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# *Principles of Clinical Pharmacology*

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**Director**  
**Clinical Pharmacology Program**

**Office of Clinical Research Training  
and Medical Education  
National Institutes of Health  
Clinical Center  
September 3, 2009**

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***Principles of Clinical Pharmacology***  
**Remote Sites 2009 - 2010**

**Cincinnati's Children's Hospital Medical Center  
Duke University Medical Center, Durham  
University of California, Los Angeles  
Harbor-UCLA Medical Center, Los Angeles  
Hoffman-La Roche, Inc., Nutley, NJ  
Indiana University-Purdue University,  
Indianapolis  
Howard University, Washington DC**



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*Principles of Clinical Pharmacology*

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**Johnson & Johnson, Titusville, NJ**

**Johnson & Johnson, San Diego, CA**

**Johnson & Johnson, Wayne, PA**

**University of Pennsylvania, Philadelphia, PA**

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



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**International Remote Sites 2009-2010**

**Dong-A Medical College**

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**Hospital Nacional Arzobispo Loayza,**

**Lima, Peru**



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# *Principles of Clinical Pharmacology*

**Remote Sites 2009-2010**

**NCI - Frederick, Maryland**

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## **COURSE MODULES**

**MODULE 1: Pharmacokinetics**

**MODULE 2: Drug metabolism and Transport**

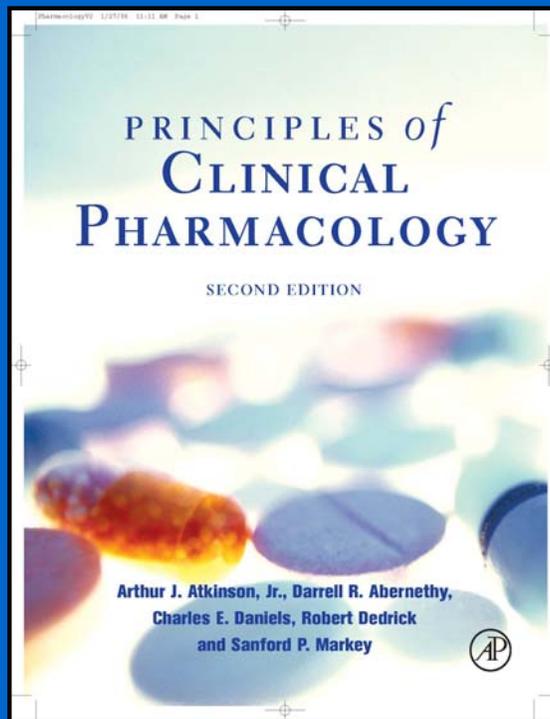
**MODULE 3: Assessment of Drug Effects**

**MODULE 4: Optimizing and Evaluating Therapy**

**MODULE 5: Drug Discovery and Development**



RECOMMENDED  
TEXT



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# PHARMACOLOGY

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

*Drugs: “small molecules”, chemicals*

*Biologics: “large molecules”,  
peptides, antibodies*

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# CLINICAL PHARMACOLOGY

*THE STUDY OF DRUGS IN  
HUMANS*

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## **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**
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## COURSE FOCUS

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

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## **“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**
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# Historical Overview

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



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**JOHN JACOB ABEL**  
1857 - 1938



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# OSWALD SCHMIEDEBERG

1838 - 1921



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# RUDOLPH BUCHEIM

1820 - 1879



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## 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*

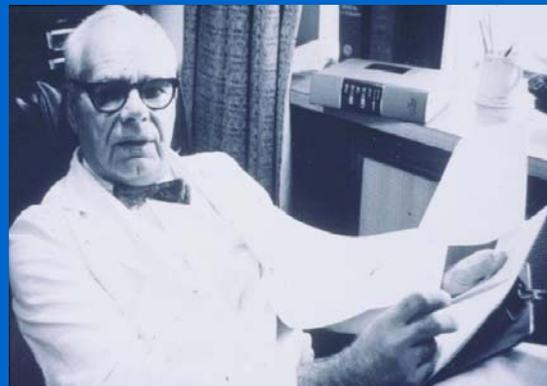
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## FOUNDERS OF AMERICAN CLINICAL PHARMACOLOGY



*HARRY GOLD*



*WALTER MODELL*

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## Partial List of GOLD and MODELL Accomplishments

1937 – Introduced Double-Blind Clinical Trial Design \*

1939 – Initiated *Cornell Conference on Therapy*

1953 – Analyzed 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.

