Principles of Clinical Pharmacology

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National Institutes of Health
Clinical Center
September 2, 2010

Principles of Clinical Pharmacology
Remote Sites 2010 - 2011

Cincinnati's Children's Hospital Medical Center
Duke University Medical Center, Durham
University of California, Los Angeles
Harbor-UCLA Medical Center, Los Angeles
Akron's Children Hospital
Cummings School of Veterinary Medicine
at Tufts University, North Grafton
Wayne State University, Detroit

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Remote Sites 2010-2011

University of Pennsylvania, Philadelphia

University of North Carolina, Chapel Hill

Walter Reed Army Institute of Research and USUHS, Silver Spring, Maryland

University of Iowa, Iowa City

Eli Lilly and Company, Indianapolis

Johnson and Johnson, San Diego

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International Sites 2010-2011

JSS University,
Mysore, India

University of Sao Paolo,
San Paolo, Brazil

National Academy of Medicine,
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Dong-A Medical College
Busan, South Korea

Inha University Hospital
Incheon, South Korea

Instituto Nacional de Enfermedades Neoplasicas (INEN), Lima, Peru

Erasmus University Medical Center
Rotterdam, The Netherlands

Principles of Clinical Pharmacology

Remote Sites 2010-2011

NCI - Frederick, Maryland

NIA - Baltimore, Maryland

NIDA - Baltimore, Maryland

COURSE MODULES

MODULE 1: Pharmacokinetics

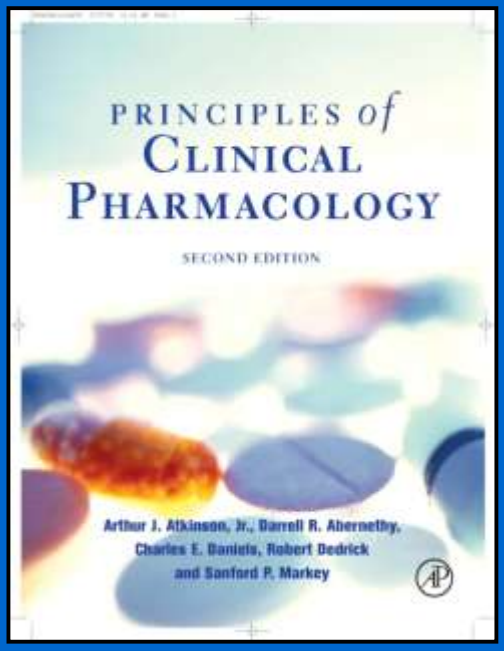
MODULE 2: Drug metabolism and Transport

MODULE 3: Assessment of Drug Effects

MODULE 4: Optimizing and Evaluating Therapy

MODULE 5: Drug Discovery and Development

RECOMMENDED TEXT



PHARMACOLOGY

The study of *drugs* and *biologics* and their actions in *living organisms*

Drugs: "small molecules", chemicals

Biologics: "large molecules", peptides, antibodies

CLINICAL PHARMACOLOGY

THE STUDY OF DRUGS IN HUMANS

CAREER GOALS OF CLINICAL PHARMACOLOGISTS

- Optimize understanding and use of existing medicines
- Discover, develop and evaluate new medicines
- Define the basis for variability in therapeutic and toxic responses to medicines

Dose – Response Relationship

- A central tenet of pharmacology
- The careful study of “drug exposure – response” relationships is central to finding “the right dose” for a given therapeutic indication
- “Exposure – response” applies to both drug efficacy and toxicity

COURSE FOCUS

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

"Introduction" Lecture Outline

- Historical overview
- The problem of adverse drug reactions (ADRs)
- Drug discovery and development
- Variability in drug responses
- 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

John Jacob Abel

"Father of American Pharmacology"

- **First fulll-time Professor in Materia Medica and Therapeutics at the University of Michigan (1891)**
- **Founder , "Journal of Pharmacology and Experimental Therapeutics" (1896)**

John Jacob Abel

Crystallization of insulin

Research on tetanus toxin

Study of the phthaleins

Invention of the artificial kidney (vividialysis or vividiffusion)

OSWALD SCHMIEDEBERG
1838 - 1921

Oswald Schmiedeberg

Professor of Pharmacology at Strassbourg (1872)

Pioneer studies on autonomic nervous system, nicotine, muscarine

Chloroform blood levels

RUDOLPH BUCHEIM
1820 - 1879

Rudolph Bucheim

Professor at the University of Dorpat (now Tartu, Estonia) (1847-1867).

