Principles of Clinical Pharmacology

Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program

Office of Clinical Research Training
and Medical Education
National Institutes of Health
Clinical Center

Principles of Clinical Pharmacology

Remote Sites 2008-2009

Darmouth Hitchcock Medical Center, Lebanon
Dong-A Medical College, Republic of Korea
Duke University Medical Center, Durham
Harbor-UCLA Medical Center, Los Angeles
Indiana University-Purdue University, Indianapolis
University of California, Los Angeles
University of California, San Francisco
University of Pennsylvania, Philadelphia
University of Puerto Rico, San Juan
Walter Reed Army Institute of Research – USUHS, Silver Spring, Maryland

Principles of Clinical Pharmacology

Remote Sites 2008-2009

NCI - Frederick, Maryland

NIA - Baltimore, Maryland

NIA – Harbor Hospital, Baltimore, MD

NIDA - Baltimore, Maryland

COURSE MODULES

MODULE 1: Pharmacokinetics

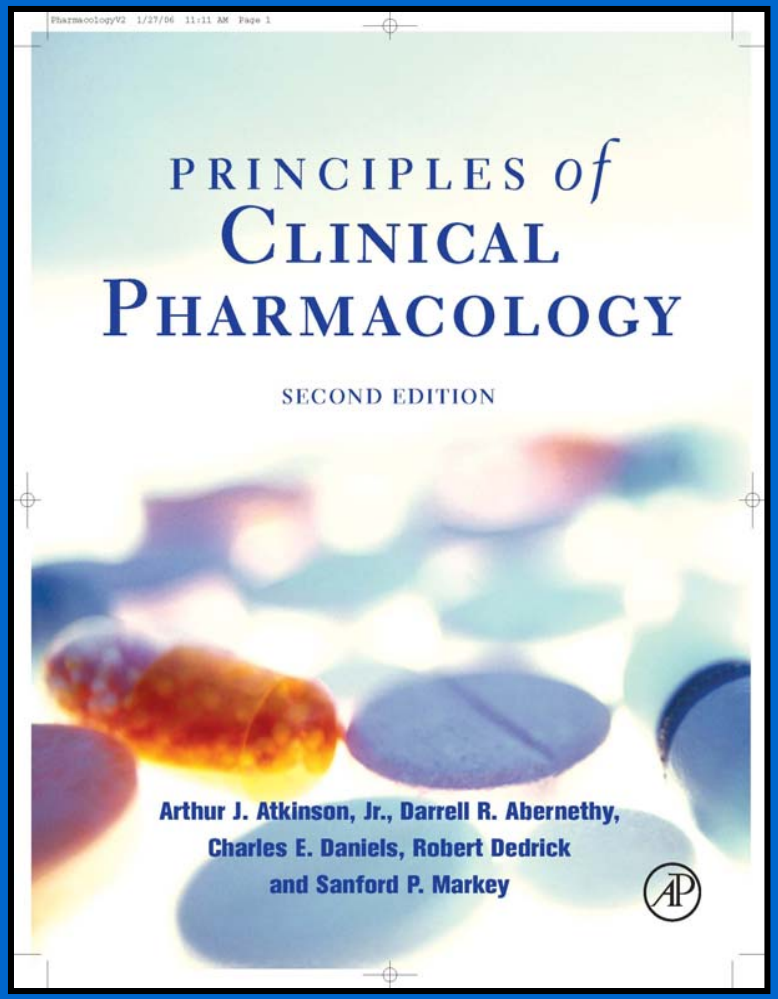
MODULE 2: Drug metabolism and Transport

MODULE 3: Assessment of Drug Effects

MODULE 4: Optimizing and Evaluating Therapy

MODULE 5: Drug Discovery and Development

RECOMMENDED TEXT



THE NATIONAL INSTITUTES OF HEALTH

Clinical Center

PRESENTS THIS CERTIFICATE TO

John B. Smith, M.D.

IN RECOGNITION OF PARTICIPATION IN THE

NIH CLINICAL CENTER COURSE IN

Principles of Clinical Pharmacology

September 4, 2008 through April 23, 2009

Juan J.L. Lertora, M.D., Ph.D.
Director
Clinical Pharmacology Program
NIH Clinical Center

PHARMACOLOGY

The study of *drugs* (chemicals, "small molecules") and *biologics* (peptides, antibodies, "large molecules") and their actions in *living organisms* (intact animals, isolated organs, tissue cultures).

CLINICAL PHARMACOLOGY

THE STUDY OF DRUGS IN HUMANS

COURSE FOCUS

- **Scientific basis of drug use, development and evaluation**
- ***Not* Therapeutics**
- **Emphasis is on *General Principles* for both “old” and “new” drugs**

CAREER GOALS OF CLINICAL PHARMACOLOGISTS

- Optimize understanding and use of existing medicines
- Develop and evaluate new medicines

“Introduction” Lecture Outline

- Historical overview
- The problem of adverse drug reactions (ADRs)
- Drug discovery and development
- Introduction to pharmacokinetics
- The concept of clearance

Historical Overview

The establishment of *experimental pharmacology* as a discipline in Europe and the USA in the 19th and 20th centuries.

JOHN JACOB ABEL
1857 - 1938

OSWALD SCHMIEDEBERG
1838 - 1921

RUDOLPH BUCHEIM
1820 - 1879

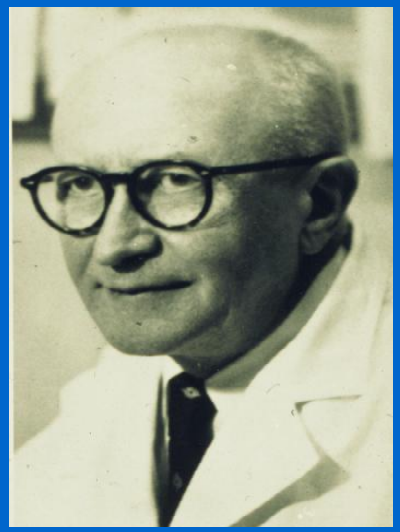
LACK OF IMPORTANCE ATTACHED TO DRUG THERAPY

"Fortunately a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago."

