

Pharmacology: Drug Toxicities and Pharmacogenomics

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**NEW YORK INSTITUTE
OF TECHNOLOGY**

College of Osteopathic
Medicine

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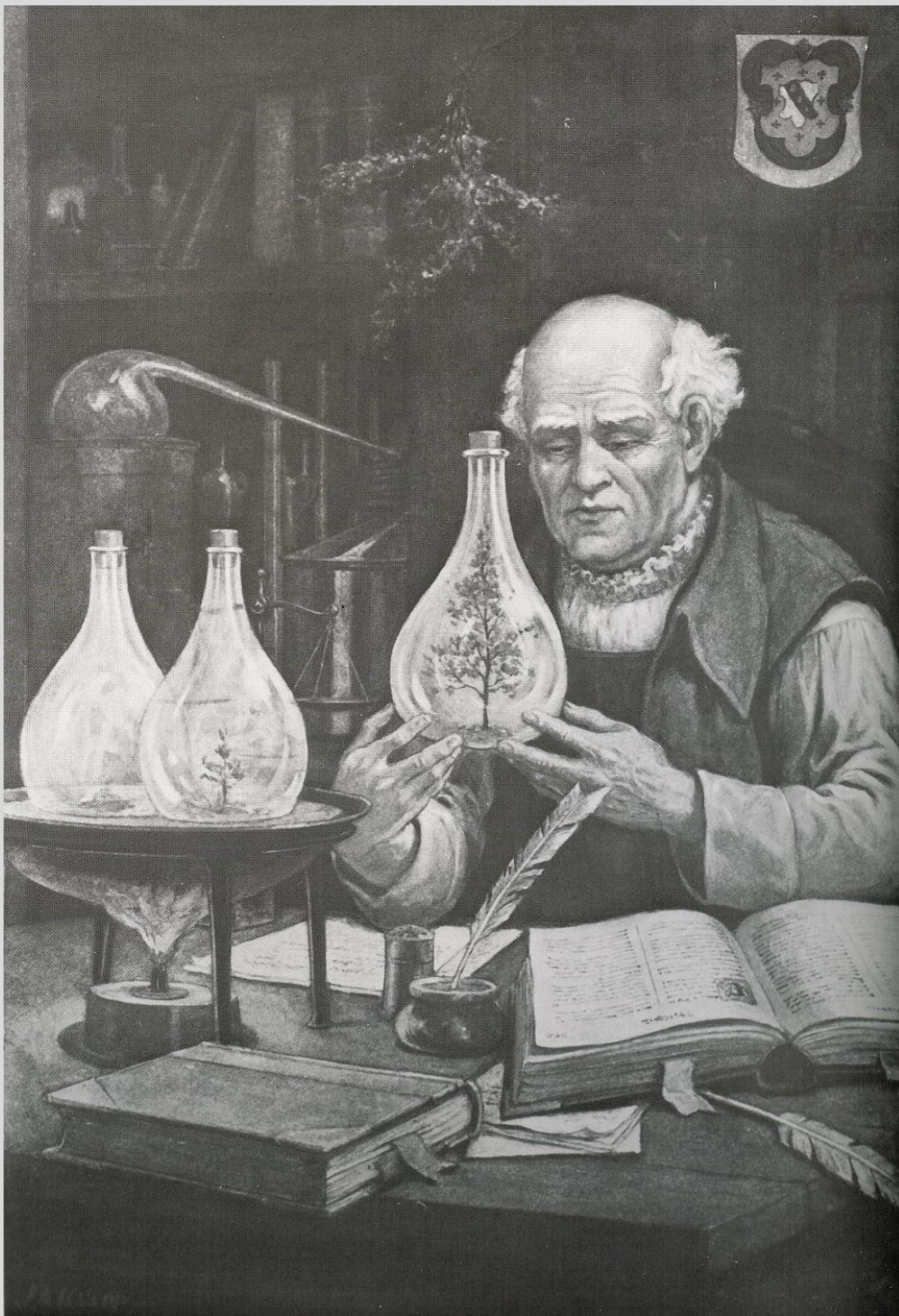
**I am available to groups and individuals for
pharmacology help and discussions by appointment.**

lgolds01@nyit.edu

Do.
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“All things are poison, for there is nothing without poisonous qualities; only the dose permits something not to be poisonous.”

Paracelsus 1493-1541



After completing the preparation materials, students should be able to:

1. Define adverse drug reactions.
2. Give examples of the personal and economic impact of adverse drug events.
3. Describe the mechanisms of drug toxicities on the cells, tissues, and organ systems.
4. Link maternal drug use during the three trimesters of pregnancy to the potential toxic effects on the fetus and neonate.
5. Apply the FDA Pregnancy and Lactation Labeling Rule to the clinical care of pregnant women, nursing infants, and females and males of reproductive potential.
6. Explain how pharmacogenomic variants in drug-metabolizing enzymes, transporters, genetic variants of metabolic disorders, and HLA variant alleles may contribute to individual variation in drug response and give examples of specific harmful consequences.

Preparation Materials (links are on the next slide)

Required

- ScholarRx Bricks | Practice Questions

Highly relevant optional materials:

- Dr. Goldstein's Word handout | Video Lectures | Guided reading questions (GRQs)

SUGGESTIONS:

- *Use the resources that work best for you.*
- *You do not need to study all of them. (ScholarRx Bricks & Practice Questions are required.)*
- *Work through the GUIDED READING QUESTIONS with pen/pencil and paper.*

Try answering them in your OWN WORDS first without looking at the readings, and then again after reviewing.

- *Practice questions (not graded) will help you assess your own learning and understanding. The practice questions consist of case vignettes to help you start integrating and applying concepts in the context of clinical scenarios.*

Links

Scholar Rx Bricks: (Required)

General Pharmacology > Principles of Pharmacology > Pharmacokinetics and Pharmacodynamics

Pharmacokinetics: Drug Administration, Metabolism, and Excretion

The following sections:

- Phases of Hepatic Drug Transformation
- What Can Affect Drug Metabolism?
- Pharmacologic Modification
- Genetic Modification
- Physiologic Modification

<https://exchange.scholarrx.com/brick/drug-administration-metabolism-and-excretion>

Optional resources by McGraw-Hill

Goodman & Gilman's The Pharmacological Basis of Therapeutics, 14e, 2023; and Chapter 7: Pharmacogenetics & Pharmacogenomics

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3191§ionid=268215725>

Goodman & Gilman's Chapter 9: Principles of Clinical Toxicology

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3191§ionid=268044850>

Katzung's Basic & Clinical Pharmacology, 16e, 2024; Chapter 5: Pharmacogenomics

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3382§ionid=281747341>

Katzung's Pharmacology: Examination and Board Review, 14e, 2024; Chapter 5: Pharmacogenomics

<https://accessmedicine-mhmedical-com.nyit.idm.oclc.org/content.aspx?bookid=3461§ionid=285589482>

What you need to know and understand: Terminology (the language of medicine)
The definitions and explanations are in the Notes Handout.

Toxicokinetics	DNA toxicity	Pregnancy and Lactation Labeling Rule
Toxicodynamics	Mutagenesis	Fetotoxicity
Adverse drug reactions	Carcinogenesis	Teratogenesis
Adverse drug events	Hepatotoxicity	Neonatal abstinence syndrome
Polypharmacy	Nephrotoxicity	Pharmacogenomics
Prescribing cascade	Pulmonary toxicity	Pharmacogenetics
On-target adverse effects	Cardiotoxicity	Genotype
Off-target adverse effects	Phototoxicity	Phenotype
Acute adverse effects	Photoallergy	Poor metabolizers
Delayed toxicity	Hypersensitivity reactions	Intermediate and extensive metabolizers
Apoptosis	Gell & Coombs classification	Ultra-rapid metabolizers
Necrosis	Hapten	Various acronyms

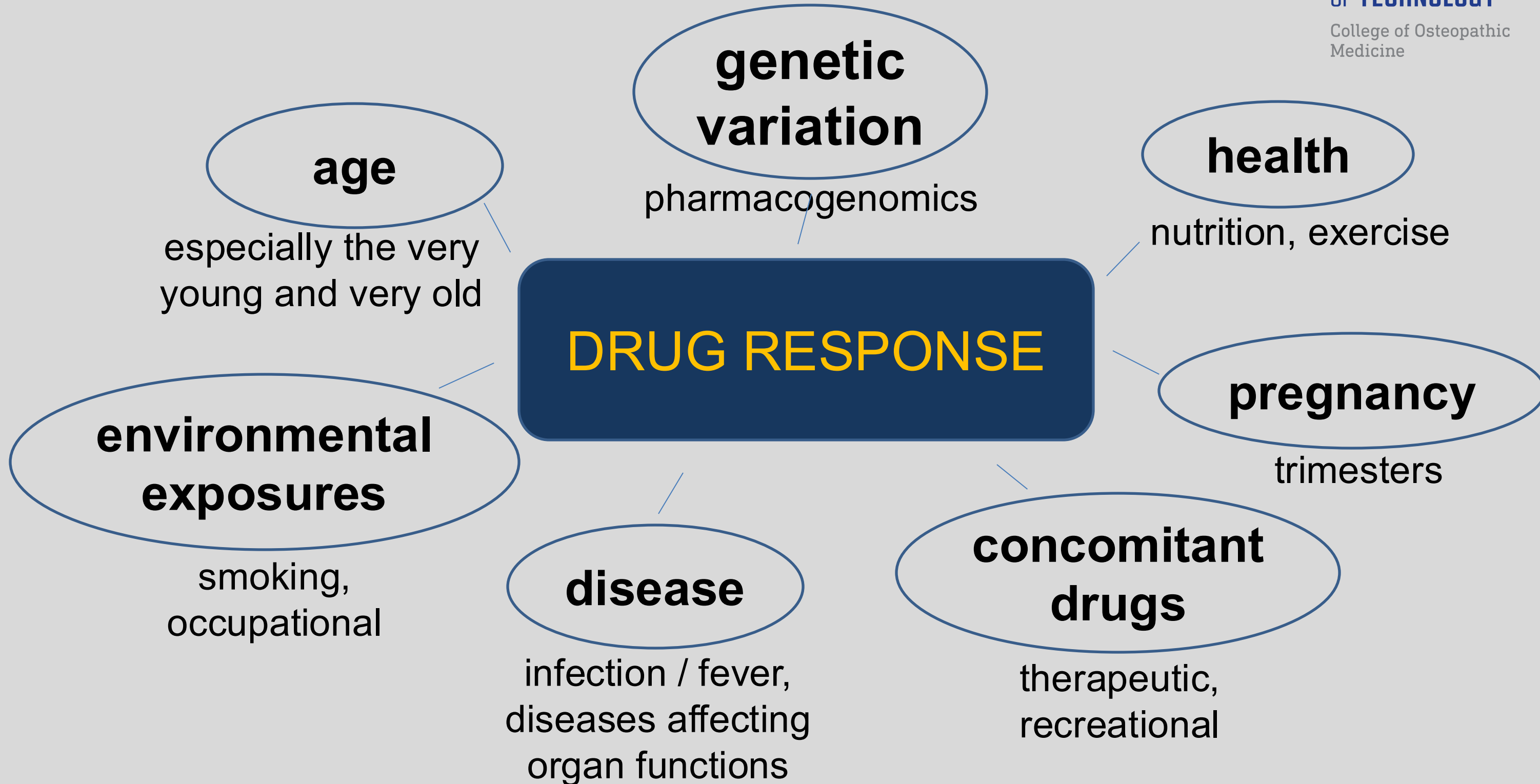
This lecture provides many examples to help students visualize the concepts and put them into a clinical context – caring for patients.

In addition to learning the terminology, be able to recognize, explain in your own words to a friend or relative, and apply the following:

- Types of adverse drug reactions (ADRs)
- Risk factors / causes of adverse drug reactions / adverse drug events
- Mechanisms, mechanisms, mechanisms of drug toxicity
- Toxic effects: acute, delayed, cumulative, local, systemic, reversability
- Harmful effects on cells and organs
- Therapeutic drug use in pregnancy and the main ideas of the Pregnancy and Lactation Labeling Rule, three subsections (no need to memorize the wording)
- Harmful effects of maternal drug use on the fetus and neonate
- Mechanisms and causes of immunological adverse drug events
- Pharmacogenomics principles
- Specific starred (*) genetic variants that increase patients' risk for ADRs.

Adverse Drug Reactions

Risk factors for adverse drug reactions



Classification of ADEs

Common and predictable

Overdose or dose reduction

Side effects
(eg dry mouth, nausea, somnolence)

Abrupt drug withdrawal

Secondary effects
(eg superinfection from antibiotic use)

Resistance or paradoxical effects

Drug interactions

Paradoxical effect:
an effect opposite of the expected effect

Rare and mostly unpredictable

Intolerance
(exaggerated sensitivity)

Idiosyncrasy
(not attributable to known
pharmacologic properties)

Immunologic drug reactions (allergy) may be predictable or unpredictable.
Allergy history and pharmacogenetic testing, if available and clinically relevant, may help predict and prevent some immunological ADRs.