Established the first experimental pharmacology laboratory in search for proof of drug actions.

LACK OF IMPORTANCE ATTACHED TO DRUG THERAPY

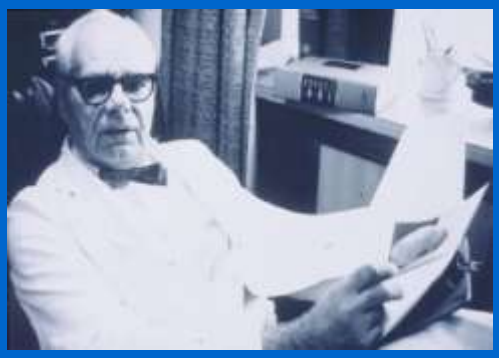
"Fortunately a surgeon who uses the wrong side of the scalpel cuts his own fingers and not the patient; if the same applied to drugs they would have been investigated very carefully a long time ago."

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	**EUROPE**
HARRY GOLD	**PAUL MARTINI**
WALTER MODELL	

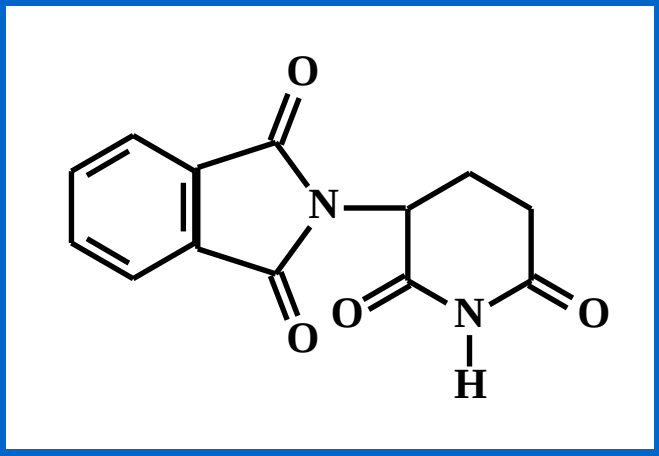
Drug Toxicity
Adverse Drug Reactions

- **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.**

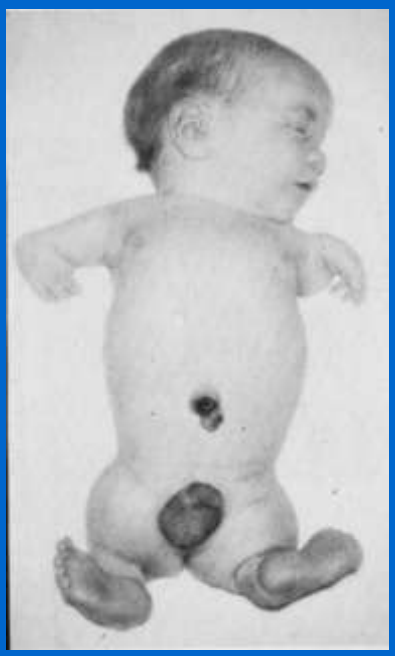
SERIOUS ADR

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

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.

A recent example - Cytokine Storm (1)

"**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.

N Engl J Med 2006;355:1018-1028

A recent example - Cytokine Storm (2)

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**

A recent example – Cytokine storm (3)

Preclinical models did not predict the risk of this reaction!