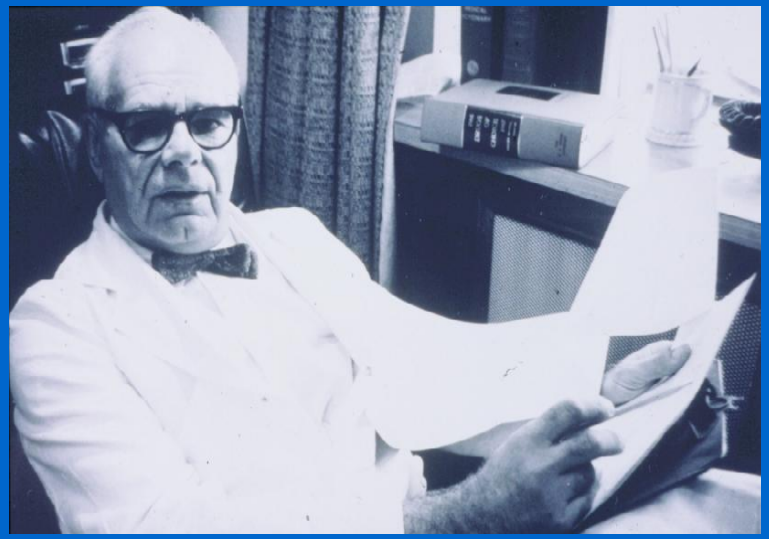
Placing emphasis on therapeutic technique and rational prescribing

Rudolph Bucheim
Beitrage zur Arzneimittellehre, 1849

FOUNDERS OF AMERICAN CLINICAL PHARMACOLOGY



HARRY GOLD



WALTER MODELL

Partial List of GOLD and MODELL Accomplishments

1937 – Introduced Double-Blind Clinical Trial Design *

1939 – Initiated *Cornell Conference on Therapy*

1953 – Analized Digoxin Effect Kinetics to Estimate Absolute Bioavailability as well as Time-Course of Chronotropic Effects†

1960 - Founded *Clinical Pharmacology and Therapeutics*

*** Gold H, Kwit NT, Otto H. JAMA 1937;108:2173-2179.**

† Gold H, Cattell McK, Greiner T, Hanlon LW, Kwit NT, Modell W, Cotlove E, Benton J, Otto HL. J Pharmacol Exp Ther 1953:109;45-57.

LINEAGE of Modern Clinical Pharmacology

PATER FAMILIAS

RUDOLPH BUCHEIM

FOUNDING FATHERS

US

HARRY GOLD

WALTER MODELL

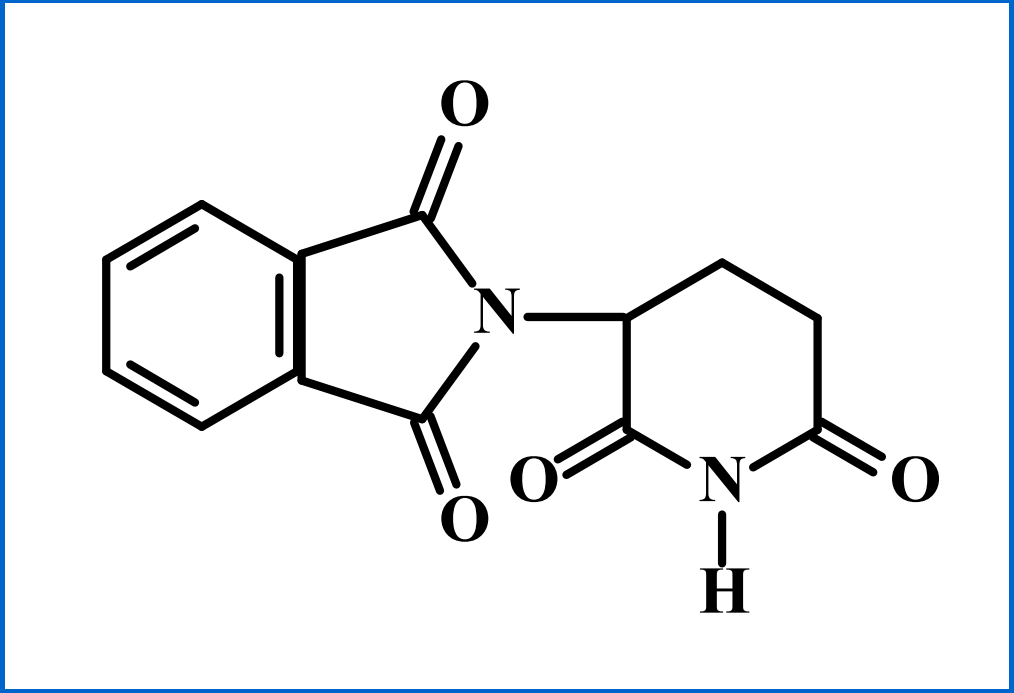
EUROPE

PAUL MARTINI

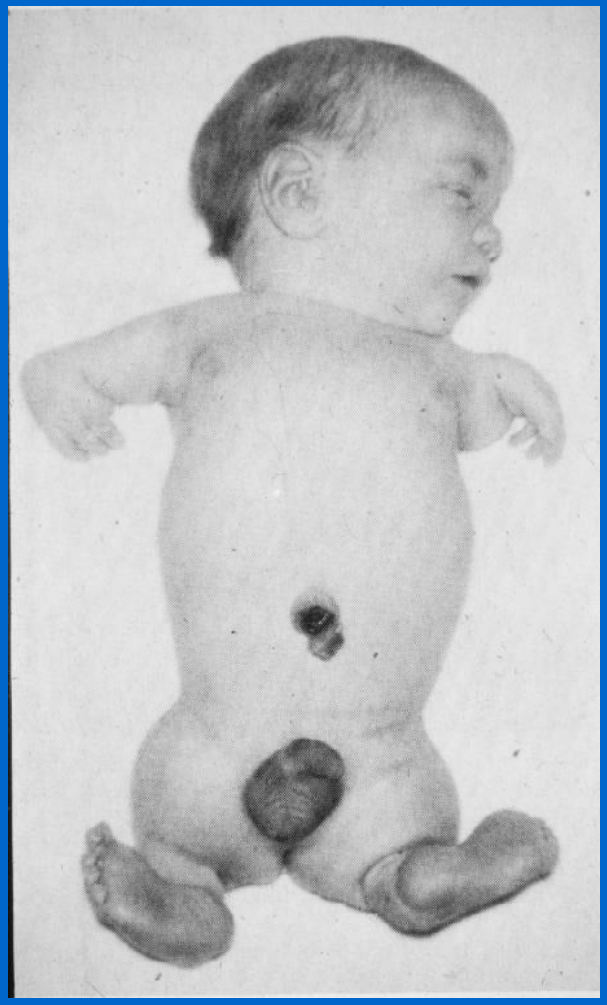
Drug Toxicity
Adverse Drug Reactions

- **We need to develop drugs that are both *effective* and *safe* for use in patients.**
- **While some toxicities can be managed and *may* be acceptable (*risk/benefit* ratio) others are by their nature and severity *unacceptable*.**
- **Covered in *Modules 2* and *4* in our course.**

THALIDOMIDE



PHOCOMELIA



Drug Exposure “in utero”

- **The problem of**

  “Drug Therapy in Pregnant and Nursing Women”

  Covered in *Module 4* in our course.