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# *LINEAGE* of Modern Clinical Pharmacology

**PATER FAMILIAS**

**RUDOLPH BUCHEIM**

**FOUNDING FATHERS**

**US**

**HARRY GOLD**

**WALTER MODELL**

**EUROPE**

**PAUL MARTINI**

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# 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.
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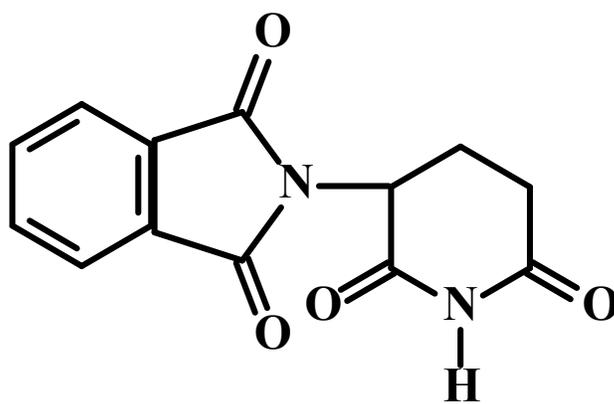
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## SERIOUS ADR

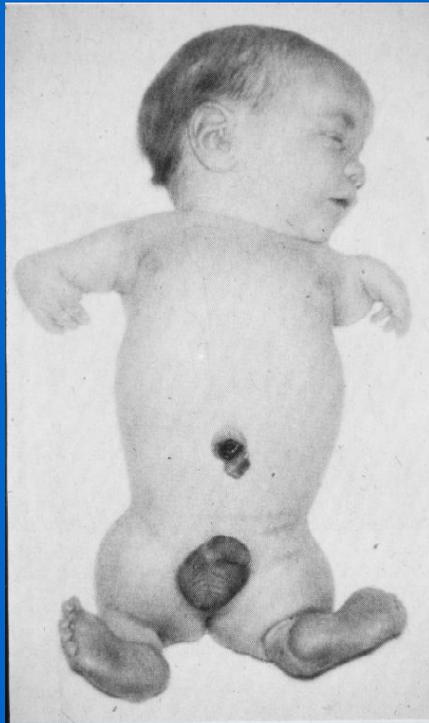
A *SERIOUS ADVERSE DRUG REACTION* is an adverse drug reaction (ADR) that *requires or prolongs hospitalization, is permanently disabling or results in death.*

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# THALIDOMIDE



# PHOCOMELIA



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## Drug Exposure “in utero”

- The problem of  
“Drug Therapy in Pregnant and  
Nursing Women”  
Covered in *Module 4* in our course.

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## 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.

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## 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

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## 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*

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## **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)**

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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*

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## 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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# *LINEAGE* OF Modern Clinical Pharmacology

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**WALTER MODELL**

**EUROPE**

**PAUL MARTINI**

**RENAISSANCE LEADERS**

**US**

**KEN MELMON  
LEON GOLDBERG  
JAN KOCH-WESER**

**JOHN OATES  
DAN AZARNOFF  
LOU LASAGNA**

**EUROPE**

**FOLKE SJÓQVIST  
COLLIN DOLLERY**

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## 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
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## ADVERSE DRUG REACTIONS