Problem of simultaneous dosing in 6 volunteers (first-in-human dosing)

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

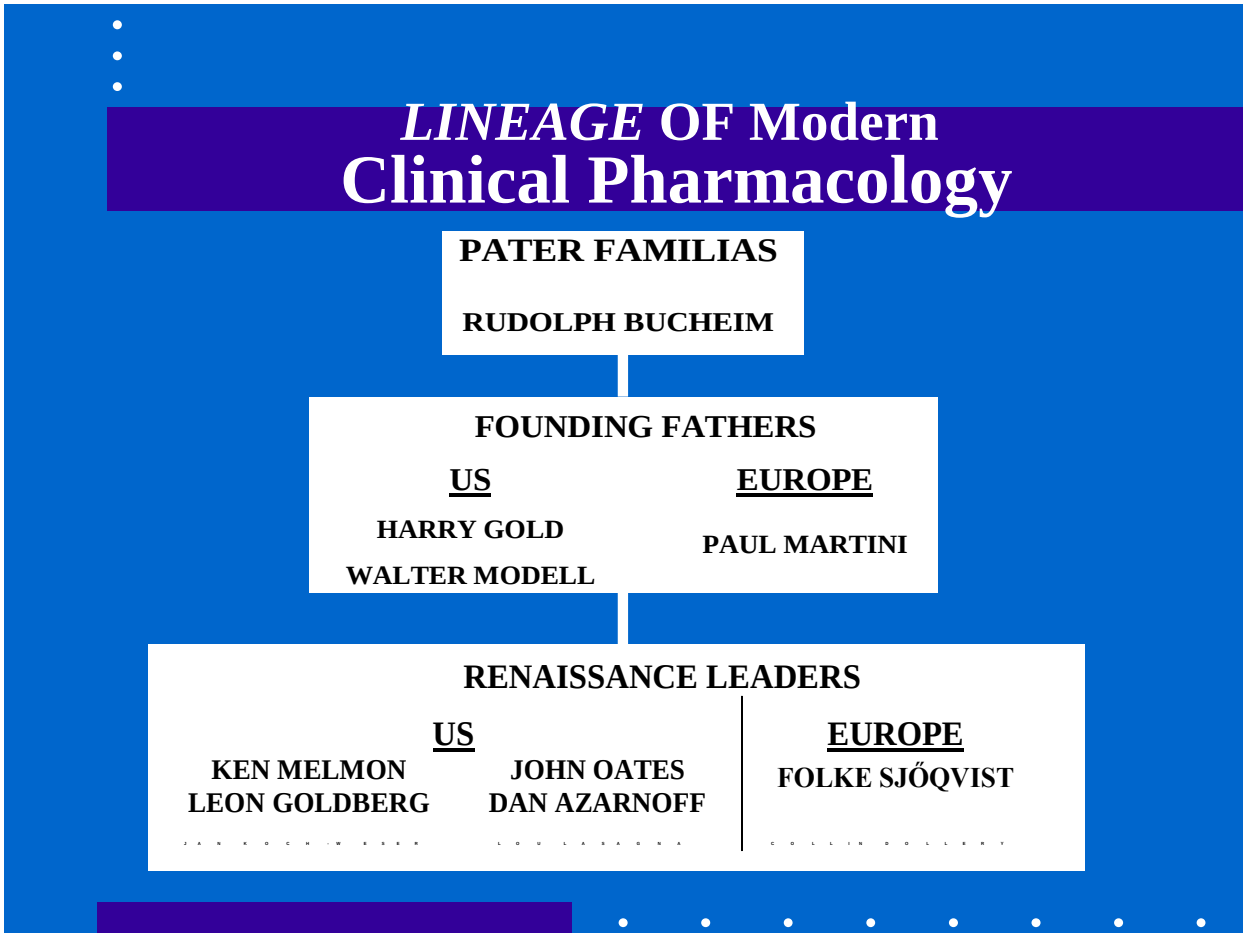
Cytokine Storm in a Phase 1 Trial of the Anti-CD28 Monoclonal Antibody TGN1412

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

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**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EUROPE
PAUL MARTINI
RENAISSANCE LEADERS
US
KEN MELMON
LEON GOLDBERG
JOHN OATES
DAN AZARNOFF
EUROPE
FOLKE SJŐQVIST

HISTORY OF CLINICAL PHARMACOLOGY

Albert Sjoerdsma, M.D., Ph.D.