Thalidomide: Therapeutic Uses

- *Erythema Nodosum Leprosum*
- Multiple Myeloma

These are *FDA-approved* indications (immunomodulatory agent)

Marketing done under a special restricted distribution program:

System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.)

Used with *extreme caution* in females of childbearing potential. Contraceptive measures are mandatory.

SERIOUS ADR

A ***SERIOUS ADVERSE DRUG REACTION*** is an adverse drug reaction (ADR) that *requires or prolongs hospitalization*, is *permanently disabling* or results in *death*.

CONSEQUENCES OF THALIDOMIDE CRISIS

- **New FDA Regulations (*KEFAUVER-HARRIS 1962 AMENDMENTS*)**
- **Institute of Medicine-National Academy of Sciences *review of Therapeutic Claims***
- **More Research on *Causes* of ADRs**
- **NIGMS created *Clinical Pharmacology Centers* in the USA**

LINEAGE OF Modern Clinical Pharmacology

PATER FAMILIAS

RUDOLPH BUCHEIM

FOUNDING FATHERS

US

HARRY GOLD

WALTER MODELL

EUROPE

PAUL MARTINI

RENAISSANCE LEADERS

US

KEN MELMON
LEON GOLDBERG
JAN KOCH-WESER

JOHN OATES
DAN AZARNOFF
LOU LASAGNA

EUROPE

FOLKE SJŐQVIST

COLLIN DOLLERY

FACTORS CONTRIBUTING TO ADR'S

1. Inappropriate *polypharmacy* resulting in adverse *drug interactions*
2. *Lack* of clear *therapeutic goals*
3. *Failure to attribute* new symptoms or abnormal laboratory test results *to drugs prescribed*
4. *Low priority* given to studying ADR's
5. *Insufficient knowledge* of pharmacology

ADVERSE DRUG REACTIONS

WHO:

***Any* untoward reaction to a drug**

CONTEMPORARY VIEW:

***Unpredictable* Adverse Drug Events**

A recent example – Cytokine Storm

"Six healthy young male volunteers at a contract research organization were enrolled in the *first phase I clinical trial of TGN1412*, a novel superagonist anti-CD28 monoclonal antibody that directly stimulates T cells.

Within 90 minutes after receiving a single intravenous dose…all six volunteers had a systemic inflammatory response…*rapid induction of proinflammatory cytokines…headache, myalgias, nausea, diarrhea, erythema, vasodilatation, and hypotension. *Within 12 to 16 hours they became critically ill…

All six patients survived."

***N Engl J Med* 2006;355:1018-1028**

Preclinical models did not predict the risk of this reaction!

The NEW ENGLAND JOURNAL of MEDICINE

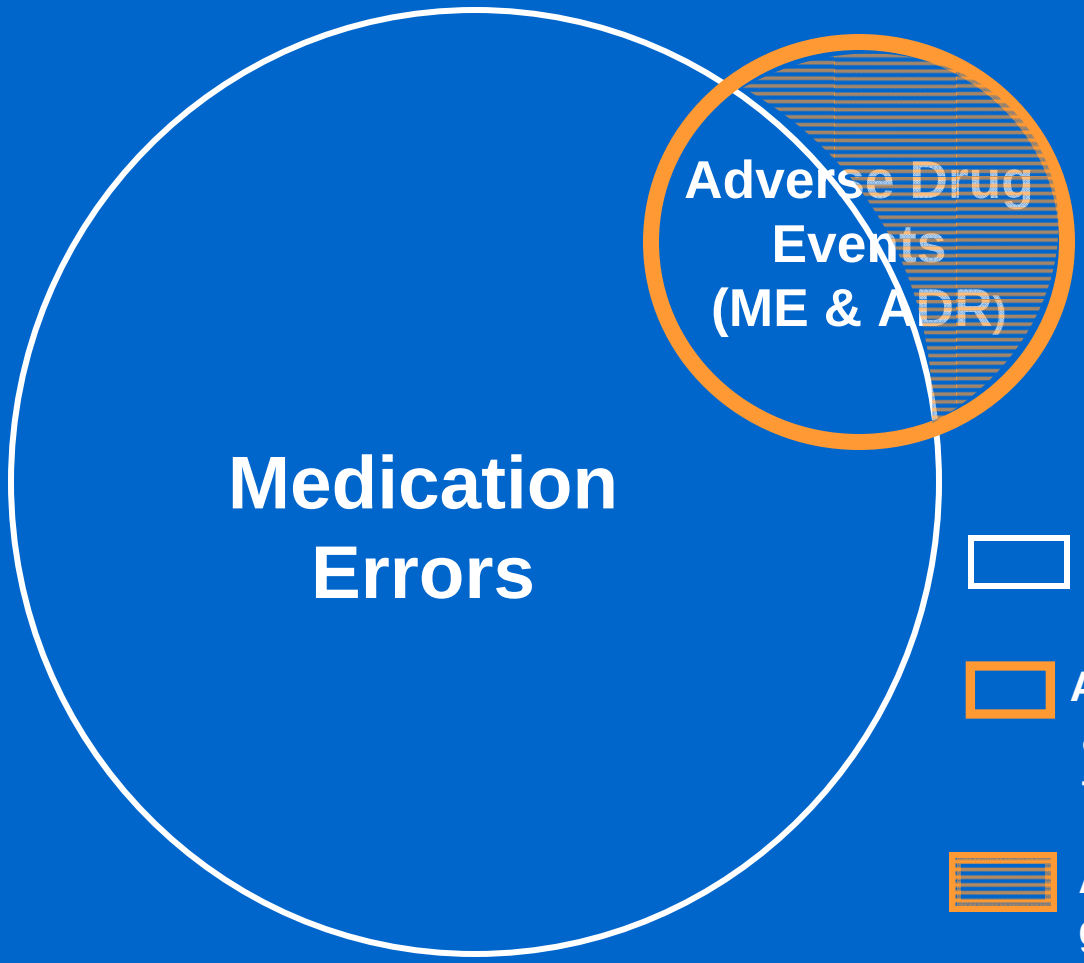
BRIEF REPORT

Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

Ganesh Suntharalingam, F.R.C.A., Meghan R. Perry, M.R.C.P.,
Stephen Ward, F.R.C.A., Stephen J. Brett, M.D., Andrew Castello-Cortes, F.R.C.A.,
Michael D. Brunner, F.R.C.A., and Nicki Panoskaltsis, M.D., Ph.D.

N Engl J Med 2006;355:1018-28

ADVERSE DRUG EVENTS*



MEDICATION ERROR: preventable ADE plus near misses

ADVERSE DRUG EVENT: preventable & unpredictable events with harm to the patient

ADVERSE DRUG REACTION: generally unpredictable ADE

* From Bates DW, et al. J Gen Intern Med 1995;10:199-205.