### WHO:

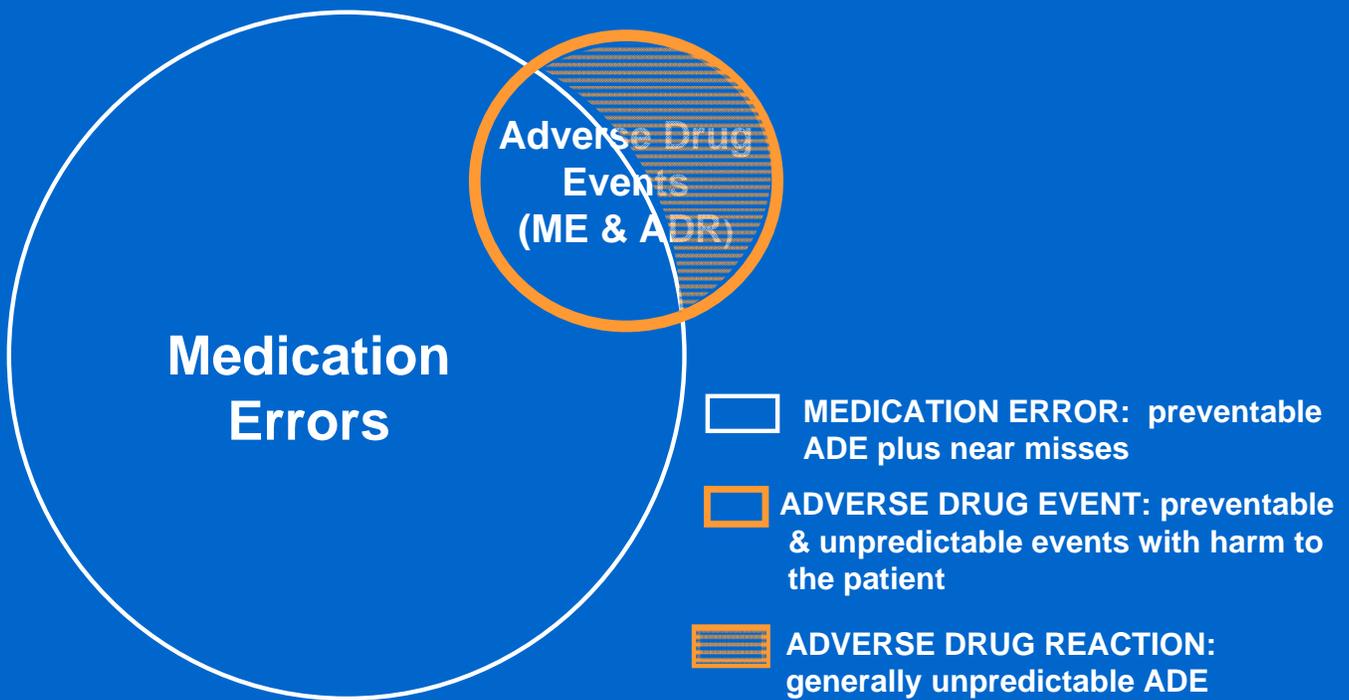
*Any untoward reaction to a drug*

### CONTEMPORARY VIEW:

*Unpredictable Adverse Drug Events*

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# ADVERSE DRUG EVENTS\*



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

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## 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.

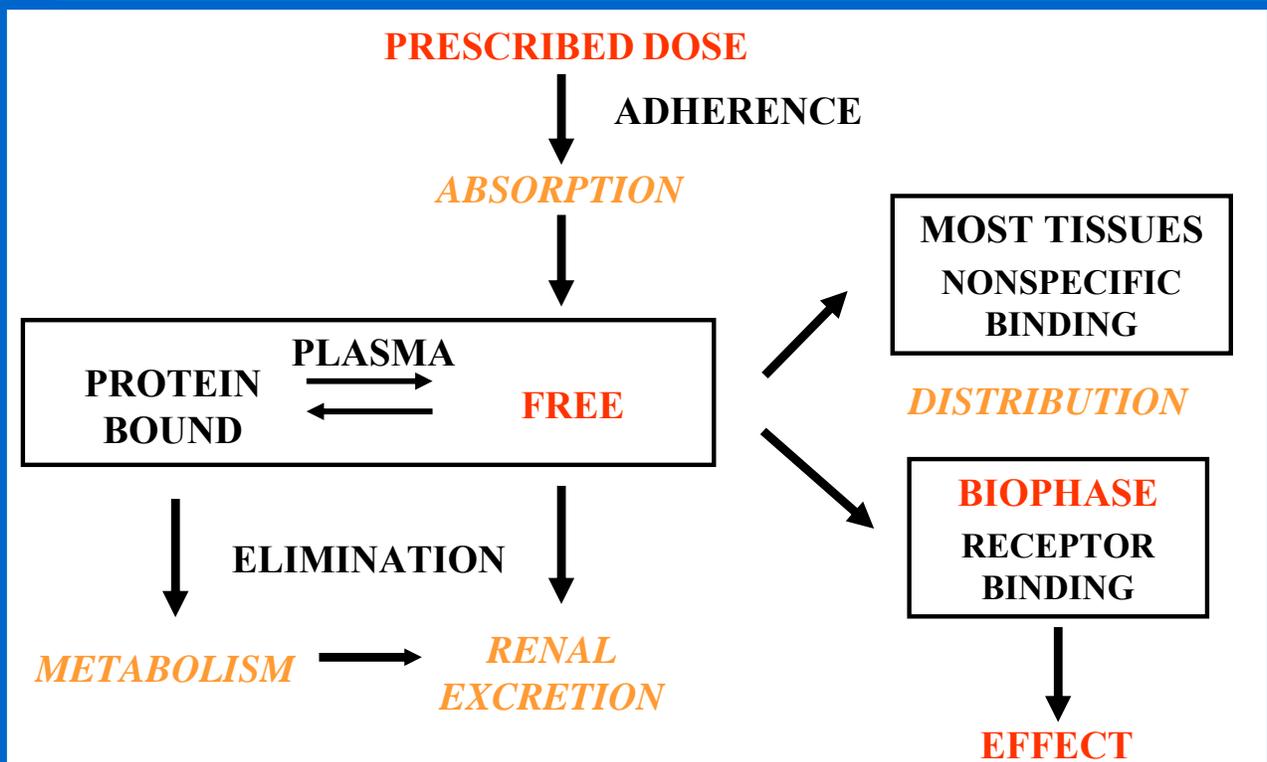
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## “Target concentration” strategy