Experimental Therapeutics Branch

National Heart Institute (1958-1971)

Lou Gillespie, John Oates, Leon Goldberg, Richard Crout, Ken Melmon

Serotonin, carcinoid syndrome, antidepressant drugs

Pheochromocytoma, antihypertensive drugs

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

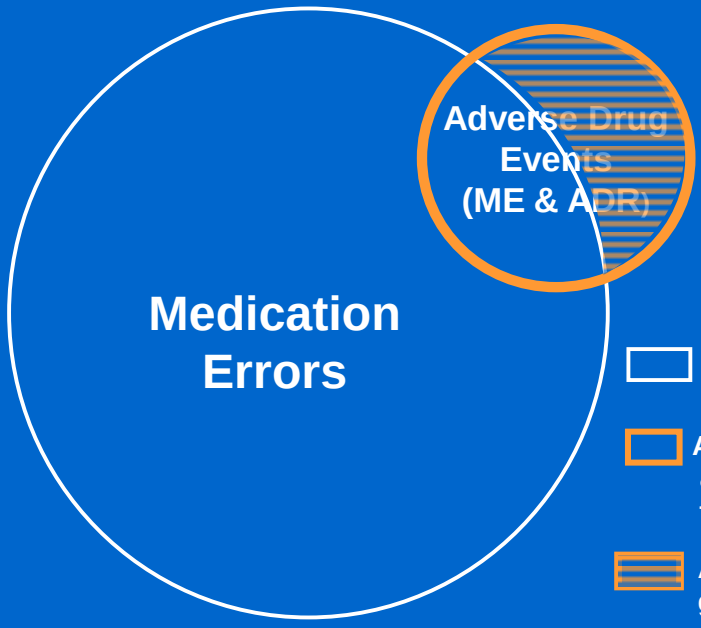
WHO:

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

CONTEMPORARY VIEW:

***Unpredictable* Adverse Drug Events**

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*

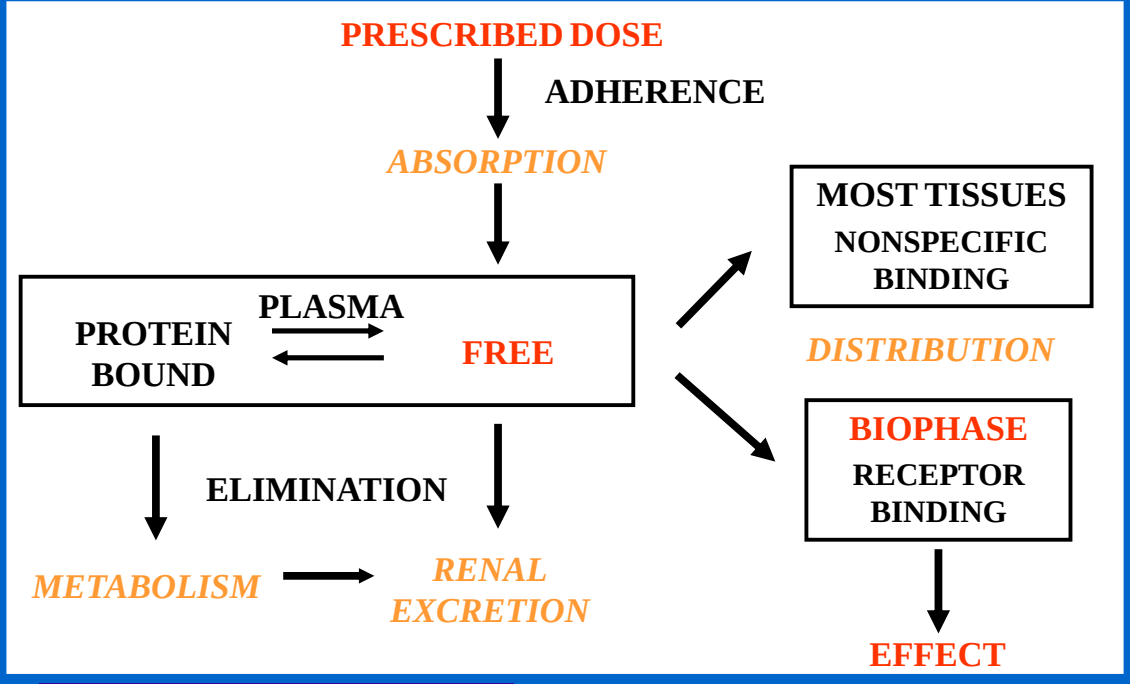
- **MOST *NOT* CAUSED BY NEW DRUGS**
- **MOST *NOT* IDIOSYNCRATIC REACTIONS**
- **~ 80% *ARE* RELATED TO DRUG DOSE**