CHARACTERISTICS OF MOST ADRs*

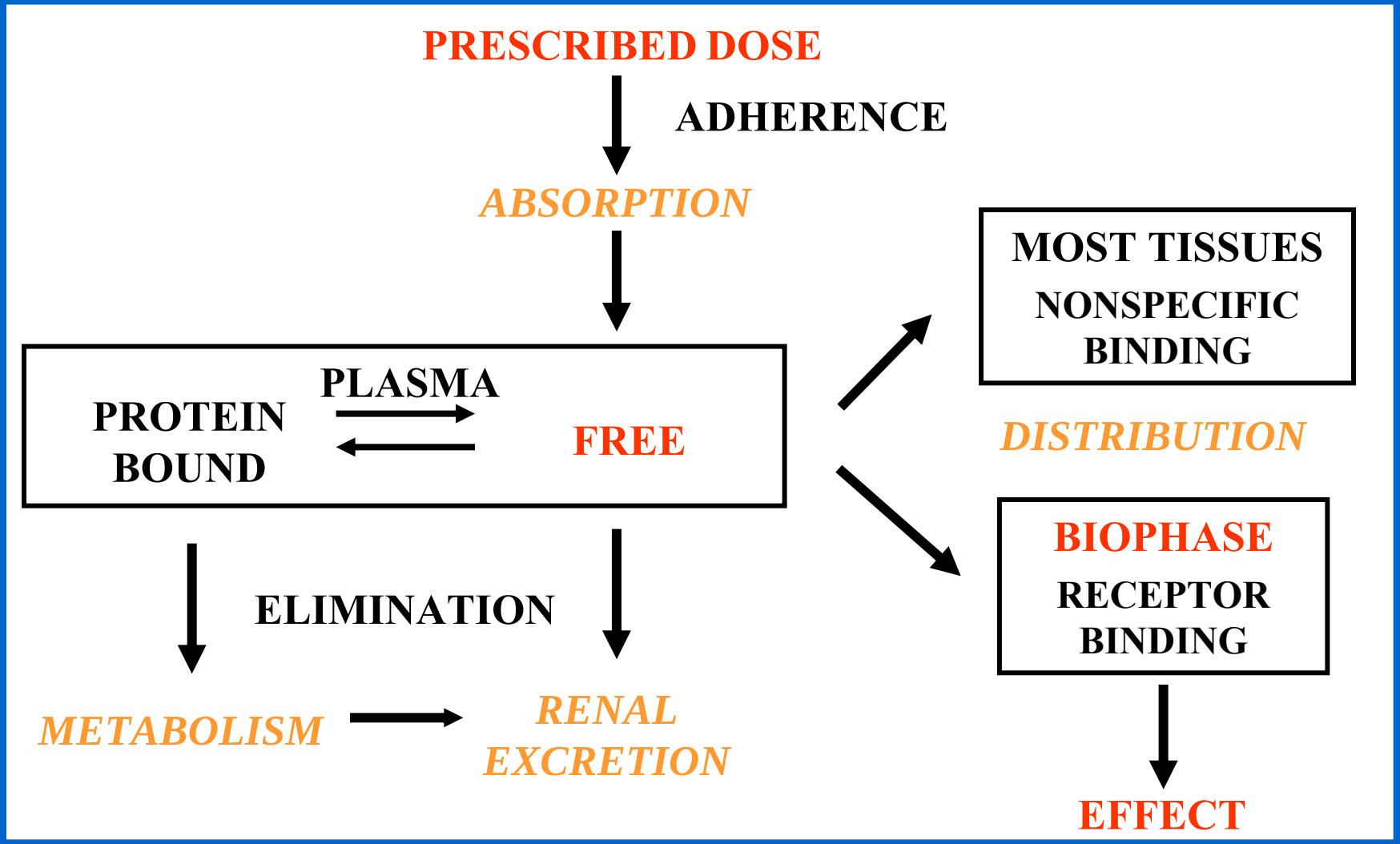
- MOST *NOT* CAUSED BY NEW DRUGS
- MOST *NOT* IDIOSYNCRATIC REACTIONS
- ~ 80% *ARE* RELATED TO DRUG DOSE

* Melmon KL. N Engl J Med 1971;284:1361-8.

“Target concentration” strategy

- **Based on observed *individual variation in drug exposure (AUC)* when “standard” doses are prescribed.**
- **Attempts to *“individualize” therapy* when therapeutic and toxic ranges of drug concentrations in plasma have been established.**

RATIONALE FOR PLASMA LEVEL MONITORING



*NONCANCER DRUGS CAUSING ADR'S**

PHENYTOIN**	**CARBAMAZEPINE****
PREDNISONE	**CODEINE**
DIGOXIN**	**LITHIUM****
AMIODARONE	**THEOPHYLLINE****
ASPIRIN**	**DESIPRAMINE****
CO-TRIMOXAZOLE	**DEXAMETHASONE**
PENTAMIDINE	**GENTAMICIN****

* **1988 NMH Data (*Clin Pharmacol Ther* 1996;60:363-7)**

** **DRUGS FOR WHICH *PLASMA LEVELS ARE AVAILABLE***

Interindividual Variation in Drug Exposure (AUC)