- 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.
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# RATIONALE FOR PLASMA LEVEL MONITORING



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## ***NONCANCER DRUGS CAUSING ADR'S\****

**PHENYTOIN\*\***

**PREDNISON**

**DIGOXIN\*\***

**AMIODARONE**

**ASPIRIN\*\***

**CO-TRIMOXAZOLE**

**PENTAMIDINE**

**CARBAMAZEPINE\*\***

**CODEINE**

**LITHIUM\*\***

**THEOPHYLLINE\*\***

**DESIPRAMINE\*\***

**DEXAMETHASONE**

**GENTAMICIN\*\***

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

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

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## **INCIDENCE OF ADRs\***

### **IN HOSPITALIZED PATIENTS**

<b>All severities</b>	<b>10.9 %</b>
<b>Serious</b>	<b>2.1 %</b>
<b>Fatal</b>	<b>0.2 %</b>

### **AS CAUSE OF HOSPITAL ADMISSION**

<b>Serious</b>	<b>4.7 %</b>
<b>Fatal</b>	<b>0.13 %</b>

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

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**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](http://www.nap.edu/reading room) (2000).**

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## Development and Evaluation of New Drugs

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

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## MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

### NEW INDICATION:

ALLOPURINOL (Gout) - *RW Rundles*

### ENDOGENOUS COMPOUND:

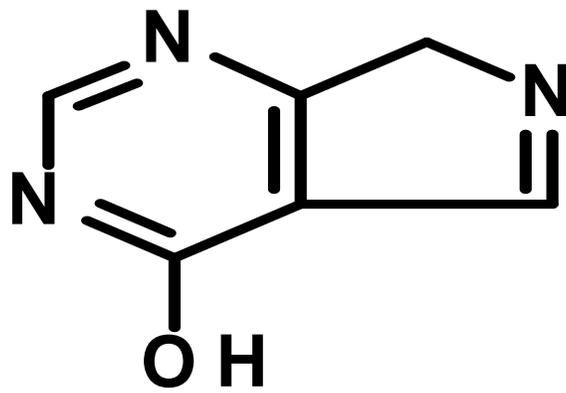
DOPAMINE (Shock) - *LI Goldberg*

### DRUG METABOLITE:

FEXOFENADINE (Antihistamine) -  
*RL Woosley at al.*

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# ALLOPURINOL\*



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

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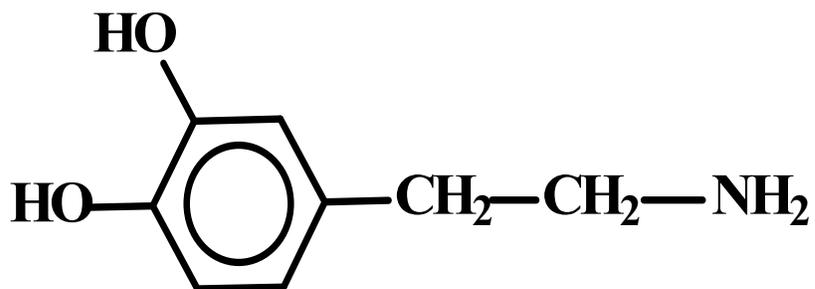
DOPAMINE (Shock) - *LI Goldberg*

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FEXOFENADINE (Antihistamine) -  
*RL Woosley et al.*