*** 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*

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*

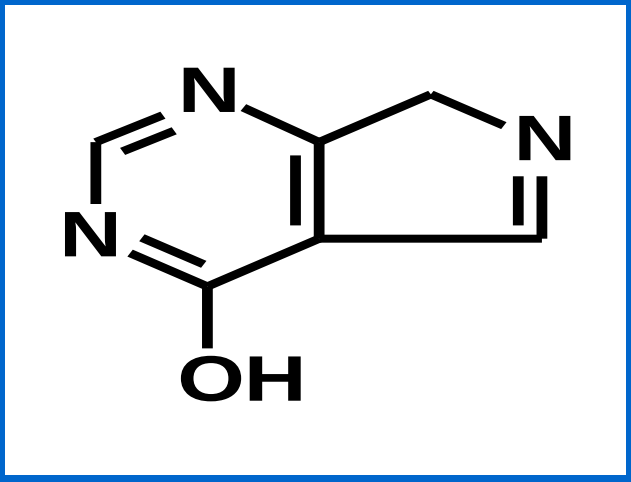
***ENDOGENOUS COMPOUND*:**

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.

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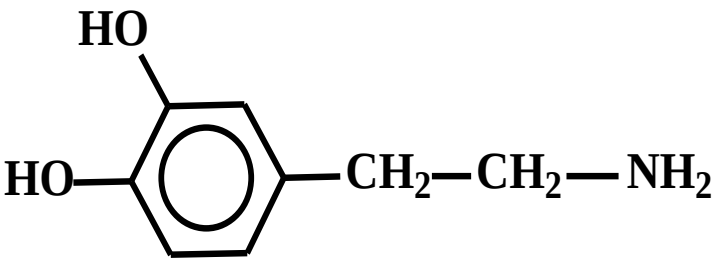

*Goldberg LI. Pharmacol Rev 1972;24:1-29.

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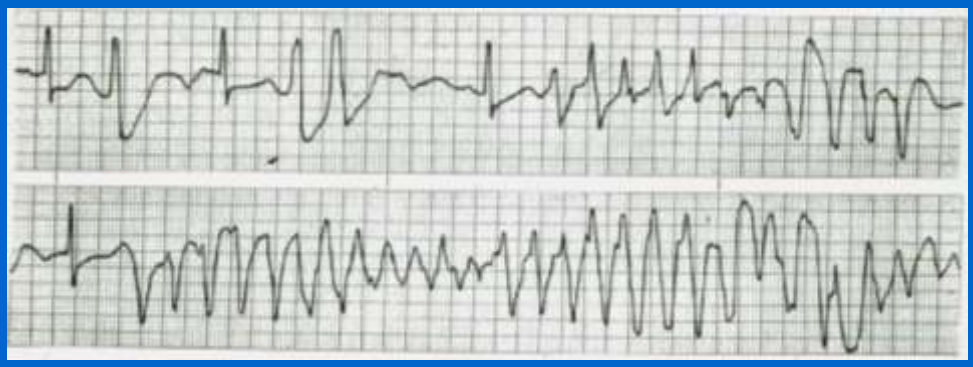
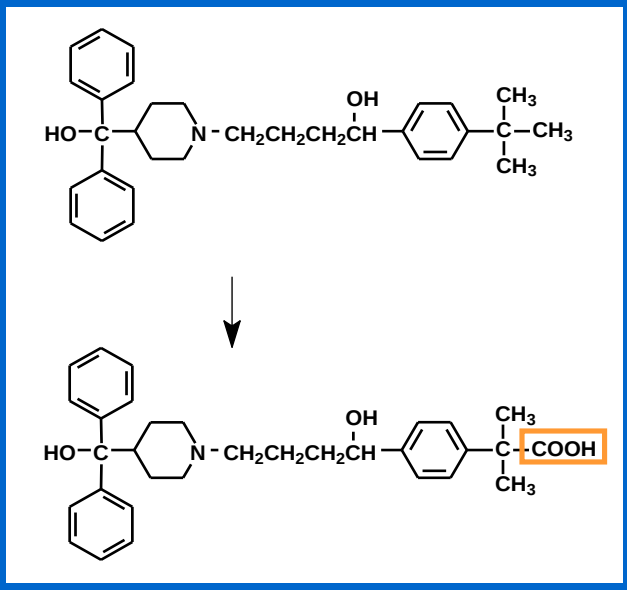
TORSADES DE POINTES