Karim A et al, 2007

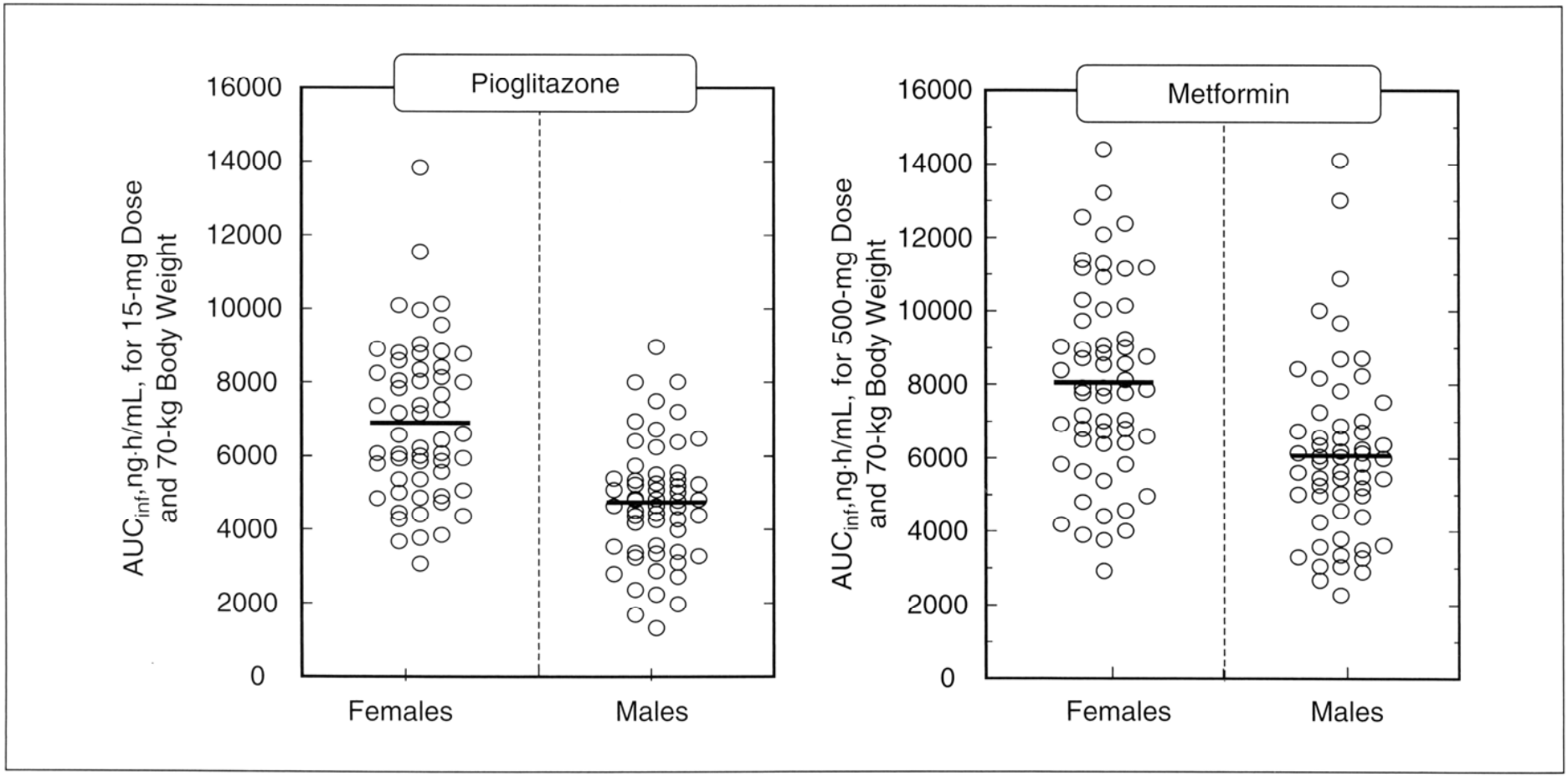


Figure 3. Body weight– and dose-adjusted arithmetic mean (—) and individual values for pioglitazone (left panel) and metformin (right panel) AUC_{∞} in females and males following single oral doses of commercial pioglitazone (15 mg) and metformin (500 mg or 850 mg) tablets given together to young healthy subjects.

INCIDENCE OF ADRs*

IN HOSPITALIZED PATIENTS

All severities	10.9 %
Serious	2.1 %
Fatal	0.2 %

AS CAUSE OF HOSPITAL ADMISSION

Serious	4.7 %
Fatal	0.13 %

* Lazarou J, et al. JAMA 1998;279:1200-05.

ATTENTION FOCUSED ON MEDICAL ERRORS

"TO ERR IS HUMAN:

BUILDING A SAFER HEALTH SYSTEM"

Committee on Quality of Health Care in America
Institute of Medicine

www.nap.edu/reading room (2000).

Development and Evaluation of New Drugs

- **Drug discovery**
- **Pre-clinical and clinical evaluation**
- **Subjects of *Module 5* in our course**

MEDICINES "DISCOVERED" BY CLINICAL INVESTIGATORS

***NEW INDICATION*:**

ALLOPURINOL (Gout) - *RW Rundles*

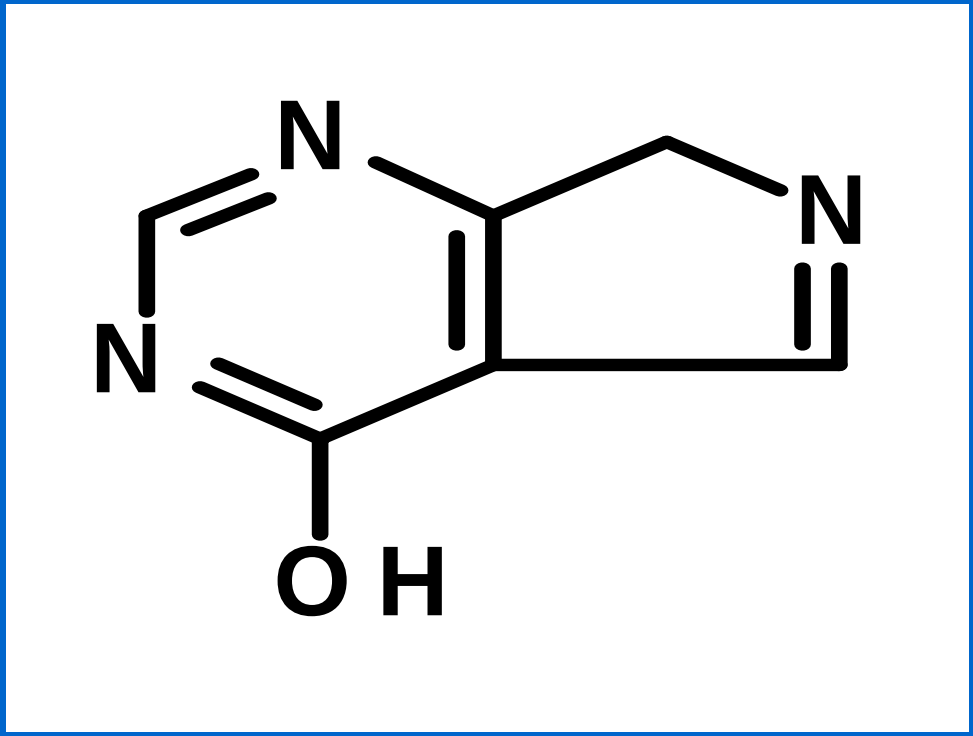
***ENDOGENOUS COMPOUND*:**

DOPAMINE (Shock) - *LI Goldberg*

***DRUG METABOLITE*:**

FEXOFENADINE (Antihistamine) -
RL Woosley at al.

ALLOPURINOL*



* Rundles RW, Metz EN, Silberman HR. Ann Intern Med 1966;64:229-57.

