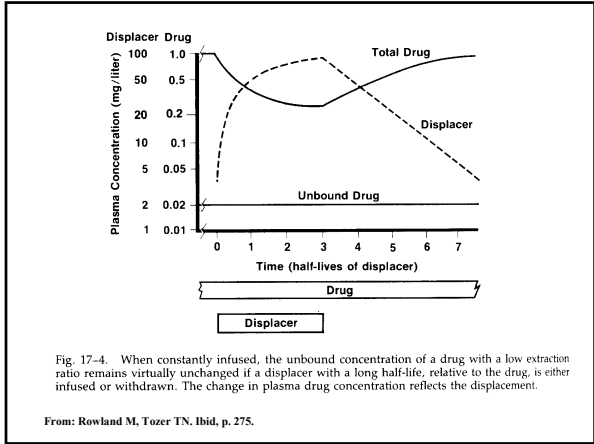
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