Adverse Drug Reactions (ADRs) and Adverse Drug Events (ADEs)

ADRs: Unwanted, uncomfortable, or dangerous effects of drugs

ADEs: Any injuries resulting from medication use, including physical harm, mental harm, or loss of function

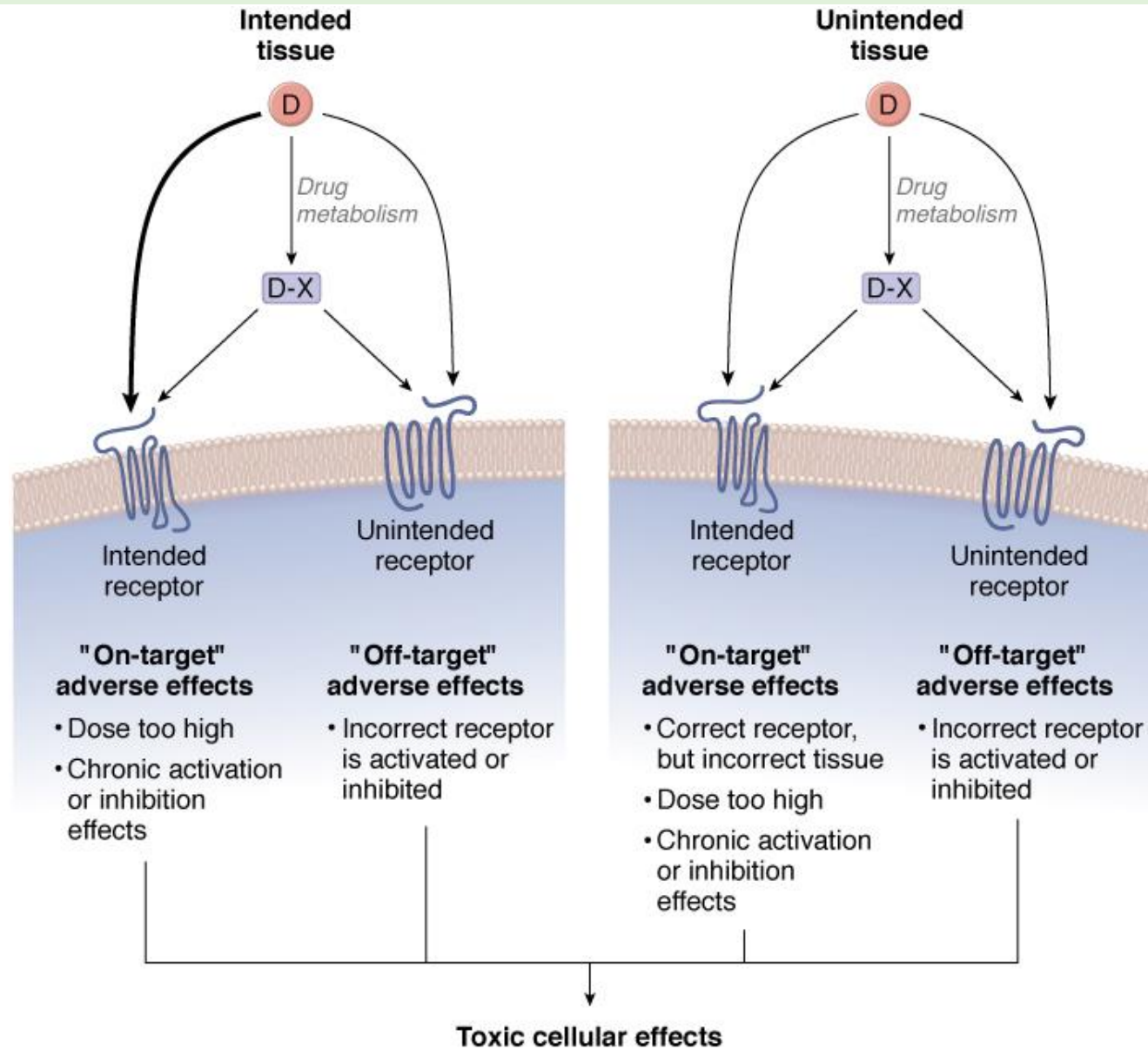
HIGH RISK POPULATIONS

Older persons	Medication toxicity is a major cause of hospitalization in older patients <ul style="list-style-type: none"> • Multiple comorbidities • Polypharmacy: Patient use of multiple drugs: prescribed / OTC / herbal • Prescribing cascade (when an adverse drug effect is misinterpreted as a new medical condition leading to an unnecessary medication being prescribed)
Pregnant persons	Certain drugs may be harmful to the fetus and neonate
Infants and young children	<ul style="list-style-type: none"> • Differences in age-dependent development of organ function • Dosing errors • Accidental ingestion

Most ADRs / ADEs are predictable \Rightarrow They are *potentially preventable*.

From: **6 Drug Toxicity**

Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy Fourth Edition, 4e, 2017



On-target and off-target adverse drug effects.

ADRs are typically,

- **Predictable:** Based on knowledge of the mechanisms of action and adverse effects, distribution to tissues, and dose-response relationship
- **Dose-dependent:** Related to the concentration of drug in the body and to the duration of the exposure

ON-TARGET effect results from the drug interacting with its therapeutic target in intended or unintended tissue.

Anticoagulants increase the time to form clots → high dose can cause hemorrhage.

Nifedipine lowers blood pressure by relaxing vascular smooth muscle (intended tissue) but hypotension at high doses by acting on cardiac tissue (unintended tissue).

OFF-TARGET effect results from the drug interacting with a target or targets other than the intended target in intended or unintended tissue.

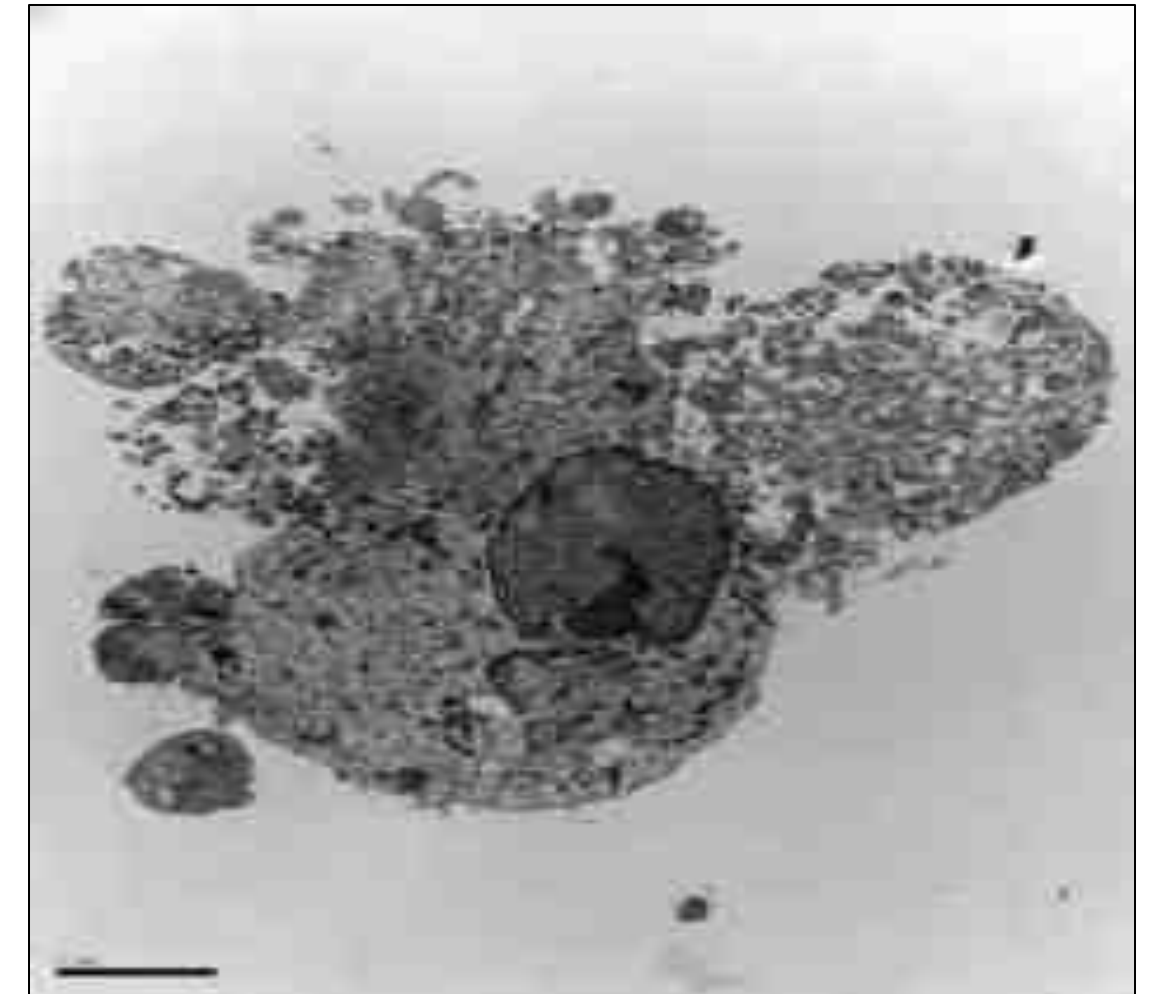
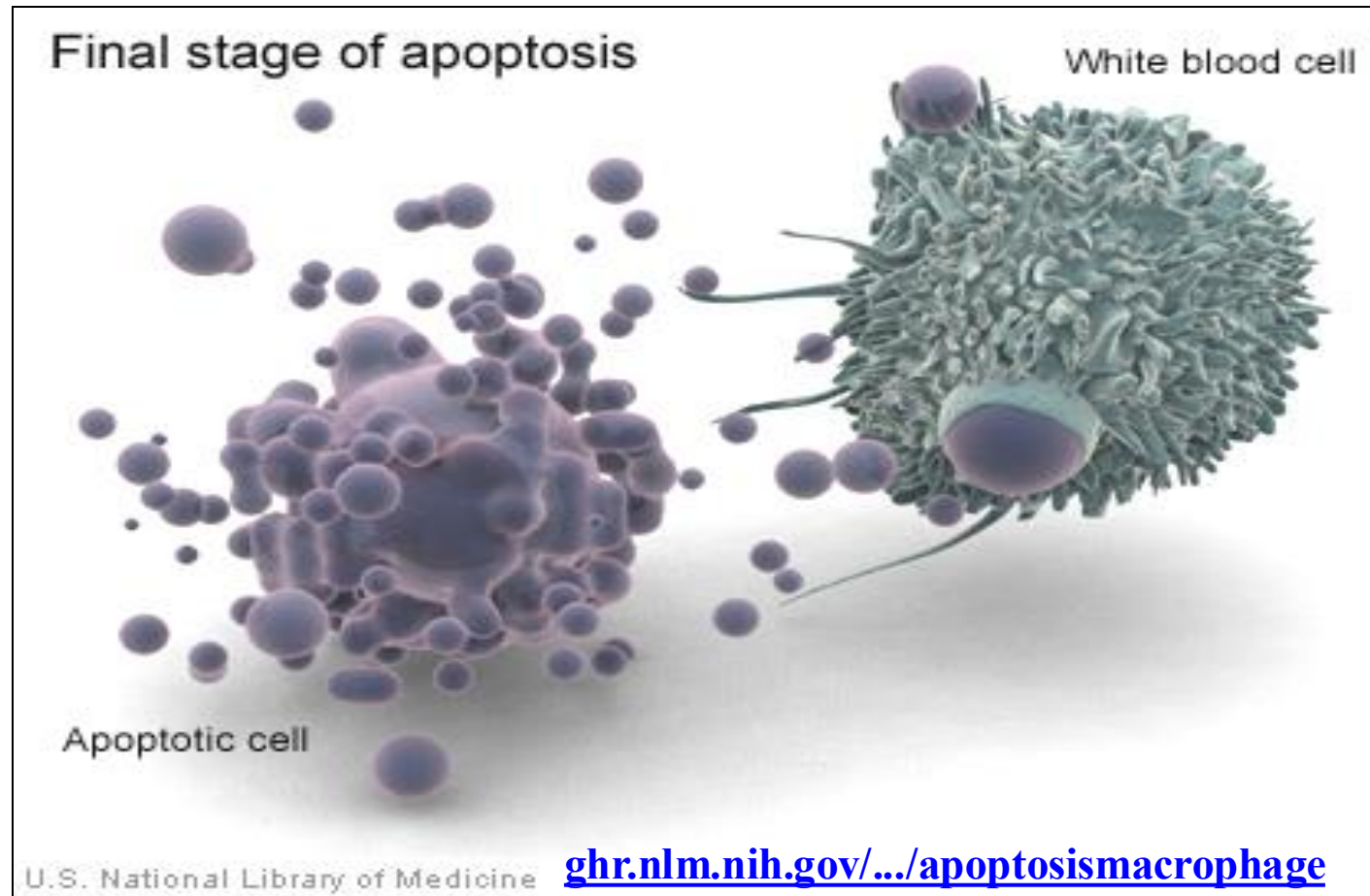
Tricyclic antidepressant → sedation, dry mouth, hypotension (blockade of histaminic, muscarinic, and adrenergic receptors)

Toxic effects may be acute, delayed, or cumulative
Adverse effects may cause ...