MEDICINES "DISCOVERED" BY CLINICAL INVESTIGATORS

***NEW INDICATION*:**

ALLOPURINOL (Gout) - *RW Rundles*

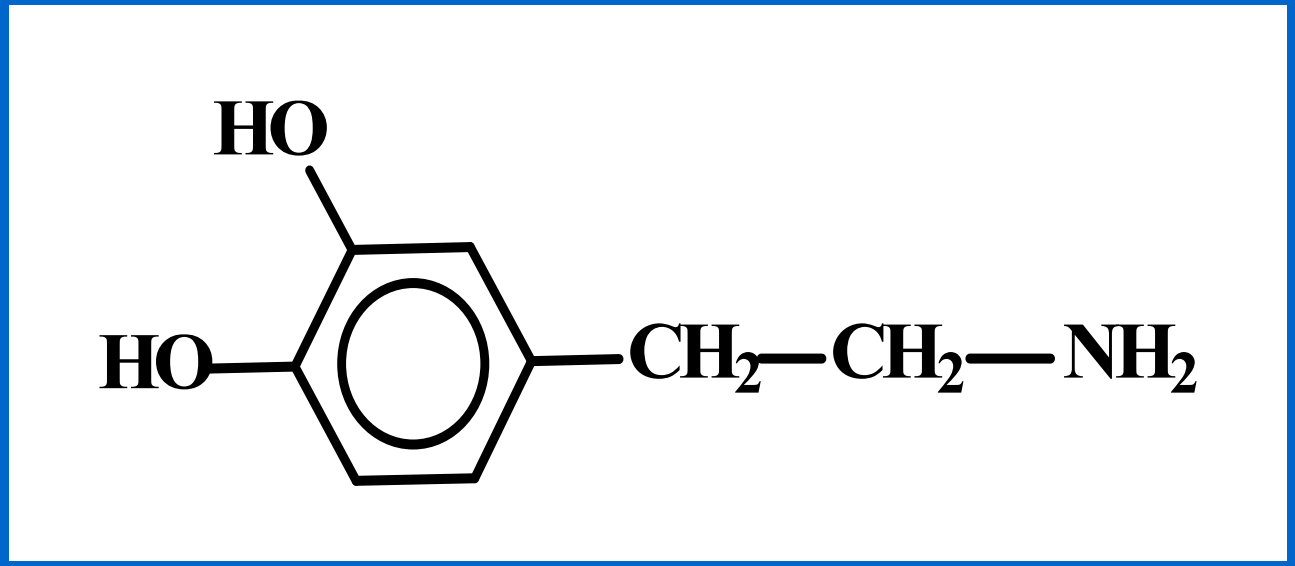
***ENDOGENOUS COMPOUND*:**

DOPAMINE (Shock) - *LI Goldberg*

***DRUG METABOLITE*:**

FEXOFENADINE (Antihistamine) -
RL Woosley et al.

DOPAMINE*



*Goldberg LI. Pharmacol Rev 1972;24:1-29.