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# DOPAMINE\*



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

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## MEDICINES “DISCOVERED” BY CLINICAL INVESTIGATORS

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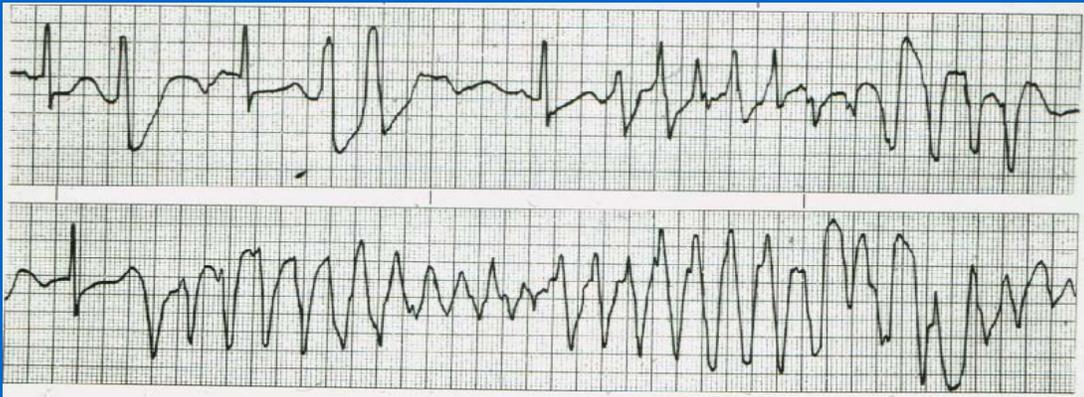
DOPAMINE (Shock) - *LI Goldberg*

### DRUG METABOLITE:

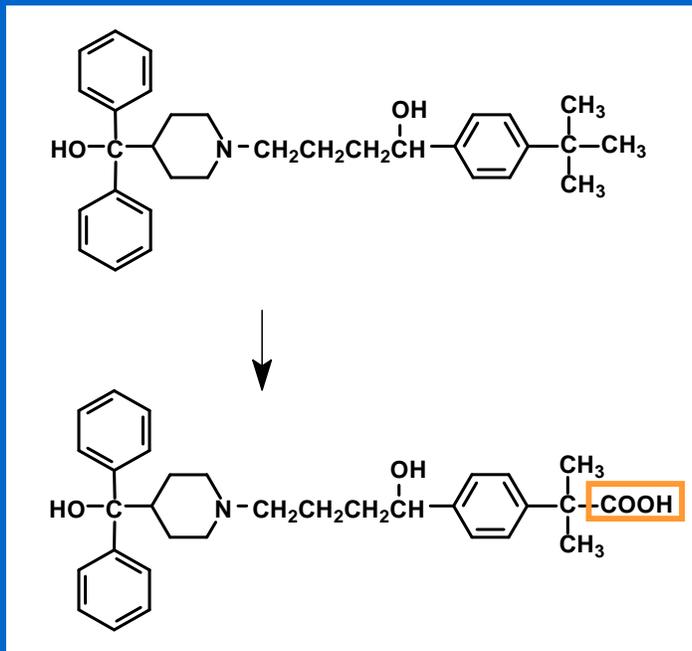
FEXOFENADINE (Antihistamine) -  
*RL Woosley et al.*

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# TORSADES DE POINTES



# TERFENADINE METABOLISM\*



TERFENADINE  
(SELDANE)

TERFENADINE  
CARBOXYLATE  
(ALLEGRA)