<p>Local reactions</p> <p>Systemic reactions</p> <p>Immunogenic reactions</p> <ul style="list-style-type: none">• Hypersensitivity reactions• Mechanism-related immune system upregulation <p>Example: anticancer immune checkpoint inhibitors</p> <p>Photosensitivity</p> <p>Fetal toxicity</p>	<p>Cellular toxicity</p> <ul style="list-style-type: none">• Apoptosis• Necrosis <p>DNA damage</p> <ul style="list-style-type: none">• Mutagenesis: Gene mutations give rise to altered proteins.• Carcinogenesis Mutations in genes that regulate cell growth may lead to induction of cancer.	<p>Organ toxicity</p> <ul style="list-style-type: none">• Liver<ul style="list-style-type: none">– Hepatitis / necrosis– Cirrhosis• Kidney<ul style="list-style-type: none">– Glomerular nephropathy– Tubular necrosis– Interstitial nephritis• Nerves<ul style="list-style-type: none">– Neuropathy– Seizures– Coma• Bone marrow toxicity<ul style="list-style-type: none">– Neutropenia– Anemia– Thrombocytopenia
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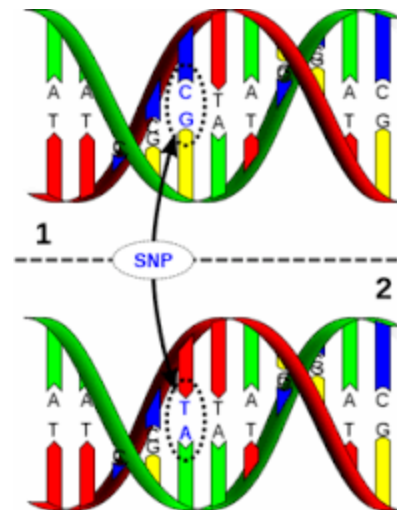
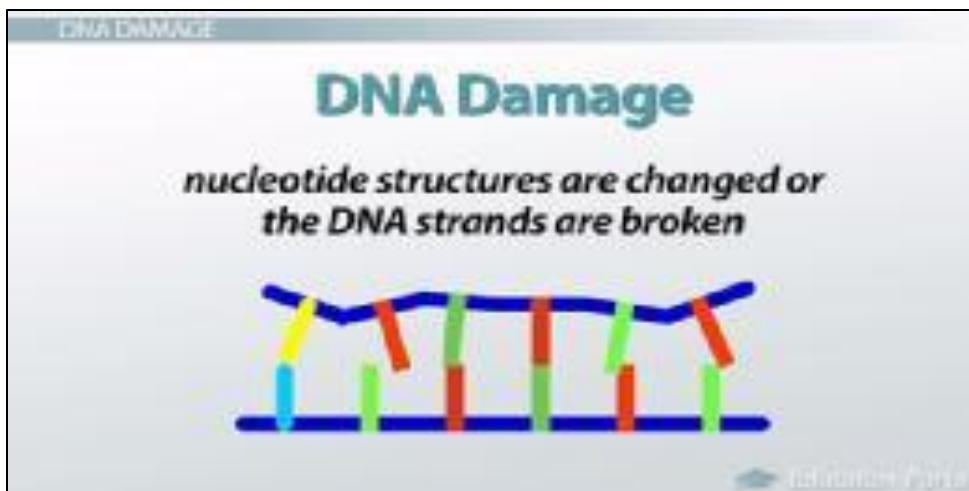
Effects may be reversible or irreversible.
Effects may range from minor discomfort to significant morbidity and mortality.

Apoptosis: Programmed cell death



Francis Ka Ming Chan PhD
<http://profiles.umassmed.edu/profiles/display/133299>

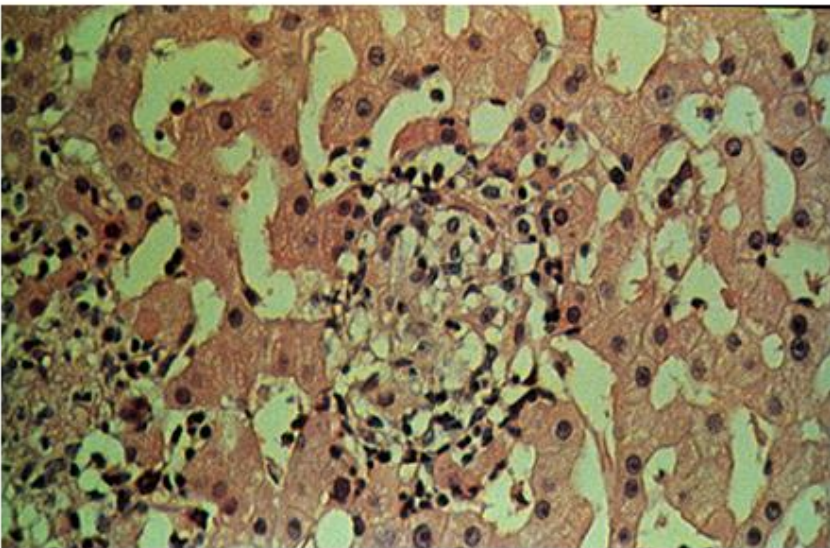
Necrosis: Traumatic cell death
Electron micrograph of a necrotic cell exhibiting extensive loss of plasma membrane integrity.



<http://study.com/academy/lesson/dna-base-excision-repair.html>
https://isogg.org/wiki/Single-nucleotide_polymorphism

Organ toxicity may result from oxidative injury or direct injury to cells or capillary endothelium with subsequent release of cytokines, recruitment of inflammatory mediators and activation of macrophages and lymphocytes.

Granulomatous hepatitis

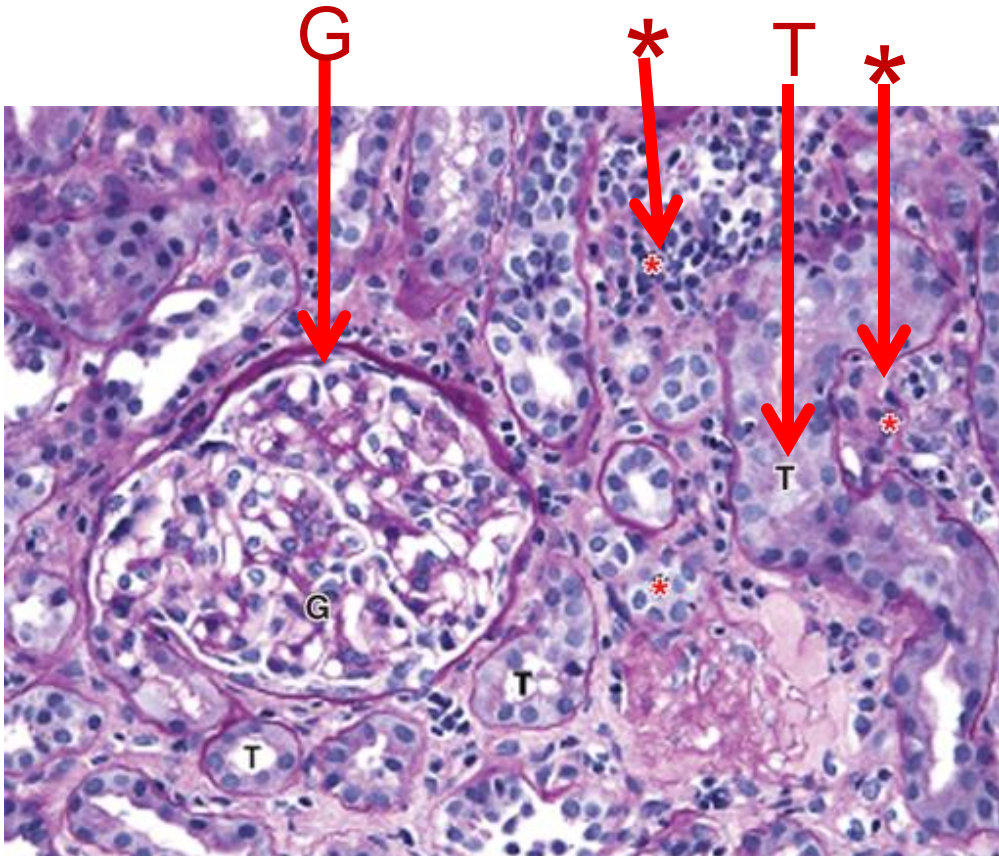


High power view of a liver biopsy shows a noncaseating granuloma and perigranulomatous mononuclear cell inflammation with hepatic necrosis.

Courtesy of Robert Odze, MD.

UpToDate®

Hepatotoxic drugs can cause hepatocellular injury, cholestatic injury, with acute or chronic hepatitis, acute or chronic cholestasis or cholestatic hepatitis.



Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e Copyright © McGraw Hill. All rights reserved.

Acute interstitial nephritis: PAS-stained renal biopsy shows a mononuclear cell interstitial infiltrate (*asterisks*) and edema separating the tubules (T) and a normal glomerulus (G)

Erlotinib-induced pulmonary toxicity



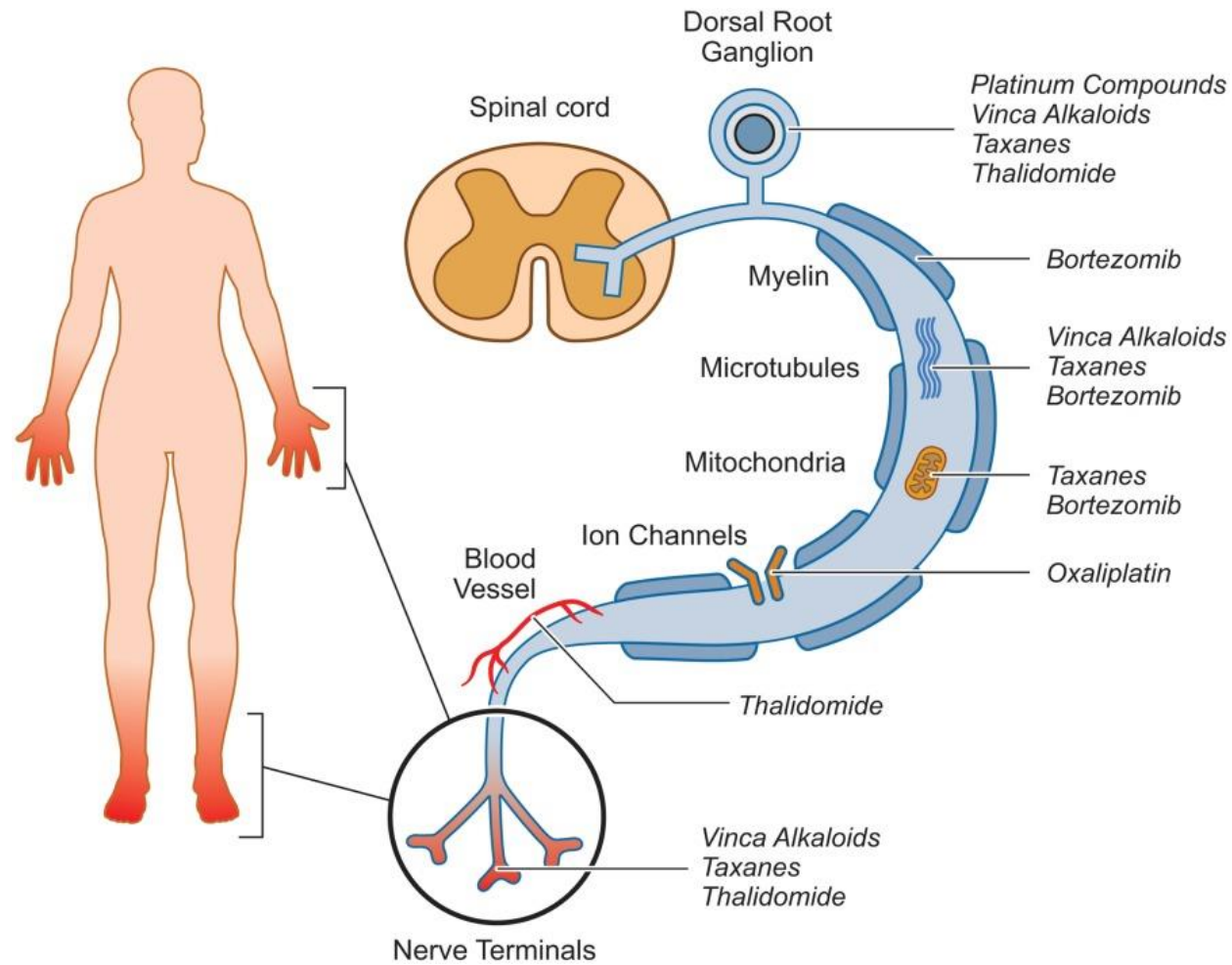
Example of erlotinib-related pulmonary toxicity. Axial image of a chest CT scan in a patient receiving erlotinib demonstrating diffuse bilateral reticular infiltrates, which resolved after discontinuation of the drug.

CT: computed tomography.

UpToDate®

Many drugs, typically anticancer drugs, induce alveolar inflammation, interstitial inflammation, and/or interstitial fibrosis.

Chemotherapy-induced peripheral neurotoxicity



CA A Cancer J Clinicians, Volume: 63, Issue: 6, Pages: 419-437,
First published: 11 November 2013, DOI: (10.3322/caac.21204)

Exposure to toxic substances that alter the normal activity of the nervous system can disrupt or kill neurons. Manifestations include limb weakness or numbness (peripheral neuropathy), autonomic nervous system toxicity, central nervous system effects.

Drug-induced photosensitivity cutaneous reactions



Phototoxicity: Topical or systemic drugs or metabolites that absorb UV radiation can induce direct cellular damage. Typically occurs immediately as an exaggerated sunburn.

<https://emedicine.medscape.com/article/1049648-overview>



<http://toxicresponsesoftheskin.wikispaces.com/Photosensitivity>

Photoallergy: Topical or systemic drugs or metabolites that absorb UV radiation can induce immune reaction that develops 24 to 48 hours after exposure.
Photo: Type IV immune reactions with delayed hypersensitivity.