MEDICINES "DISCOVERED" BY CLINICAL INVESTIGATORS

***NEW INDICATION*:**

ALLOPURINOL (Gout) - *RW Rundles*

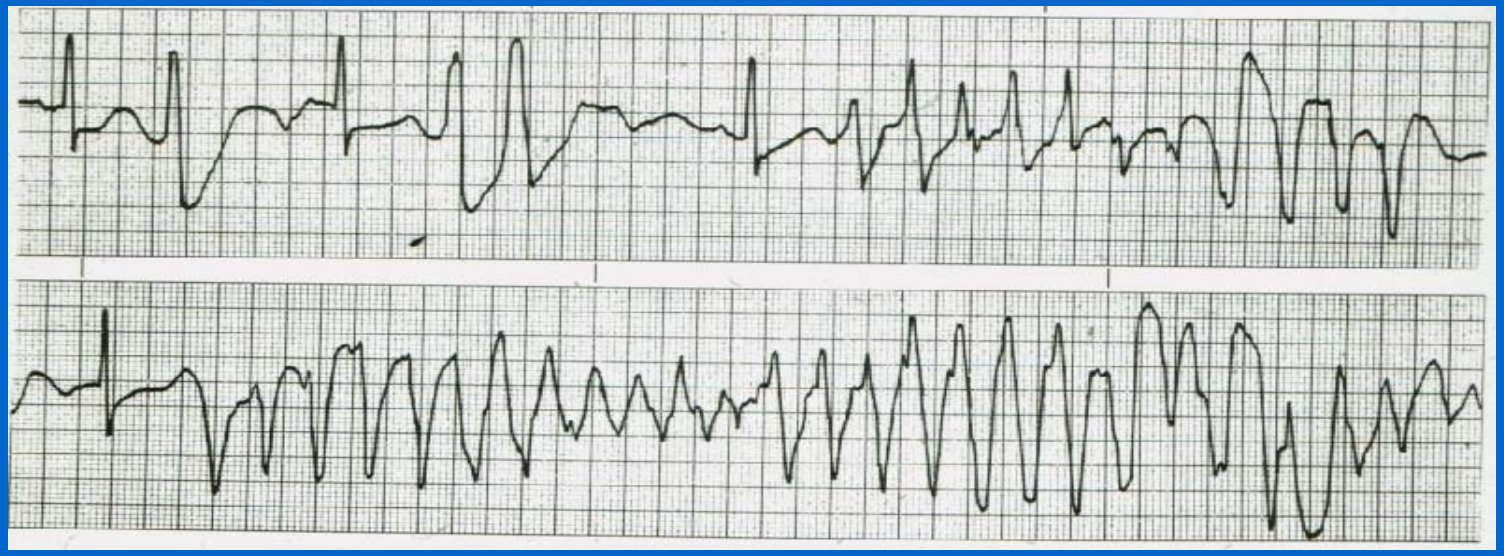
***ENDOGENOUS COMPOUND*:**

DOPAMINE (Shock) - *LI Goldberg*

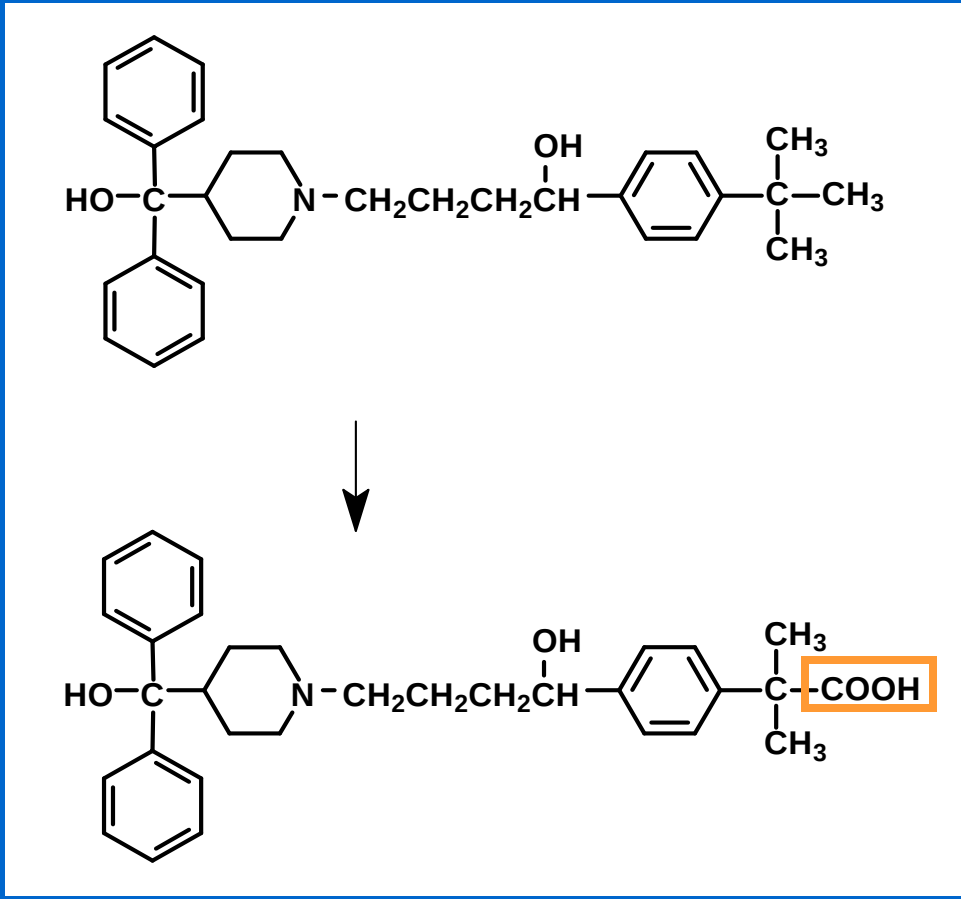
***DRUG METABOLITE*:**

FEXOFENADINE (Antihistamine) -
RL Woosley et al.

TORSADES DE POINTES



TERFENADINE METABOLISM*



TERFENADINE
(SELDANE)

TERFENADINE CARBOXYLATE
(ALLEGRA)

*** From Woosley RL, et al. JAMA 1993;269:1532-6.**

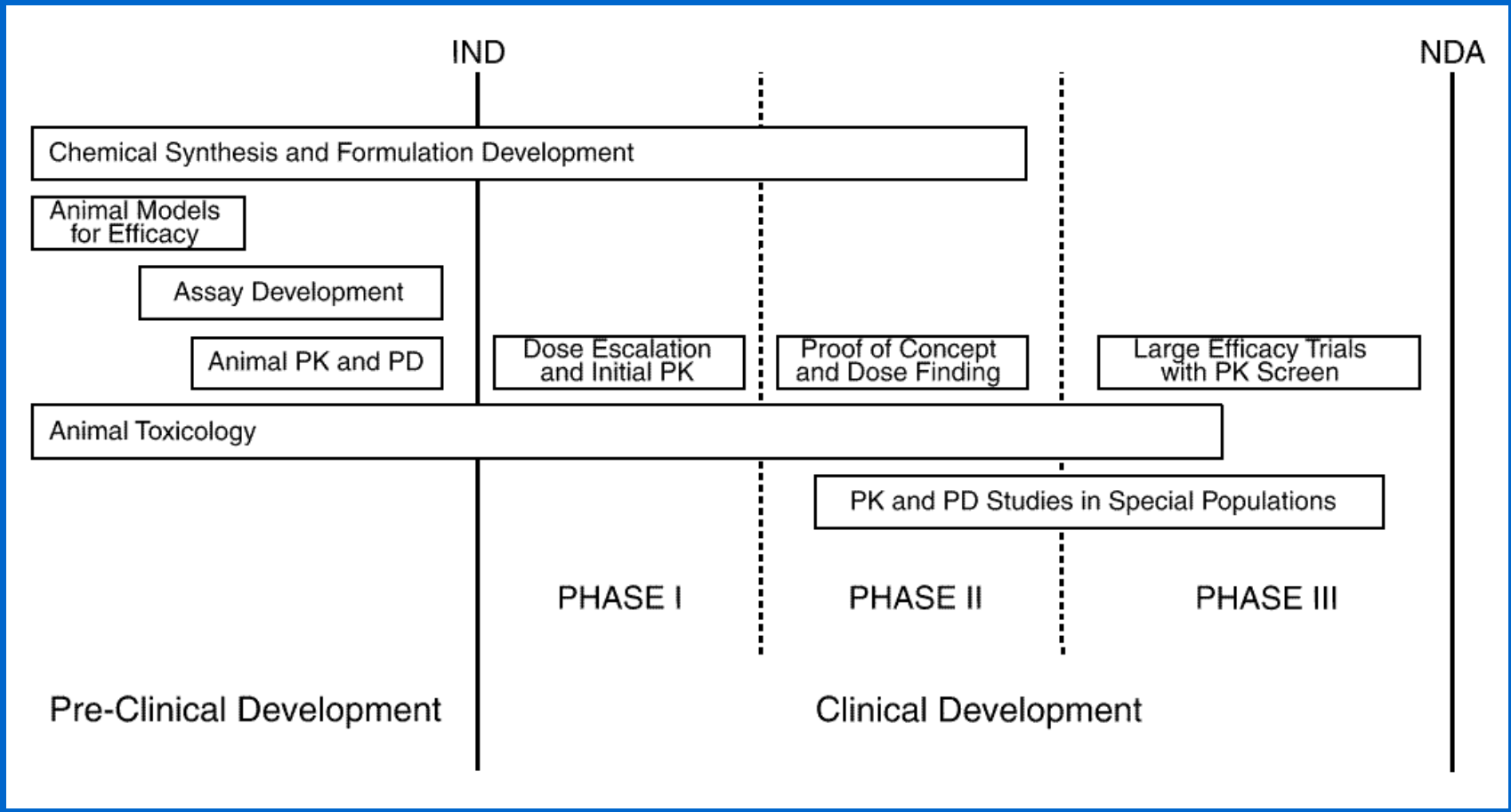
DRUG DEVELOPMENT COST PER APPROVED DRUG*

	COST ($ x 10^6)†	
	OUT-OF-POCKET	CAPITALIZED
TOTAL COSTS	403	802
CLINICAL COSTS (% TOTAL)	274 (68%)	453 (56%)

† BASED ON 21.5% SUCCESS RATE

* DiMasi JA, et al. J Health Econ 2003;22:151-85.