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

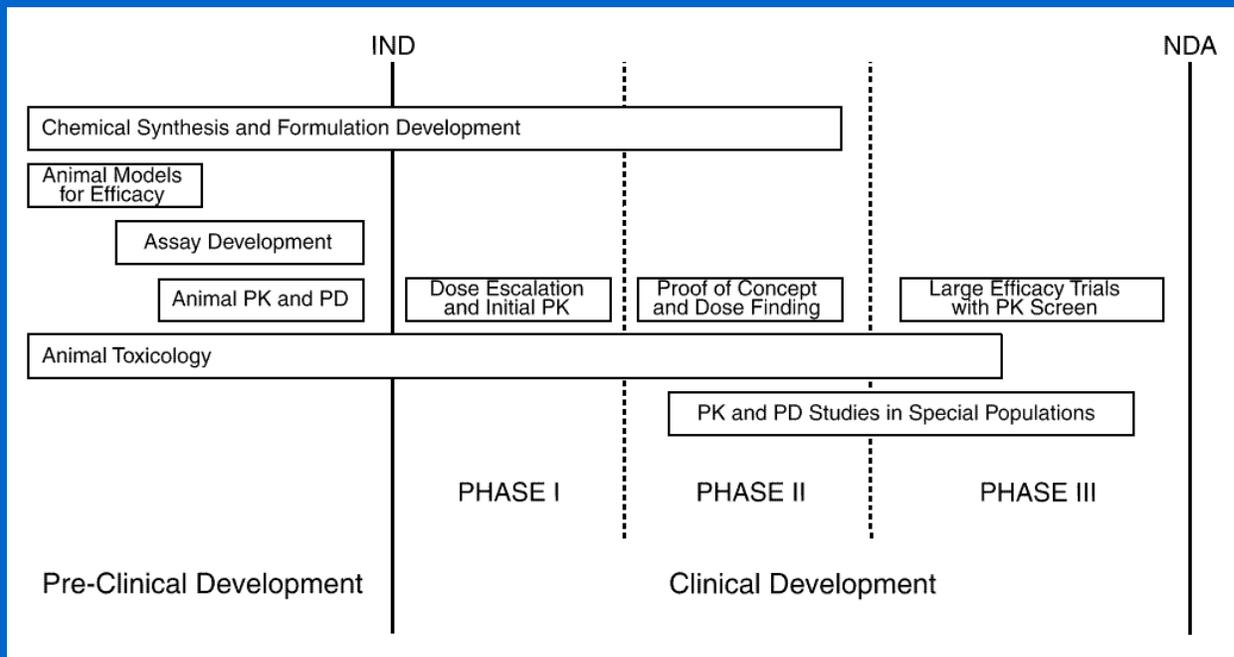
## DRUG DEVELOPMENT COST PER APPROVED DRUG\*

	COST (\$ x 10 <sup>6</sup> ) <sup>†</sup>	
	OUT-OF-POCKET	CAPITALIZED
TOTAL COSTS	403	802
CLINICAL COSTS (% TOTAL)	274 (68%)	453 (56%)

<sup>†</sup> BASED ON 21.5% SUCCESS RATE

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

# PHASES OF PRE-MARKETING DRUG DEVELOPMENT



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## Variability in Drug Response

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

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

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# Interindividual Variation in Drug Exposure (AUC)