Recall questions. Please pause the video and try to answer them without looking back at the slides.

- What are the causes of the common and predictable adverse effects?
- What is the meaning of on-target and off-target effects?
- What cellular and organ damage can occur as a result of drug-induced adverse effects?

Therapeutic Drug Use During Pregnancy

The therapeutic benefit of medication use in the expectant mother must be weighed against the potential adverse effects on fetal growth and development.

Health risks and benefits of drug therapy to both the mother and the fetus must be considered.

The vast majority of drugs are not recommended during pregnancy.

All prescribers have the responsibility of educating pregnant patients not to take any medications, prescription, over-the-counter, or recreational, during pregnancy.

Consult a pharmacist and the obstetrician before taking and medication.

Pregnancy and Lactation (Drug) Labeling Rule

Labeling to facilitate prescriber counseling for patients of reproductive potential.

Three subsections:

1. **Pregnancy including labor and delivery:**

- **Pregnancy registry** collects data and notes any potential risk of medication use on the developing fetus and the mother.
- **Risk summary** provides information on potential adverse effects on developing fetus throughout pregnancy and PK parameters altered during pregnancy.
- **Clinical considerations** are provided about initiation, continuation, and withdrawal of treatment during pregnancy and the data are listed in the drug monographs.

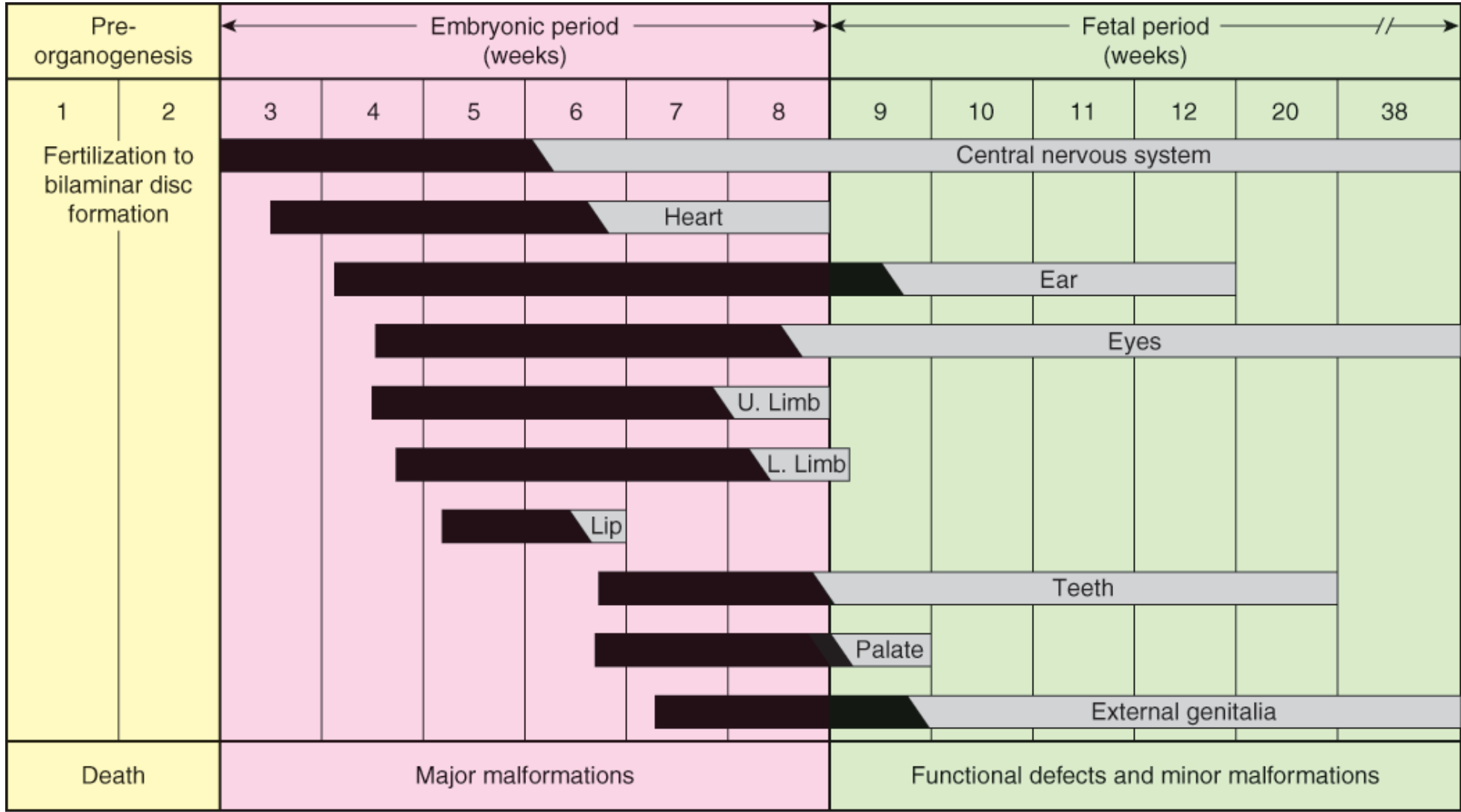
2. **Lactation:**

- **Risk summary** of information about the timing of breastfeeding, excretion of drugs in breast milk, and risks to the infant are provided. **Clinical considerations** and **data** supporting the recommendations are listed in the drug monographs.

3. **Reproductive considerations for females and males**

- **Pregnancy testing recommendations** prior to beginning drug therapy
- **Contraception advice** for female of reproductive potential about the use of contraception during and after therapy with specific drugs
- **Information for males** who wish to father a child about infertility as it relates to specific drugs and Manufacturers may provide recommendations for contraception with partners who may become pregnant during and after therapy.

A teratogen exerts its effects on target organs at a particular stage of fetal development during the limited time period of organogenesis of the target organs.



Source: F. Gary Cunningham, Kenneth J. Leveno, Steven L. Bloom, Catherine Y. Spong, Jodi S. Dashe, Barbara L. Hoffman, Brian M. Casey, Jeanne S. Sheffield: *Williams Obstetrics*, 25th Edition
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Timing of organogenesis during the embryonic period.

(Reproduced with permission from Salder TW: *Langman’s Medical Embryology*, 6th ed. Baltimore, Williams & Wilkins; 1990.)

Harmful effects of drugs taken by the mother during pregnancy on the fetus and the neonate

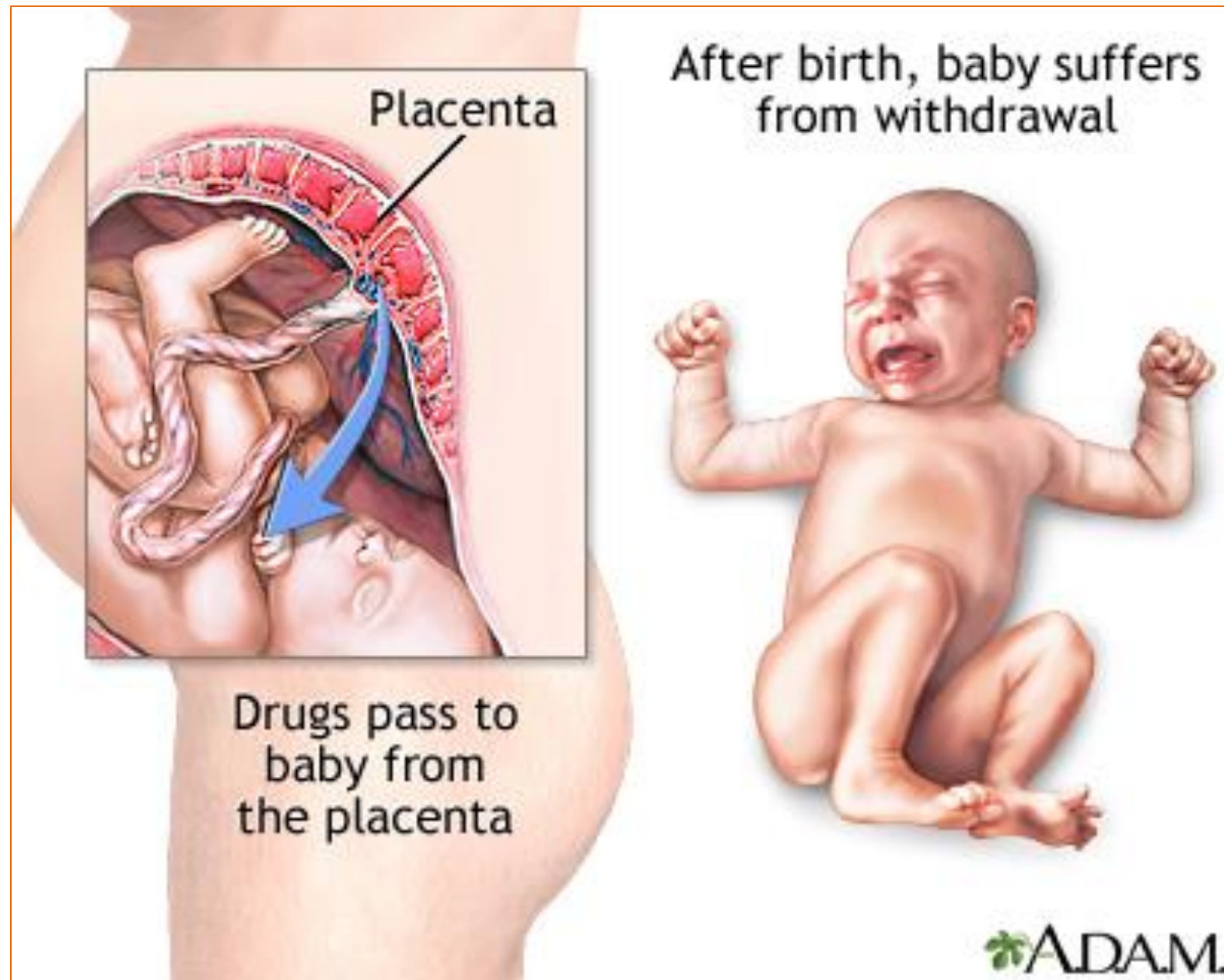
Fetal effects

Fetotoxicity	Injury to the fetus from a substance that enters the maternal and placental circulation, which may cause fetal malformations, altered growth, or in utero death
Teratogenicity	The induction of defects of the fetus; exposure must occur during a critical developmental period
Teratogen	Any agent that acts during embryonic or fetal development to produce a permanent alteration of form or function

Neonatal effects

Neonatal abstinence syndrome	Symptoms of withdrawal that babies can develop after birth if their mothers have taken addictive drugs during their pregnancy. due to exposure to opioids, alcohol, benzodiazepines, barbiturates, and certain antidepressants (SSRIs) while in the womb.
Other adverse effects on neonate	Other adverse effects of drugs taken by the mother include premature birth, low birth weight, heart defects, and other birth defects.

Neonatal abstinence syndrome: A drug-withdrawal syndrome that follows in utero exposure to maternal opioids, alcohol, benzodiazepines, barbiturates, others



Other adverse effects of drug on the newborn include:

- premature birth,
- low birth weight,
- and the teratogenic or otherwise fetotoxic effects of specific drugs such as heart defects, pulmonary hypoplasia, cerebral complications and other birth defects.

Question

- What information is provided in the Pregnancy and Lactation Labeling Rule that can be helpful to clinicians in educating pregnant patients and individuals with reproductive potential about drug use during pregnancy?

Drug-Immune System Interactions → Hypersensitivity Reactions

- The drug may act as an antigen and elicit a hypersensitivity response.
- The drug may interact with immune receptors and lead to activation of specific immune cells.
- **Adverse drug events: Drugs can induce all types of immune-mediated hypersensitivity – allergic – reactions that can cause significant morbidity and lead to death.**

Mechanisms of drug-immune system reactions

Haptens	Small chemicals (drugs or their metabolites) that are not reactive in their original state become immunogenic by covalent binding to host proteins on cells or in plasma forming hapten-carrier complexes. Hapten-peptide fragments are presented by antigen presenting cells to T cells, ultimately eliciting allergic reactions.
Biologic drugs	Protein drugs, such as monoclonal antibodies, recombinant proteins, solubilized receptors, cytokines, enzymes, antisera, and vaccines can preferentially stimulate antibody responses and some T cell responses.
Drug-induced autoimmunity	An autoimmune phenomenon where the patient develops symptoms similar to the autoimmune disease. The pathogenesis is not understood. Examples: lupus-like disorder, pemphigus-like disorder, IgA bullous dermatosis

Most drugs are small molecular weight compounds with simple chemical structures, which are not easily recognized by the immune cells and too small to interact with immune receptors with enough strength to activate T and B cells.