TERFENADINE METABOLISM*



TERFENADINE

(SELDANE)

TERFENADINE CARBOXYLATE

(ALLEGRA)

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

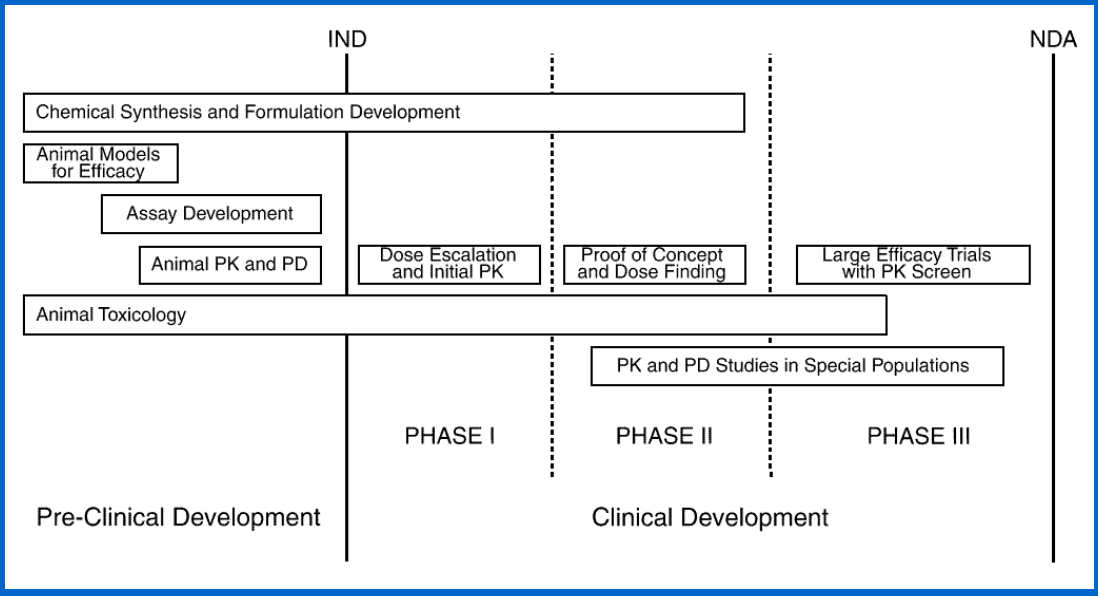
DRUG DEVELOPMENT COST PER APPROVED DRUG*

	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



Phases of Drug Development

"Learn and Confirm" Paradigm

Phase I and II: The learning phases.

Phase III: The confirmatory phase.

Phase IV: Postmarketing - learning continues with focus on ADRs and special populations if required.

Variability in Drug Response

- **Pharmacokinetic (PK) basis**
- **Pharmacodynamic (PD) basis**

Both PK and PD variability may be due to *genetic* and/or *environmental* factors

Interindividual Variation in Drug Exposure (AUC)