Karim A et al, 2007

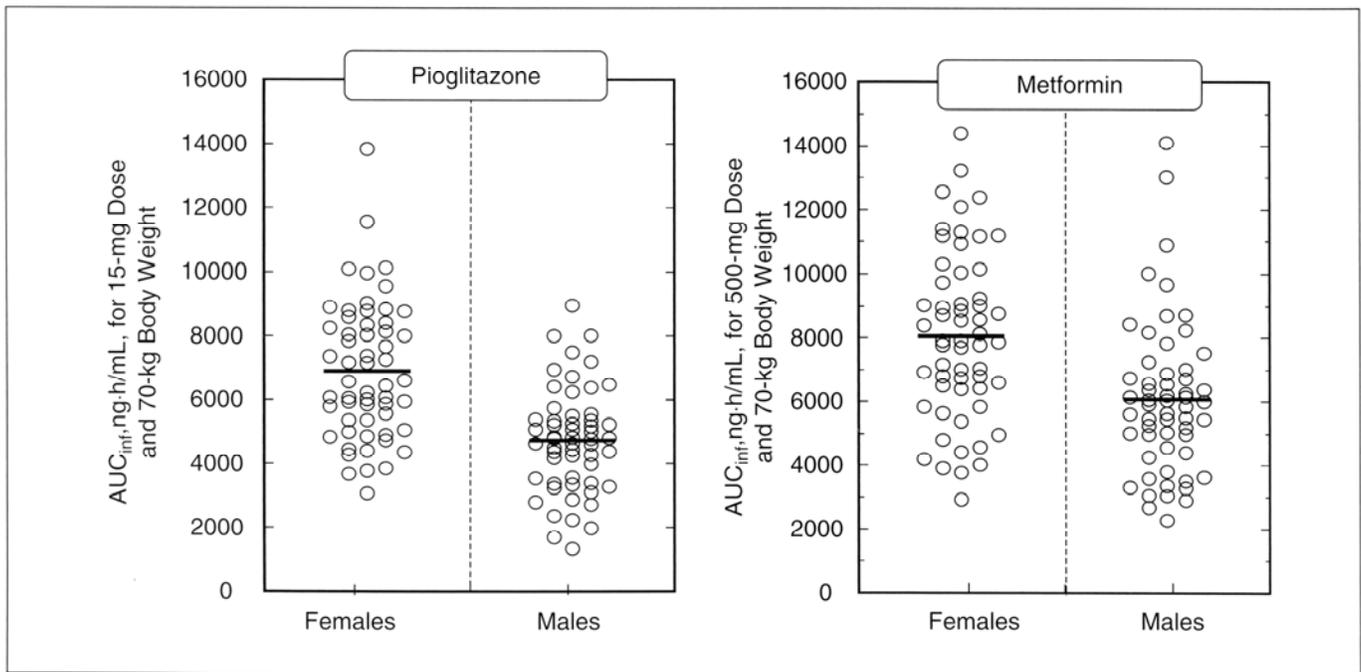


Figure 3. Body weight- and dose-adjusted arithmetic mean (—) and individual values for pioglitazone (left panel) and metformin (right panel) AUC<sub>inf</sub> in females and males following single oral doses of commercial pioglitazone (15 mg) and metformin (500 mg or 850 mg) tablets given together to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