Gell and Coombs Classification of Immunologic Drug Interactions

Type	Description	Manifestations
Type I	IgE-mediated immediate hypersensitivity reactions Exposure to allergen causes IgE antibodies to be formed and bound to cells expressing FcεR1. On subsequent exposure, IgE crosslinking on sensitive cells causes degranulation and release of inflammatory mediators.	Anaphylaxis Angioedema Bronchospasm Urticaria Hypotension
Type II	Antibody-dependent cytotoxic reactions, delayed onset Preformed antigen-(drug-)specific IgG and IgM antibodies are directed against cellular or extracellular matrix antigens, resulting in cellular destruction, functional loss, or tissue damage by complement activation, antibody-dependent cellular cytotoxicity, and binding cell surface receptors that alters receptor activity.	Hemolytic anemia Thrombocytopenia Neutropenia
Type III	Immune complex-mediated reactions, IgG predominantly Circulating antigen-antibody immune complexes preformed during immune response precipitate in glomeruli, vessels, joints, and skin, which triggers the classical complement pathway, leading to activation of monocytes and neutrophils, which release lysosomal enzymes and free radicals at the site of complex deposition causing tissue damage.	Serum sickness Arthus reaction
Type IV	T cell-mediated delayed-type reaction Antigen exposure causes an initial local inflammatory response that attracts leukocytes. Antigen engulfed by macrophages is presented to T cells, which become sensitized and activated and release cytokines and chemokines, causing tissue damage.	Contact dermatitis Severe skin reactions Interstitial nephritis Drug-induced hepatitis Others

Question:

- Small chemicals are not easily recognized by the immune cells and too small to interact with immune receptors with enough strength to activate T and B cells. How do these drugs / metabolites elicit an allergic reaction?

Pharmacogenomics:

The systematic examination of genes, gene products, and variation in gene expression and function, using tools for surveying the entire genome. Pharmacogenomics researchers evaluate multigenic determinants of drug response in an individual or across a population.

Pharmacogenetics:

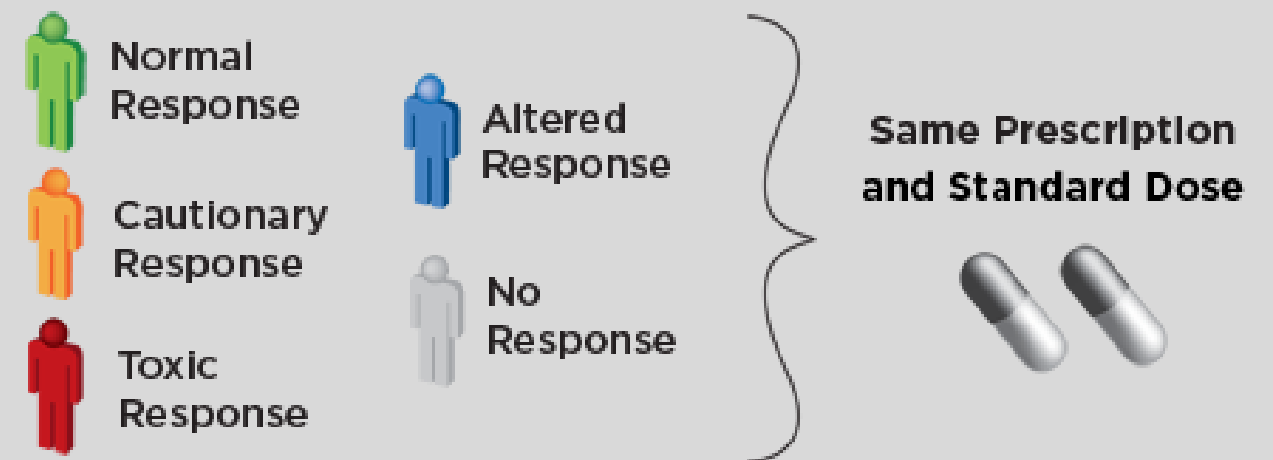
The effect of a person's genetic factors on that person's responses to drugs.

Pharmacogenomics and pharmacogenetics are often used interchangeably.

Precision (personalized) medicine:

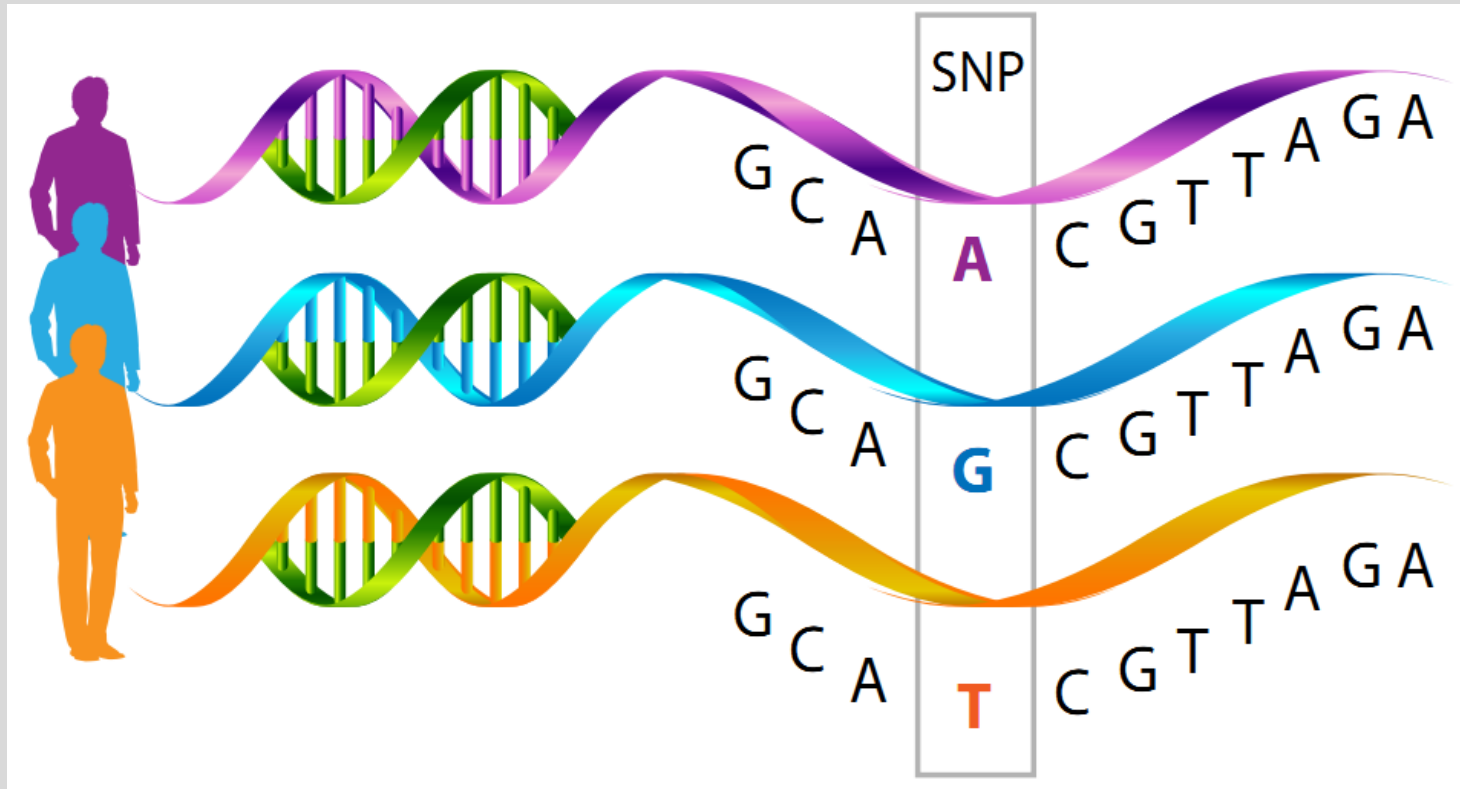
Pharmacogenomic information may be included in the labeling of specific drugs, which may help clinicians select the drugs and doses best suited for the individual patient.

TRADITIONAL TREATMENT:



<http://www.admerahealth.com/pharmacogenomics-physicians/>

Single Nucleotide Polymorphism (SNP)



Single Nucleotide Polymorphisms are a single nucleotide changes in an area of an organism's DNA that is different in more than 1% of the population. SNPs occur in the DNA in **1 out of every 300 nucleotides**. In the human genome, this means that there are at least 1 million SNPs in the human's 3 million-nucleotide genome. They can have varying degrees of effect, depending on where they are located.

WHATISDNA DNA Encyclopedia

<http://www.whatisdna.net/wiki/single-nucleotide-polymorphisms/>

Pharmacogenomics looks at variations in genes for proteins, such as metabolic enzymes, drug transporters, and drug targets.

- Many vary by only a single difference in their DNA sequence.
- Others have larger changes.
- Most of these variants don't affect how people respond to the drug.

NIH National Institute of General Medical Sciences:
Pharmacogenomics

<https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx>

Gene Variants Affecting Pharmacokinetics

Genotype

Phenotype

Two alleles encoding for a nonfunctional protein

Poor metabolizers (PM)

One functional allele
(phenotypically may be similar to EMs)

Intermediate metabolizers

Individuals with two functional alleles

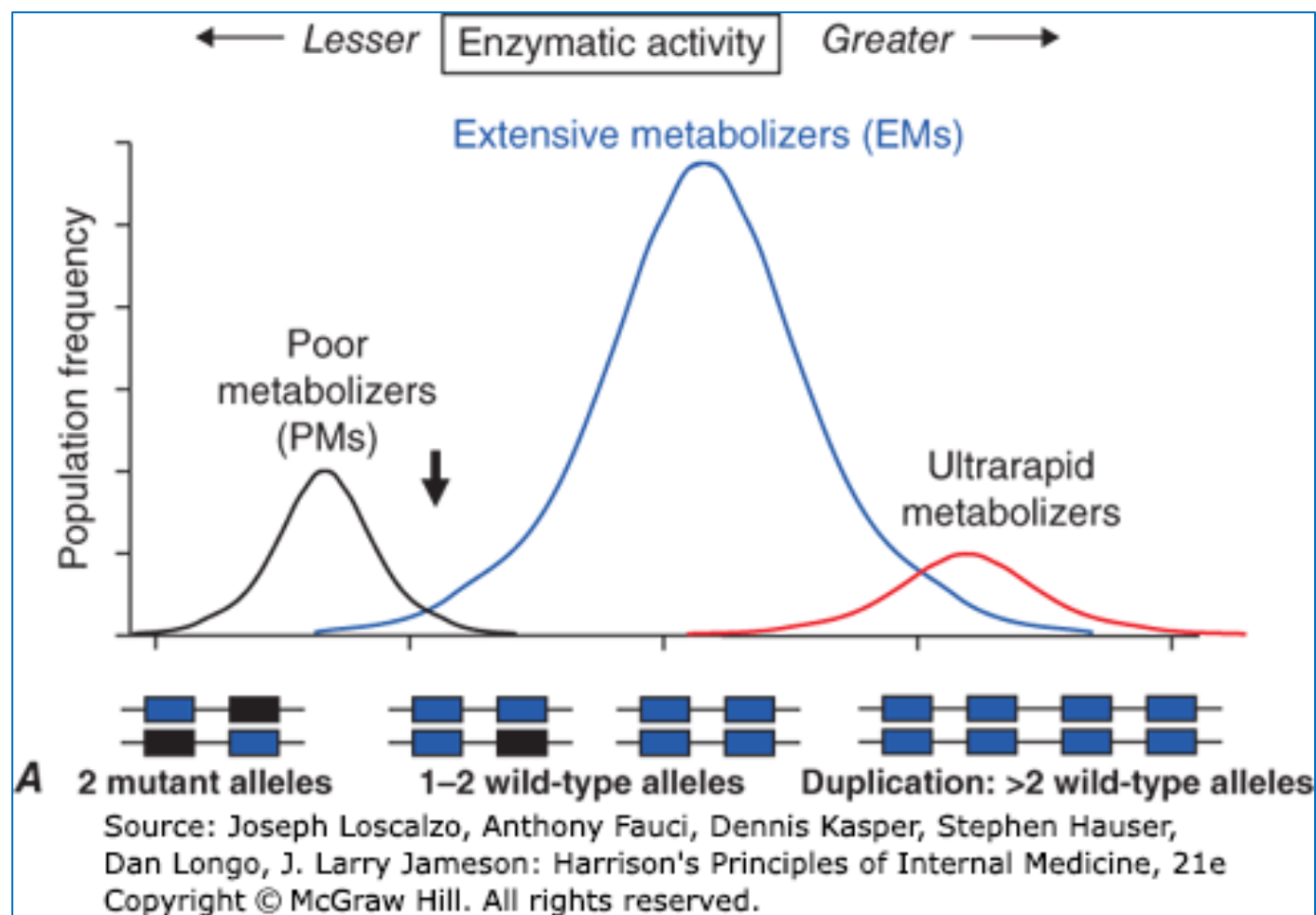
Extensive metabolizers, (EM)