Karim A et al, 2007

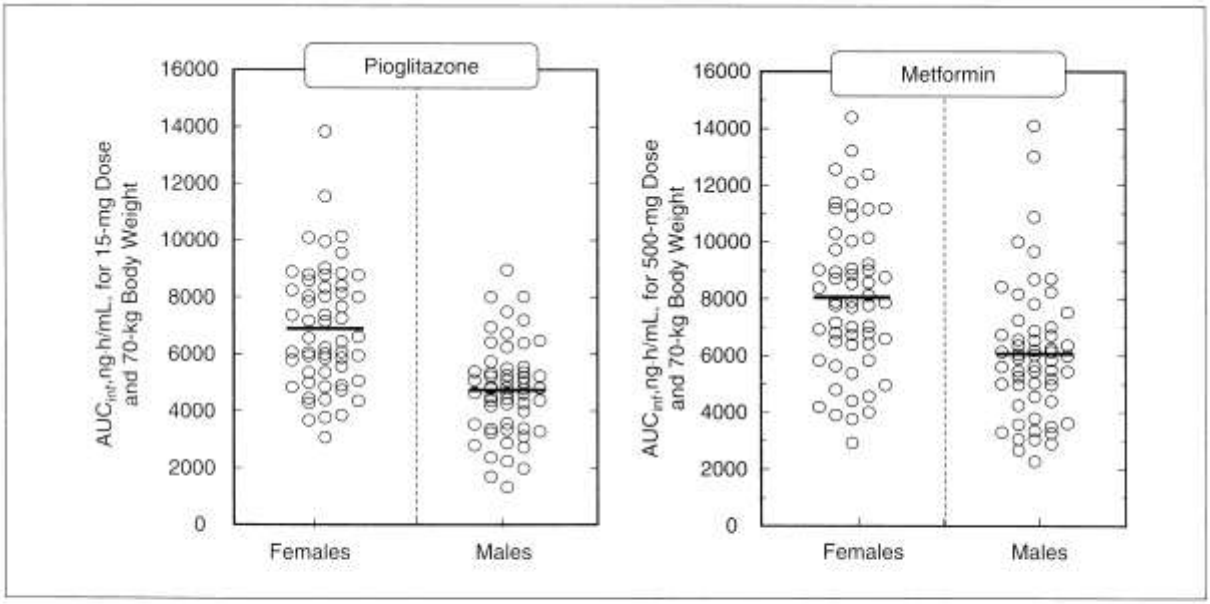
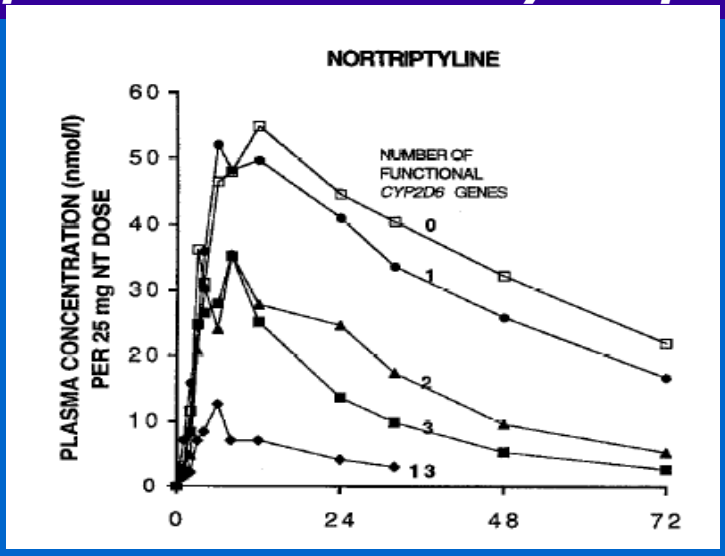


Figure 3. Body weight– and dose-adjusted arithmetic mean (—) and individual values for pioglitazone (left panel) and metformin (right panel) AUC_{inf} in females and males following single oral doses of commercial pioglitazone (15 mg) and metformin (500 mg or 850 mg) tablets given together to young healthy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