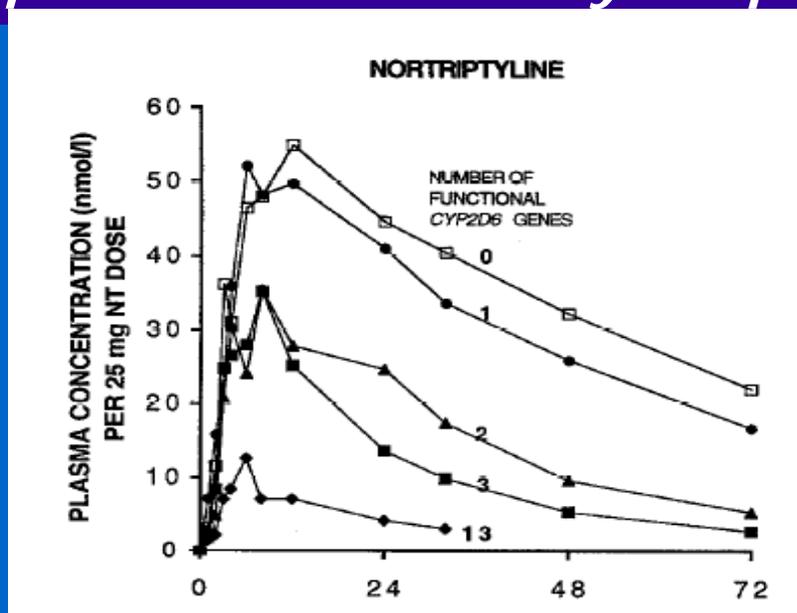
44 • J Clin Pharmacol 2007;47:37-47

## Cytochrome P450 2D6

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

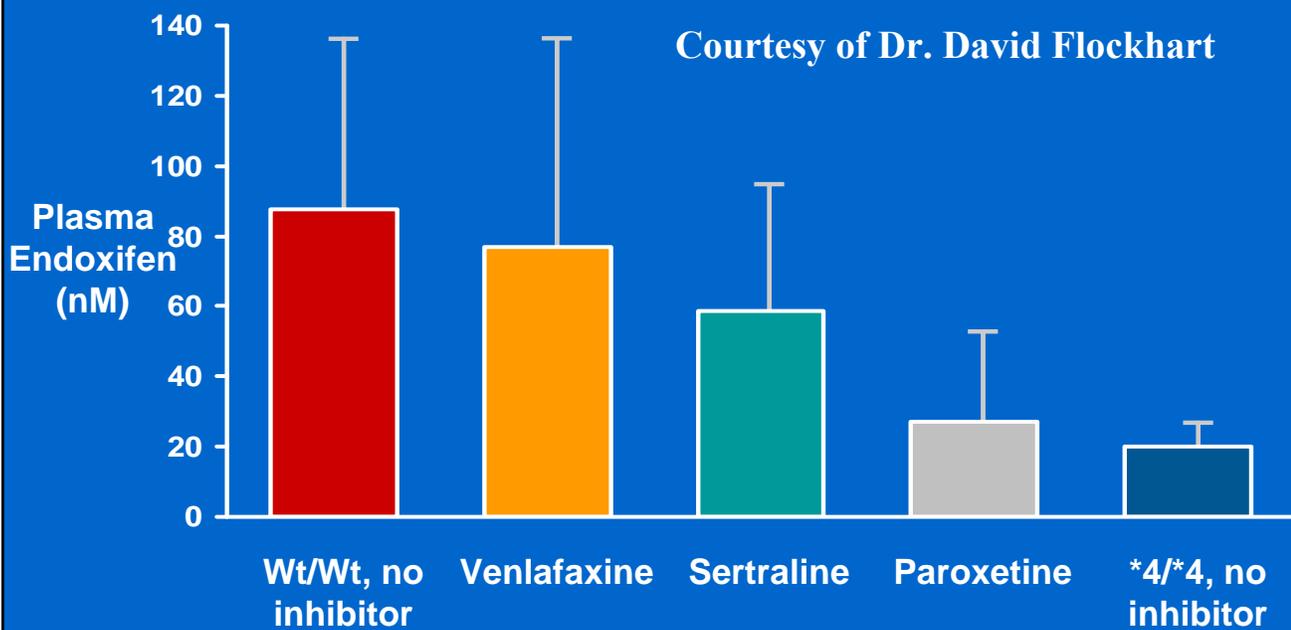
# Nortriptyline Drug Exposure

## *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

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## Genetics and Severe Drug Toxicity

### HLA-B\*5701

Abacavir hypersensitivity

Flucoxacillin liver injury (DILI)

### HLA-B\*1502

Carbamazepine-induced

Stevens-Johnson syndrome

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## Introduction to Pharmacokinetics

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

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# PHARMACOKINETICS

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

**A**BSORPTION,  
**D**ISTRIBUTION,  
**M**ETABOLISM, and  
**E**XCRETION

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## PHARMACOKINETICS

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

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## DRUG DOSE SELECTION

### TRADITIONAL:

Look up “usual” dose in PDR

Memorize “usual” dose

### IMPROVED:

*Individualize dosing*

Apply pharmacokinetics and the “*target concentration strategy*”

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## 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.

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## 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**

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## STEADY STATE CONCENTRATION

CONTINUOUS CREATININE SYNTHESIS:

$$C_{ss} = \frac{I}{CL_{cr}}$$

CONTINUOUS DRUG INFUSION:

$$C_{ss} = \frac{I}{CL_E}$$

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## 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]

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

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## 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.

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

SERUM Cr (mg %)	Cl <sub>Cr</sub> (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.

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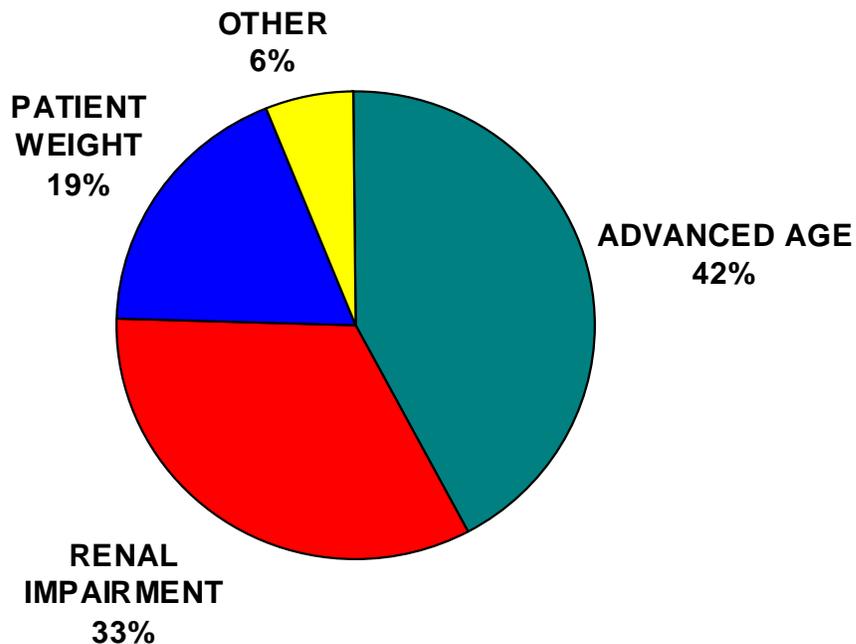
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## ESTIMATED $Cl_{Cr}$

- *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

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**PATHOPHYSIOLOGIC FACTORS *NOT* ACCOUNTED FOR IN DRUG DOSING\***



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