Very high enzymatic activity, occasionally due to
gene duplication

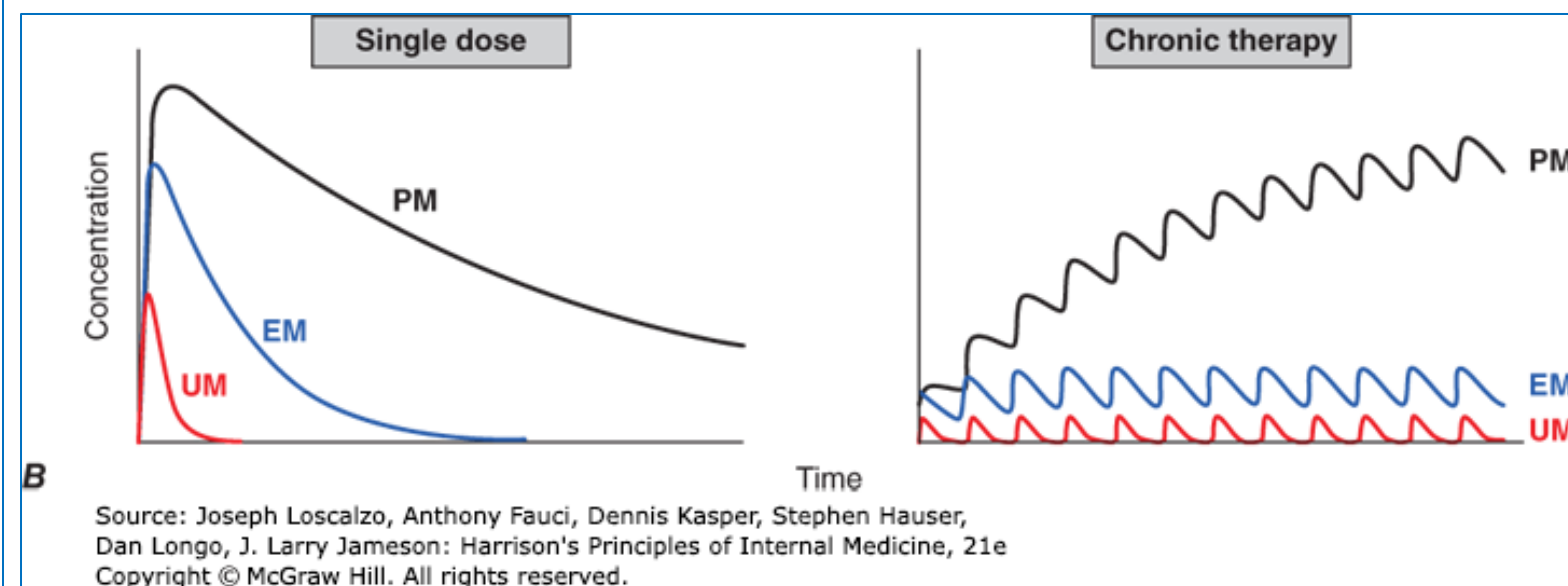
Ultra-rapid metabolizers

Polymorphisms in genes for transporters and
major histocompatibility complex

Gene variants in transporters and
HLA-A and HLA-B

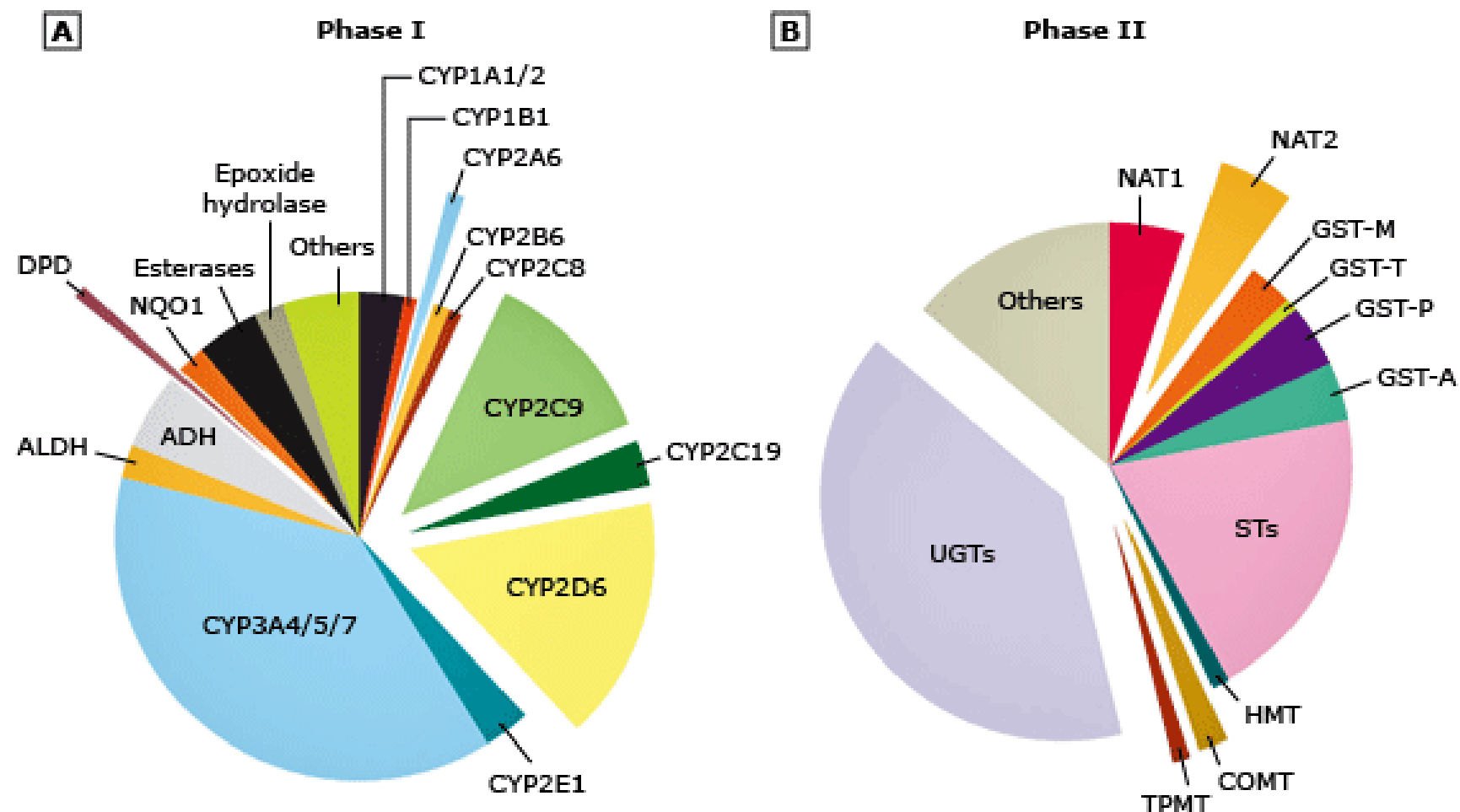


A. Distribution of CYP2D6 metabolic activity across a population. The heavy arrow indicates an antinode, separating poor metabolizer subjects (PMs, black), with two loss-of-function CYP2D6 alleles (black), indicated by the intron-exon structures below the chart. Individuals with one or two functional alleles are grouped together as extensive metabolizers (EMs, blue). Also shown are ultra-rapid metabolizers (UMs, red), with 2–12 functional copies of the gene, displaying the greatest enzyme activity.



B. These simulations show the predicted effects of CYP2D6 genotype on disposition of a substrate drug. With a single dose (left), there is an inverse “gene-dose” relationship between the number of active alleles and the areas under the time-concentration curves (smallest in UM subjects; highest in PM subjects); this indicates that clearance is greatest in UM subjects. In addition, elimination half-life is longest in PM subjects.

The right panel shows that these single-dose differences are exaggerated during chronic therapy: steady-state concentration is much higher in PM subjects (decreased clearance), as is the time required to achieve steady state (longer elimination half-life).



The pie charts show clinically relevant genetic polymorphisms in drug-metabolizing enzymes, which result in interindividual alterations in the rates of metabolism, thus the systemic drug levels, of affected drugs.

Most drug-metabolizing enzymes exhibit clinically relevant genetic polymorphisms.

Panel A: Phase 1 drug-metabolizing enzymes.

Panel B: Phase 2 drug-metabolizing enzymes.

The enzyme polymorphisms already associated with changes in drug effects are separated from the corresponding pie charts. The percentage of phase 1 and phase 2 metabolism of drugs that each enzyme contributes is estimated by the relative size of each section of the corresponding chart.

Examples of genetic polymorphisms influencing drug response

Stars * on examples on the following list mean students should learn the *Mechanisms* of these specific examples and be able to apply them in a clinical context.

Gene product	Drugs	Responses affected
* <i>NAT2</i> N-acetyl transferase Poor metabolizer	<ul style="list-style-type: none"> hydralazine isoniazid procainamide 	<ul style="list-style-type: none"> Lupus-like syndrome Hepatotoxicity QTc interval prolongation (arrhythmia)
* <i>CYP2D6</i>	<ul style="list-style-type: none"> codeine antipsychotics antidepressants beta-blockers 	<ul style="list-style-type: none"> Codeine ultrarapid metabolizers: Increased risk of respiratory depression Codeine ^{CYP2D6 UM} → ↑ morphine concentration for a given dose → respiratory depression risk
* <i>UGT1A1</i> UDP-glucuronosyl transferase	<ul style="list-style-type: none"> Bilirubin Lipophilic molecules 	Deficient UGT1A1 <ul style="list-style-type: none"> → unconjugated bilirubin can accumulate blood → jaundice in neonate and adult → increased toxicity of a certain cancer chemotherapeutic that is detoxified by UGT1A1

Know mechanisms and effects not drug names



Butterfly rash

Image source:
© 2009 Nucleus Medical Art, I

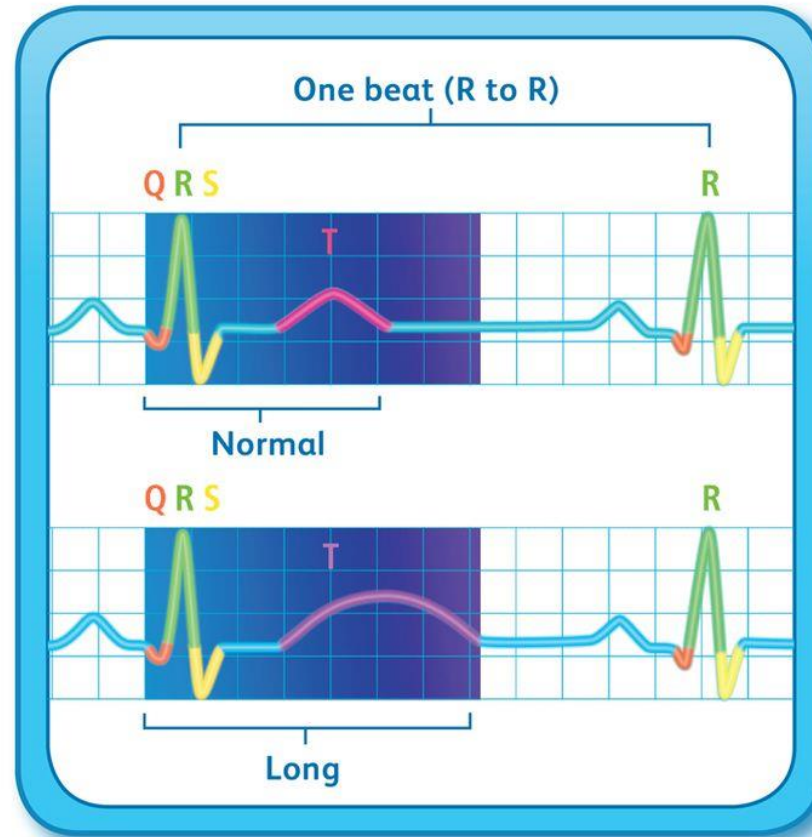
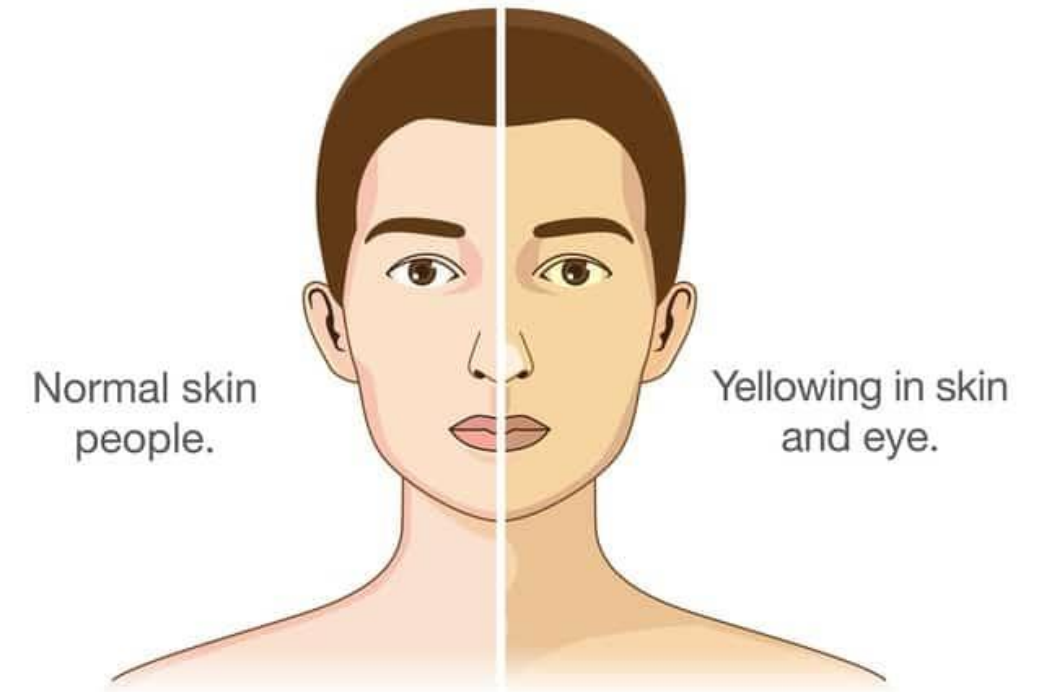


Illustration showing prolonged QT interval on an electrocardiogram (ECG)



<https://www.pinterest.com/icedraspberries/prolonged-qt/> <https://andrea-digestive-clinic.com/gilberts-syndrome/>

NAT2 PMs

Lupus-like syndrome
(immune reaction)

CYP PMs

QT interval prolongation can
lead to ventricular arrhythmia
Decreased CYP metabolism
of drugs that ↑QT interval or
patients with *long QT syndrome*