Cytochrome P450 2D6

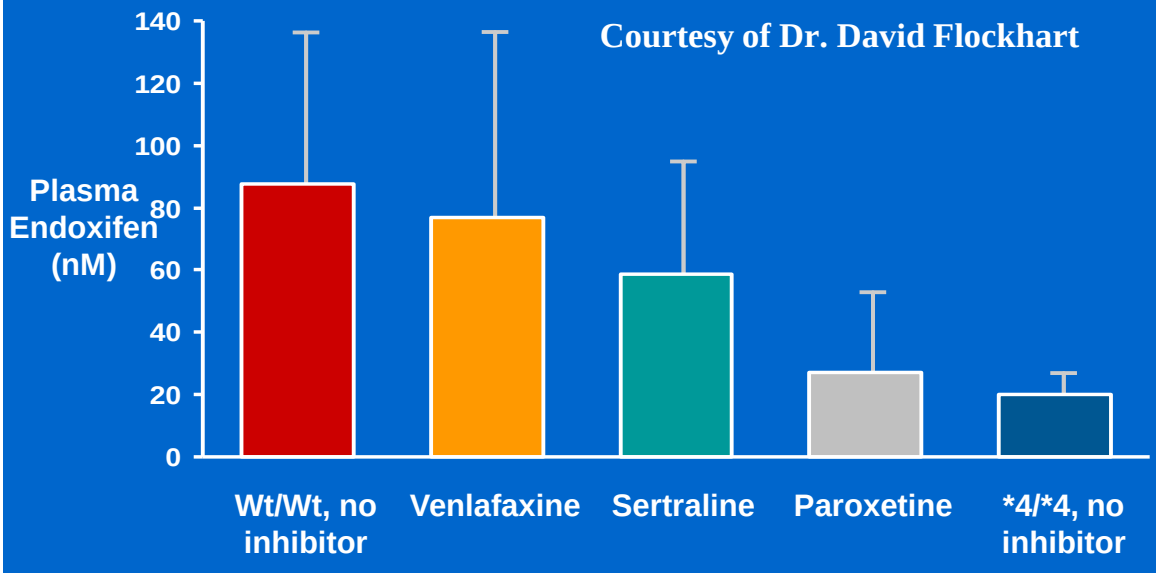
- Absent in 7% of Caucasians
- Hyperactive in up to 30% of East Africans
- Catalyzes primary metabolism of:
  - propafenone
  - codeine
  - β-blockers
  - tricyclic antidepressants
  - tamoxifen
  - **Inhibited** by: quinidine, paroxetine, sertraline, venlafaxine

Nortriptyline Drug Exposure
Impact of CYP2D6 Polymorphism



Dalen P *et al. Clin Pharmacol Ther* 1998;63:444-452

CYP2D6 and Endoxifen Concentrations



Jin Y et al: J Natl Cancer Inst 97:30, 2005

Genetics and Severe Drug Toxicity

HLA-B*5701

Abacavir hypersensitivity

Flucoxacillin liver injury (DILI)

HLA-B*1502

Carbamazepine-induced

Stevens-Johnson syndrome

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.

MDRD Study Equation

- Modification of Diet in Renal Disease (MDRD)
- This equation (many versions) provides an estimate of glomerular filtration rate (eGFR)
- To be discussed in lecture on PK alterations in renal disease

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

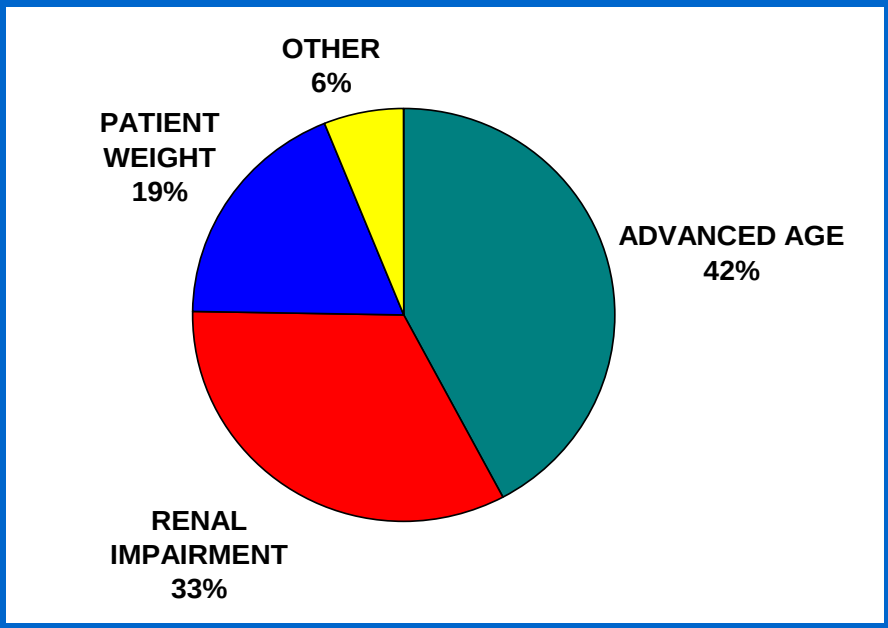
SERUM Cr (mg %)	Cl_{Cr} (mL/min) ≥ 50	< 50	
≤ 1.7	4	19	52%
> 1.7	0	21	48%

* 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.