PHASES OF PRE-MARKETING DRUG DEVELOPMENT



Introduction to Pharmacokinetics

- **This will be the subject of *Module 1* in our course.**
- ***Essential* for integration of material in subsequent course modules.**

PHARMACOKINETICS

The *QUANTITATIVE ANALYSIS* of the *TIME COURSE* of DRUG

ABSORPTION,
DISTRIBUTION,
METABOLISM, and
EXCRETION

PHARMACOKINETICS

Because it is *quantitative*, pharmacokinetics is of necessity *mathematical*

DRUG DOSE SELECTION

TRADITIONAL:

Look up "usual" dose in PDR
Memorize "usual" dose

IMPROVED:

***Individualize* dosing**

Apply pharmacokinetics and the *"target concentration strategy"*

Introduction to Clearance

- ***Clearance*** **is a "primary" parameter in the pharmacokinetic analysis of drug distribution and elimination.**

- **Understanding the concept of clearance is *essential* for drug evaluation and use in clinical medicine.**

CREATININE CLEARANCE EQUATION

$$CL_{Cr} = \frac{U \times V}{P}$$

U = URINE CONCENTRATION

V = URINE VOLUME / TIME

P = PLASMA CONCENTRATION

CREATININE CLEARANCE REVISITED

RATE OF APPEARANCE OF Cr IN URINE (dE/dt):

$$dE/dt = CL_{Cr} \times P$$

RATE OF CHANGE OF Cr IN BODY (dX/dt):

$$dX/dt = I - CL_{Cr} \times P$$

AT STEADY STATE:

$$P = I / CL_{Cr}$$

I = RATE OF CREATININE SYNTHESIS

STEADY STATE CONCENTRATION

***CONTINUOUS CREATININE SYNTHESIS*:**

$$C_{SS} = \frac{I}{CL_{Cr}}$$

***CONTINUOUS DRUG INFUSION*:**

$$C_{SS} = \frac{I}{CL_{E}}$$

COCKCROFT & GAULT EQUATION*

$$CL_{Cr} = \frac{(140 - \text{age})\,(\text{weight in kg})}{72\,(\text{serum Cr in mg/dL})}$$

[reduce estimate by 15% for women]

* Cockroft DW, Gault MH: Nephron 1976;16:31-41.

COCKCROFT & GAULT EQUATION

$$CL_{Cr} = \frac{I}{P}$$

$$CL_{Cr} = \frac{(140 - \text{age})\ (\text{weight in kg})}{72\ (\text{serum Cr in mg/dL})}$$

[reduce estimate by 15% for women]

Terms in red estimate creatinine synthesis rate.

RENAL FUNCTION IN PATIENTS *TOXIC* FROM *DIGOXIN**

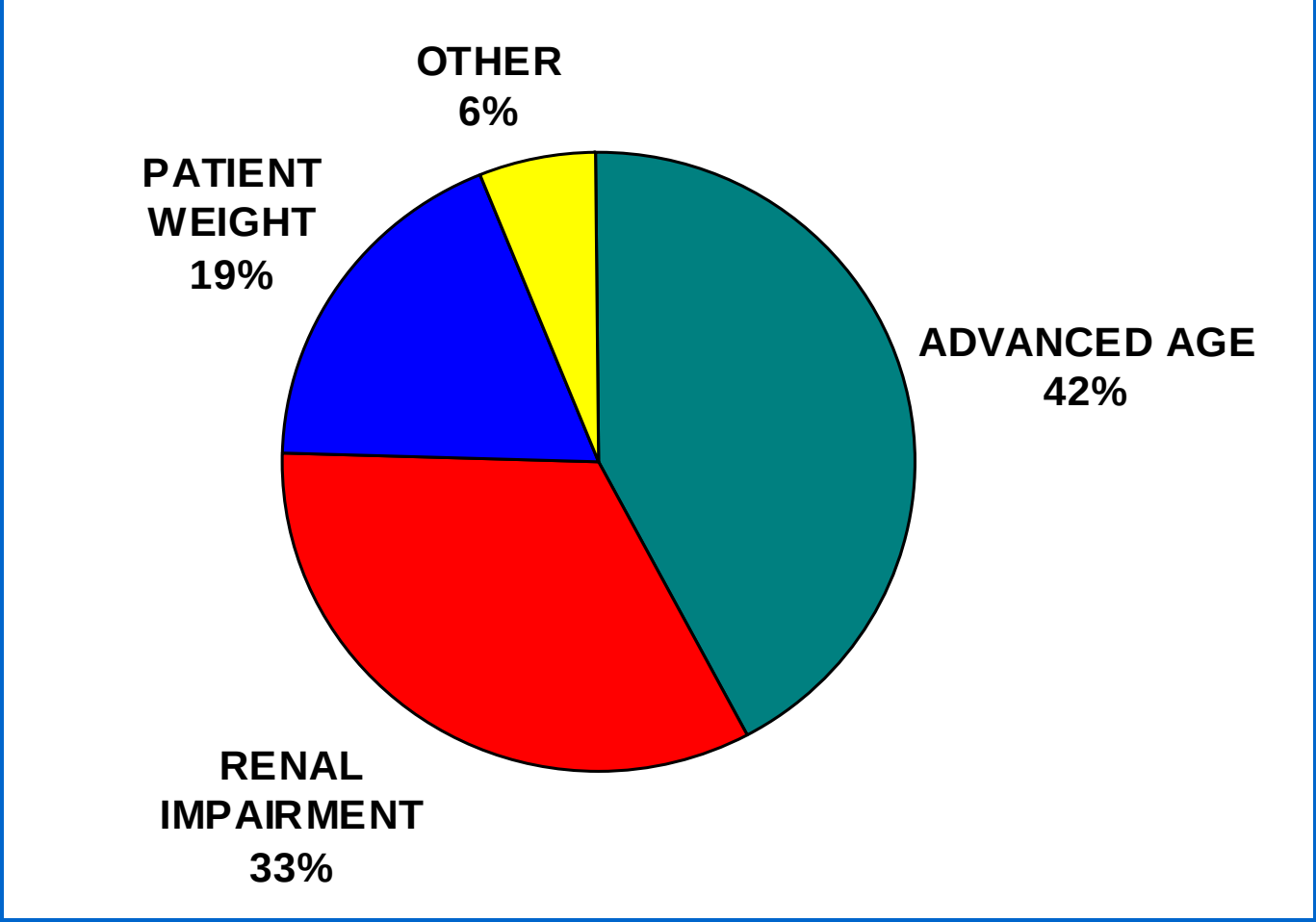
SERUM Cr (mg %)	Cl_{Cr} (mL/min) ≥ 50	< 50	
≤ 1.7	4	19	52%
> 1.7	0	21	48%

* From Piergies AA, et al. Clin Pharmacol Ther 1994;55:353-8.

ESTIMATED Cl_{Cr}

- ***ESSENTIAL*** **for safe and effective use of *renally* eliminated drugs**
- **Important *PREREQUISITE* for application of pharmacokinetic principles**
- **Need to automate - *BUT*:**
  - **Laboratory system often does not "talk" with patient database**
  - **Patients often not weighed**

PATHOPHYSIOLOGIC FACTORS *NOT ACCOUNTED FOR* IN DRUG DOSING*



* Lesar TS, Briceland L, Stein DS. JAMA 1997;277:312-7.