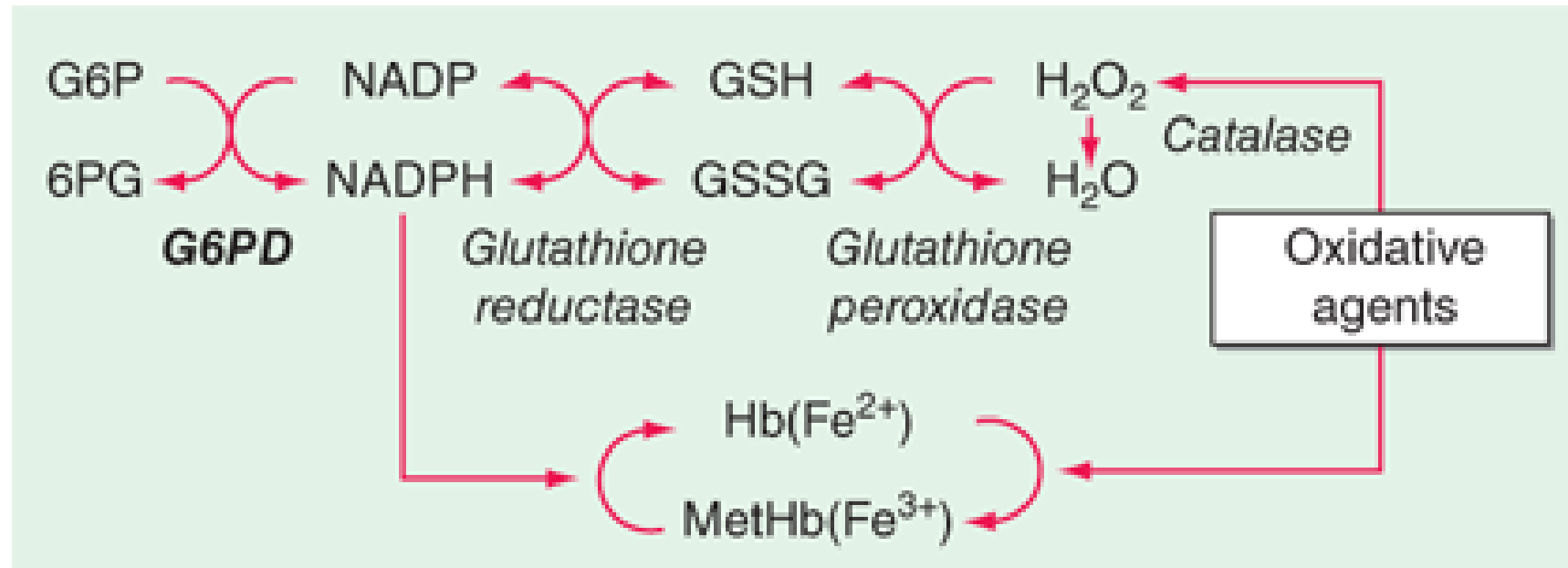
Gilbert's syndrome

Conjugation of bilirubin is reduced in
UGT1A1 poor metabolizers.
Unconjugated bilirubin accumulates
in the blood, which can deposit in
tissues causing yellowing of the skin
or eyes.

Potential ADRs in patients with inherited metabolic disorders

Gene product	Effect
<p>✱ <i>G6PD</i> deficiency</p> <p>G6PD: glucose-6-phosphate dehydrogenase</p>	<ul style="list-style-type: none">• Hemolytic anemia• Triggered by drugs that cause oxidative stress <p>G6PD in erythrocytes is necessary for the production of reduced glutathione</p>
Heme synthesis enzyme deficiencies	<ul style="list-style-type: none">• CYP inducers can increase the activity of enzymes proximal to a deficient enzyme in the pathway, which can cause accumulation of porphyrins• Trigger or exacerbate porphyrias
<p><i>RYR1</i></p> <p>Ryanodine receptor</p>	<ul style="list-style-type: none">• Malignant hyperthermia• Triggered by inhalational anesthetics / succinylcholine
<i>VKORC1</i>	<ul style="list-style-type: none">• Polymorphisms may confer sensitivity or resistance to standard warfarin doses, resulting in greater risk of bleeding or thromboembolism, respectively

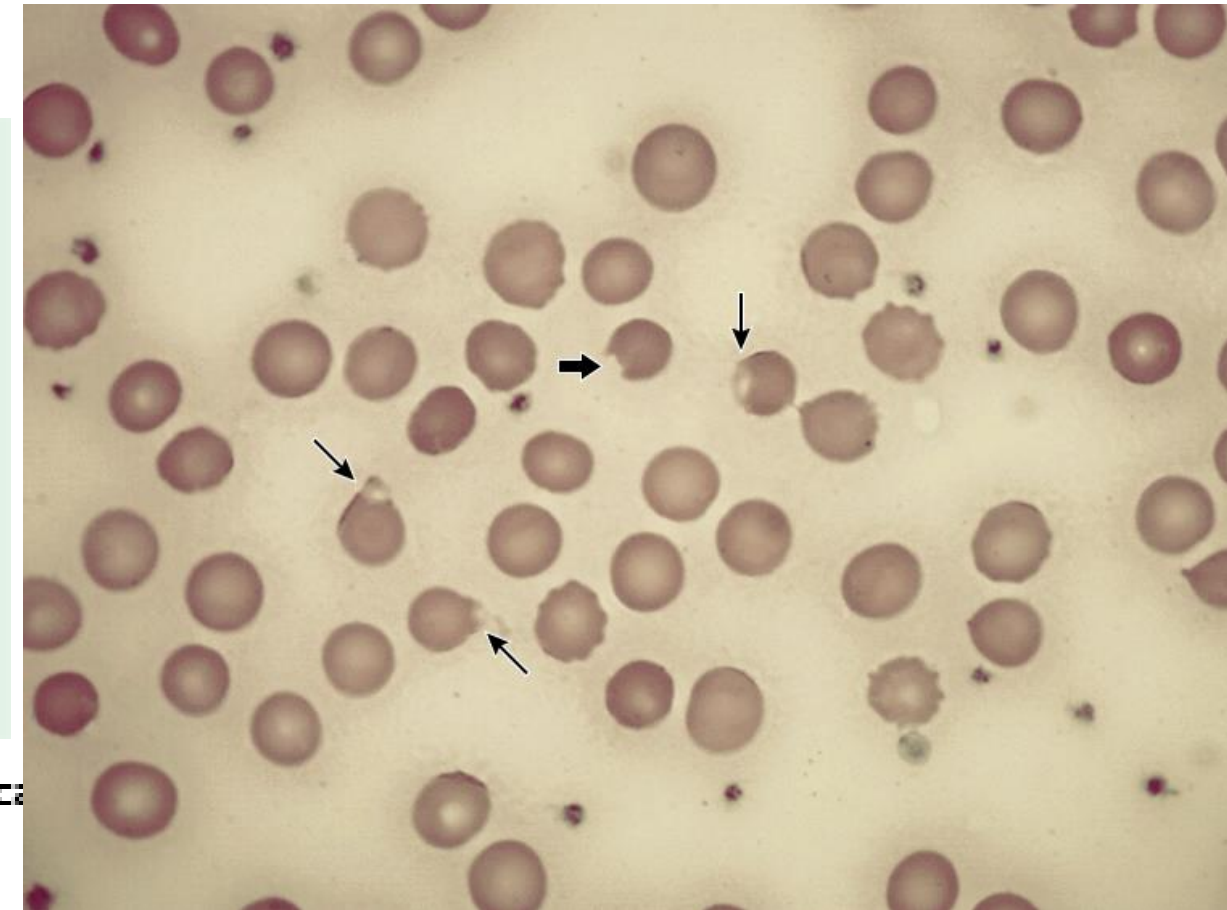
G6PD participates in the pentose phosphate pathway.
G6PD deficiency is an X-linked recessive inborn error of metabolism that predisposes to hemolysis.



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo. www.accessmedicine.com

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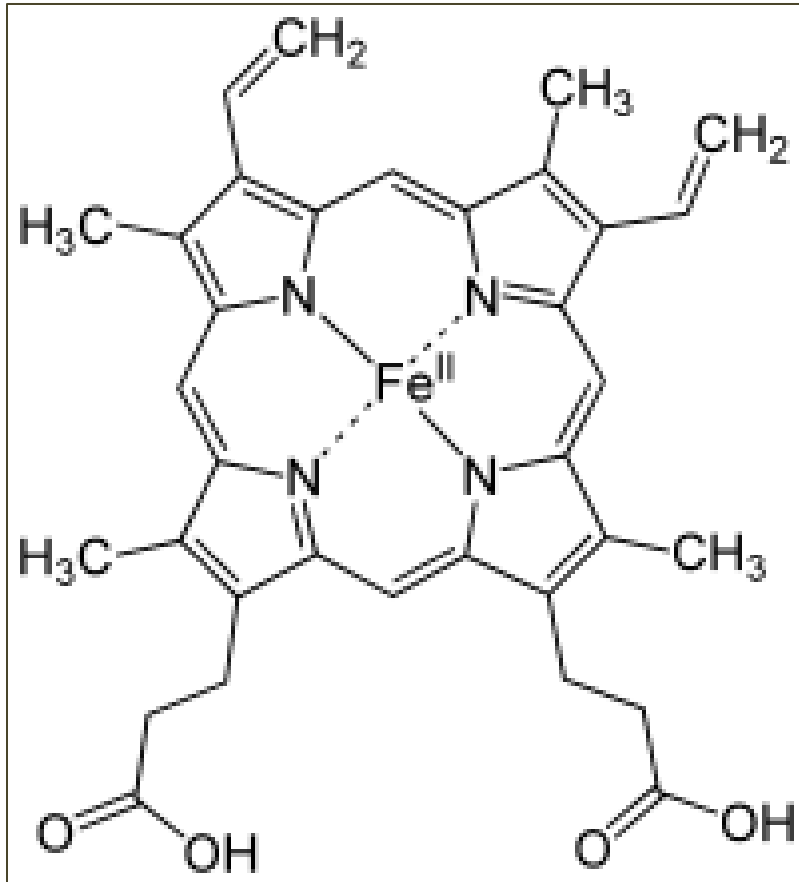
Left: Harrison's Principles of Internal Medicine, 19e, 2015; Figure 129-5



Examples of a bite cell (thick arrow) and blister cells (arrows) in a patient with G6PD deficiency.

UpToDate Graphic 117737 version 1.0

Certain drugs can precipitate porphyria attacks.



Heme biosynthesis involves eight enzymatic steps in the conversion of glycine and succinyl-CoA to heme. The eight enzymes are encoded by nine genes as the first enzyme in the pathway is encoded by two genes.

The porphyrias are metabolic disorders, each resulting from a deficiency of increased activity of a specific enzyme in the heme biosynthetic pathway. Certain drugs can precipitate attacks.



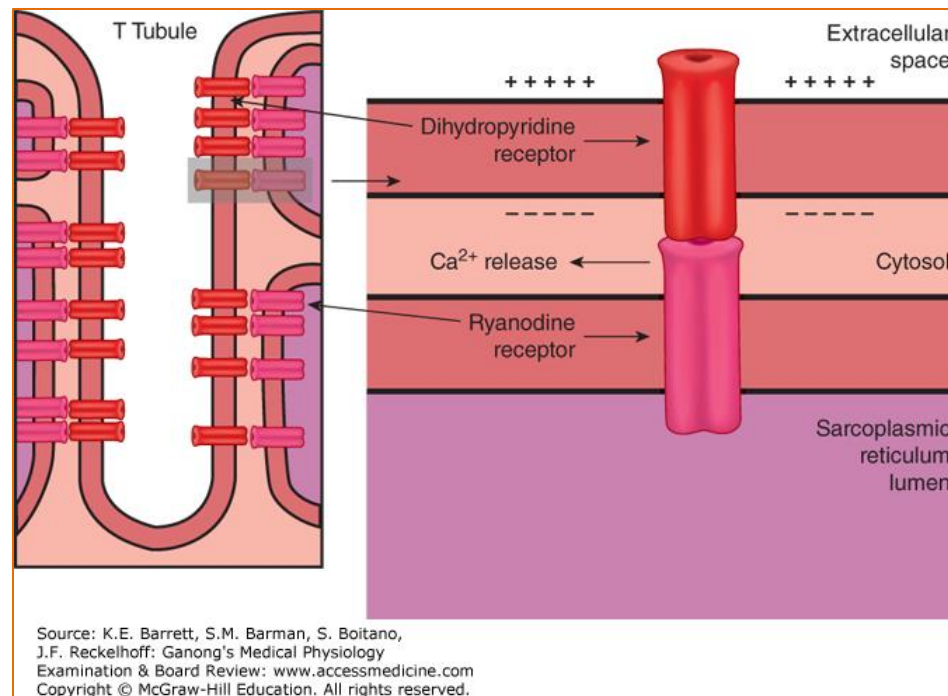
Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e
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Typical cutaneous lesions in a patient with porphyria cutanea tarda. Chronic, crusted lesions resulting from blistering due to photosensitivity on the dorsum of the hand of a patient with porphyria cutanea tarda.
Harrison's Principles of Internal medicine, 21e
Figure 416-3



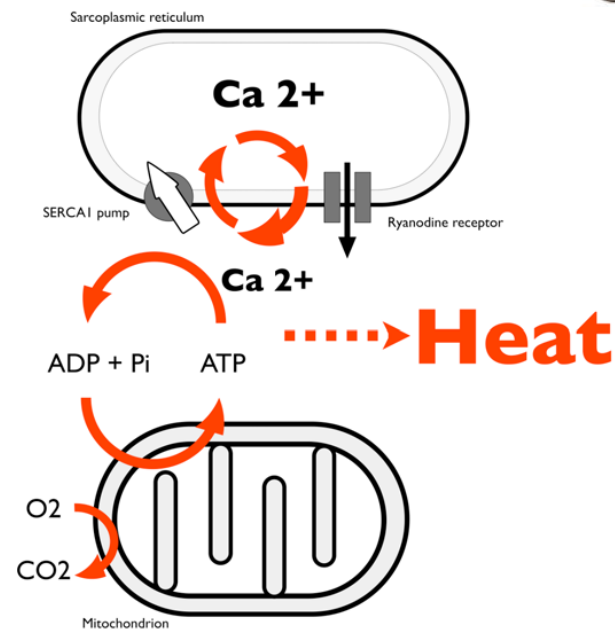
Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e
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Erythema and edema of the hands due to acute photosensitivity in a 10-year-old boy with erythropoietic protoporphyria
Harrison's Principles of Internal medicine, 21e Figure 416-4:

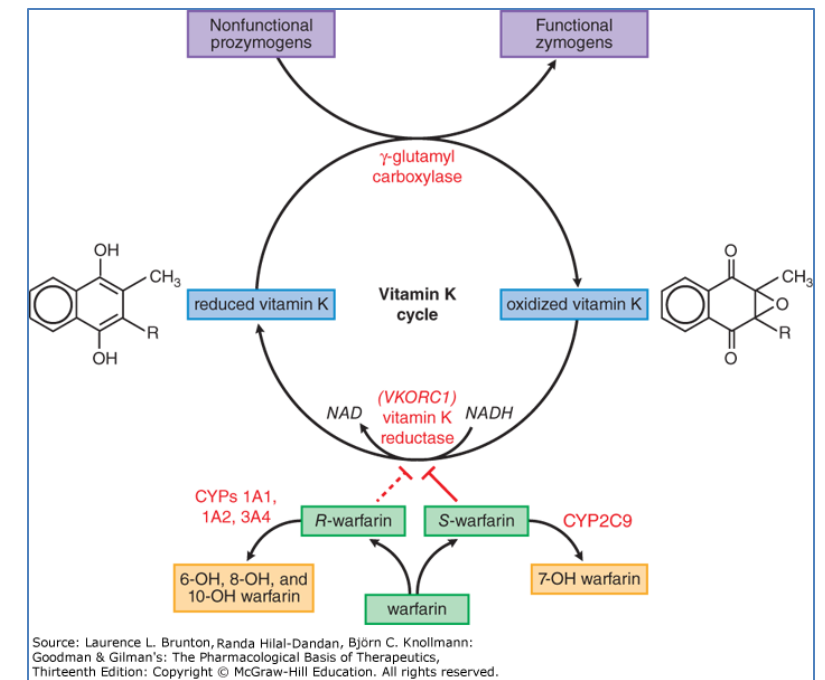


In skeletal muscle, the voltage-gated dihydropyridine receptor in the T tubule triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) via the ryanodine receptor (RyR). In patients with RyR1 channelopathy, succinylcholine and halogenated anesthetics can trigger Ca^{2+} release in muscle cells, causing sustained contraction and heat production → **malignant hyperthermia**.

Malignant hyperthermia



- Brain
increase in metabolism, neuronal damage
- Heart
ST-segment alterations, cardiac dysfunction
- Kidneys
acute renal failure
- Gastrointestinal tract
increase in permeability of gut epithelium, translocation of endotoxins
- Coagulation
disseminated intravascular coagulation
- Muscle
mitochondrial damage, rhabdomyolysis



Vitamin K is a cofactor essential in the formation of the coagulation factors synthesized in the liver: II, VII, IX, X, protein C and protein S. VKORC1: vitamin K epoxide reductase complex subtype 1 polymorphisms may increase sensitivity or resistance to standard warfarin doses.

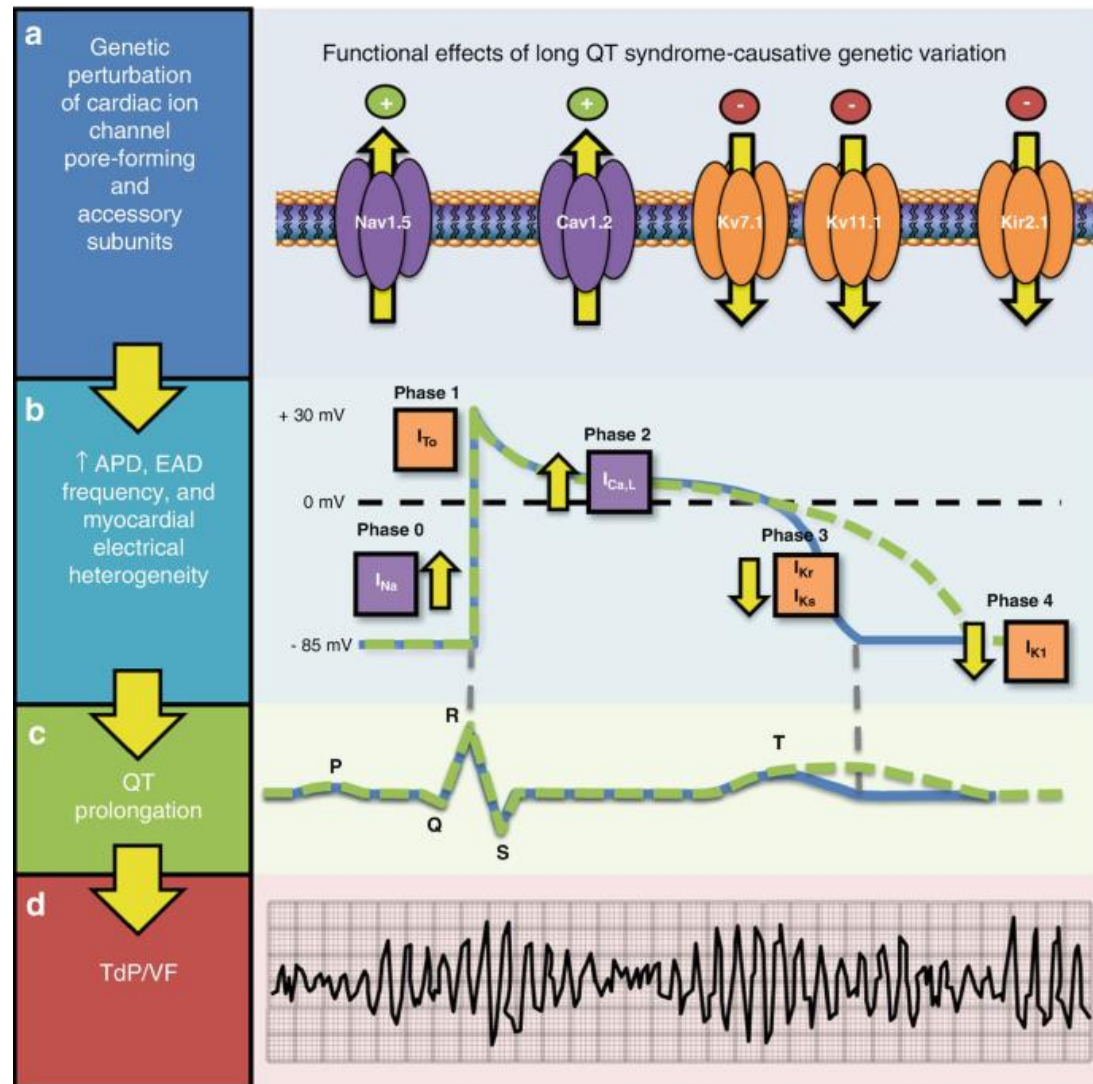
Left: Barret, Barnum, et.al. Ganong's Medical Physiology Examination & Board Review, 2017; Figure 5-7

Middle: <https://www.thinglink.com/scene/705211532971081729>; Freiermuth & Iazzo; <https://www.researchgate.net/publication/259978859>

Right: Goodman & Gilman's *The Pharmacological Basis of Therapeutics*, 13e, 2018 Figure 32-6

Potential ADRs in patients with inherited metabolic disorders

Gene product	Effect
*Long QT syndrome genetically heterogenous	<ul style="list-style-type: none">• Congenital and acquired• Serious and unpredictable ventricular arrhythmia• Administration of drugs that prolong the QTc interval on the ECG can cause marked QT interval prolongation and torsades de pointes ventricular arrhythmia.• Inhibition of metabolism and increased systemic levels of drugs that cause QT interval prolongation can increase the risk of arrhythmia in susceptible patients.
*HLA variants	<ul style="list-style-type: none">• Several HLA alleles have been associated with increased risk of drug-induced serious and life-threatening hypersensitivity reactions related to certain medications.• HLA typing may be required to prior to drug therapy to help prescribers in the prediction and prevention of serious adverse drug reactions.



Long-QT syndrome is a clinically and genetically heterogeneous disorder of cardiac repolarization characterized on the ECG by heart-rate-corrected QT interval (QTc) prolongation and clinically by a propensity for torsadogenic syncope, seizures, and sudden death. Drugs that increase QTc increase the risk of ventricular arrhythmia.



Positive patch test to abacavir in a HLA-B*57:01 patient with HIV infection who developed an hypersensitivity reaction with exanthema, fever, and gastrointestinal symptoms.
https://www.researchgate.net/figure/Positive-patch-test-to-abacavir-in-a-HLA-B5701-patient-with-HIV-infection-who-developed_fig5_330739876

Some strategies for reducing the risk of adverse drug events

- › **Right drug | Right patient | Right dose | Right route | Right time**
- › Discontinuing medications
- › Prescribing new medications sparingly
- › Reducing the number of prescribers
- › Frequently reconciling medications
- › Educating prescribers
- › Educating patients

American Family Physician 2013 Mar 1;87(5): 331-336 Reducing the Risk of Adverse Drug Events in Older Patients

<https://pubmed.ncbi.nlm.nih.gov/23547549/#:~:text=Strategies%20to%20reduce%20the%20risk,prescribers%2C%20and%20frequently%20reconciling%20medications.>

Question

- What is an aim of pharmacogenomics research?

Summary of Drug Toxicities and Pharmacogenomics

- Adverse drug reactions and adverse drug events from overdose, dose reductions, abrupt withdrawal of a drug, resistance to therapy, paradoxical effects, and drug-disease, drug-drug-, drug-supplement, and drug-food interactions. Effects may range from relatively benign to serious, causing significant morbidity or death. They may be acute, delayed, and chronic.
- ADRs/ADEs can result from overdose, dose reductions, abrupt withdrawal of a drug, resistance to therapy, paradoxical effects, and drug interactions.
- Drug-induced deleterious effects to cells and organs can be caused by the parent drug, toxic metabolites, or reactive oxygen species. Small chemicals may form hapten-protein complexes that activate the immune system against the complex. Some drugs can directly activate a hypersensitivity reaction (allergy) in sensitive individuals.
- Mechanisms include “on-target” (desired target in intended and unintended tissue) and “off-target” (unintended target in intended and unintended tissue) drug actions.
- Drugs taken by a pregnant person can cause teratogenicity or other fetotoxicity. Neonates can manifest abstinence syndrome resulting from maternal use of addictive drugs. Other effects on neonate include premature birth and low birth weight. The Pregnancy and Lactation Labeling Rule helps prescribers communicate the risks of pharmacologic treatment to pregnant and breastfeeding patients and preconception advice to females of reproductive potential and males who wish to father a child.

- Polymorphisms in metabolic enzymes, are thought to underlie individual differences in the rate at which drugs are metabolized. The categories are poor, intermediate, extensive, and ultra-rapid metabolizers. Genetic variants in transporters, drug targets, and variant HLA alleles may also relate to an individual's response to drug therapy.
- Pharmacogenomics research is the systematic examination of genes, gene products, and variation in gene expression and function, using tools for surveying the entire genome. Pharmacogenomics researchers evaluate multigenic determinants of that may predict drug response – efficacy and safety or drug toxicity – in an individual or across a population.
- An aim of pharmacogenomics research is to guide decisions on prevention, diagnosis, and disease management strategies using an individual's clinical and genetic information. This information may be included in the labeling of specific drugs, which may help clinicians select the drugs and doses best suited for the individual patient based on their individual genes.
- Precision medicine is an approach to tailoring disease prevention and treatment that accounts for differences in patients' genes, lifestyles, and environment.

Right drug | Right patient | Right dose | Right route | Right time

References

- Access Medicine Goodman & Gilman's The Pharmacological Basis of Therapeutics 14e, 2023; Chapter 7: Pharmacogenetics & Pharmacogenomics; Chapter 9: Principles of Clinical Toxicology; Chapter 38: Introduction to Immunity and Inflammation
- Access Medicine Harrison's Principles of Internal medicine, 21e. 2023; Chapter 416: The Porphyrrias
- Access Medicine Katzung's Basic & Clinical Pharmacology 16e, 2024: Chapter 5: Pharmacogenomics and Chapter 58: Management of the Poisoned Patient
- Access Medicine Williams Obstetrics, 24e; Chapter 12: Teratology, Teratogens, and Fetotoxic Agents
- US Food & Drug Administration Pregnancy and Lactation Labeling (Drugs) Rule (last reviewed Mar 5, 2021) <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

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<https://comresearchdata.nyit.edu/redcap/surveys/?s=HRCY448FWYXREL4R>