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

lgolds01@nyit.edu

Do.
Make.
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Innovate.
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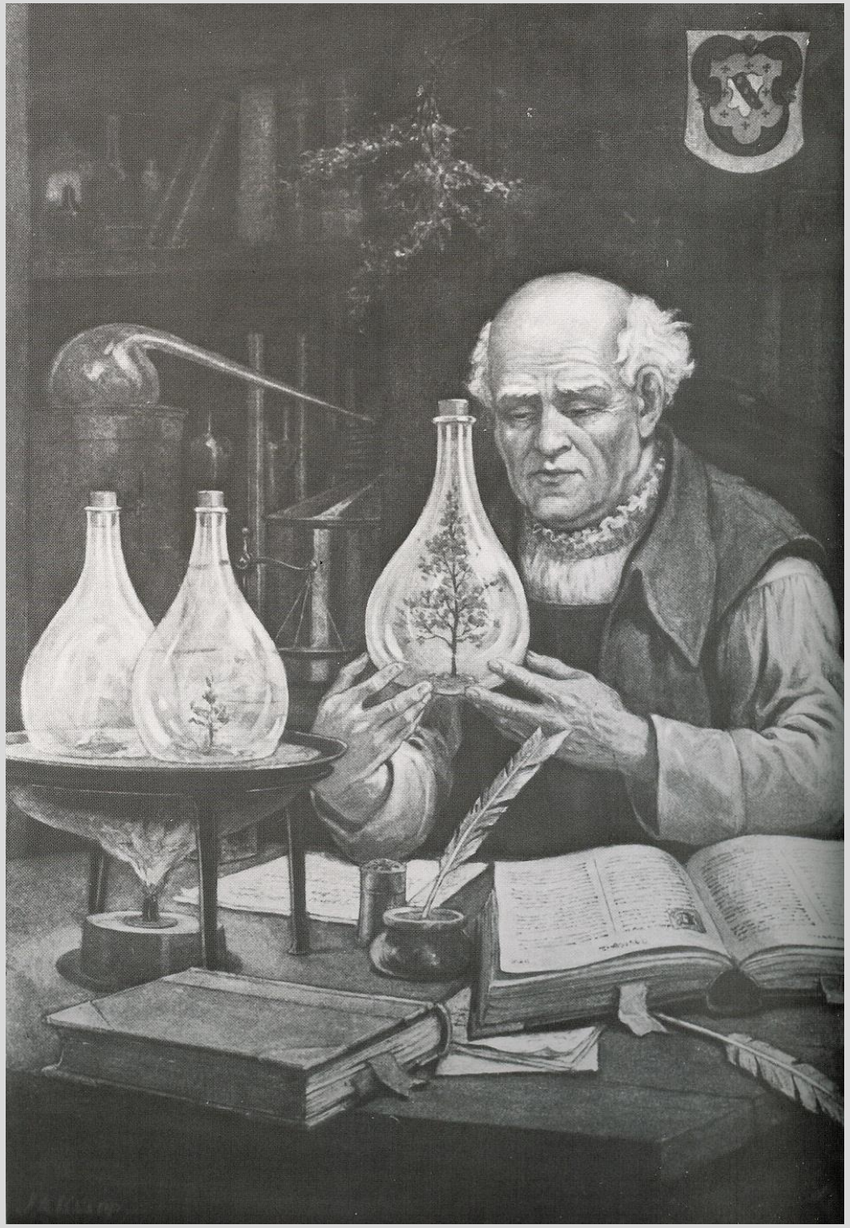

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"All things are poison, for there is nothing without poisonous qualities; only the dose permits something not to be poisonous."

Paracelsus 1493-1541

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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.

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

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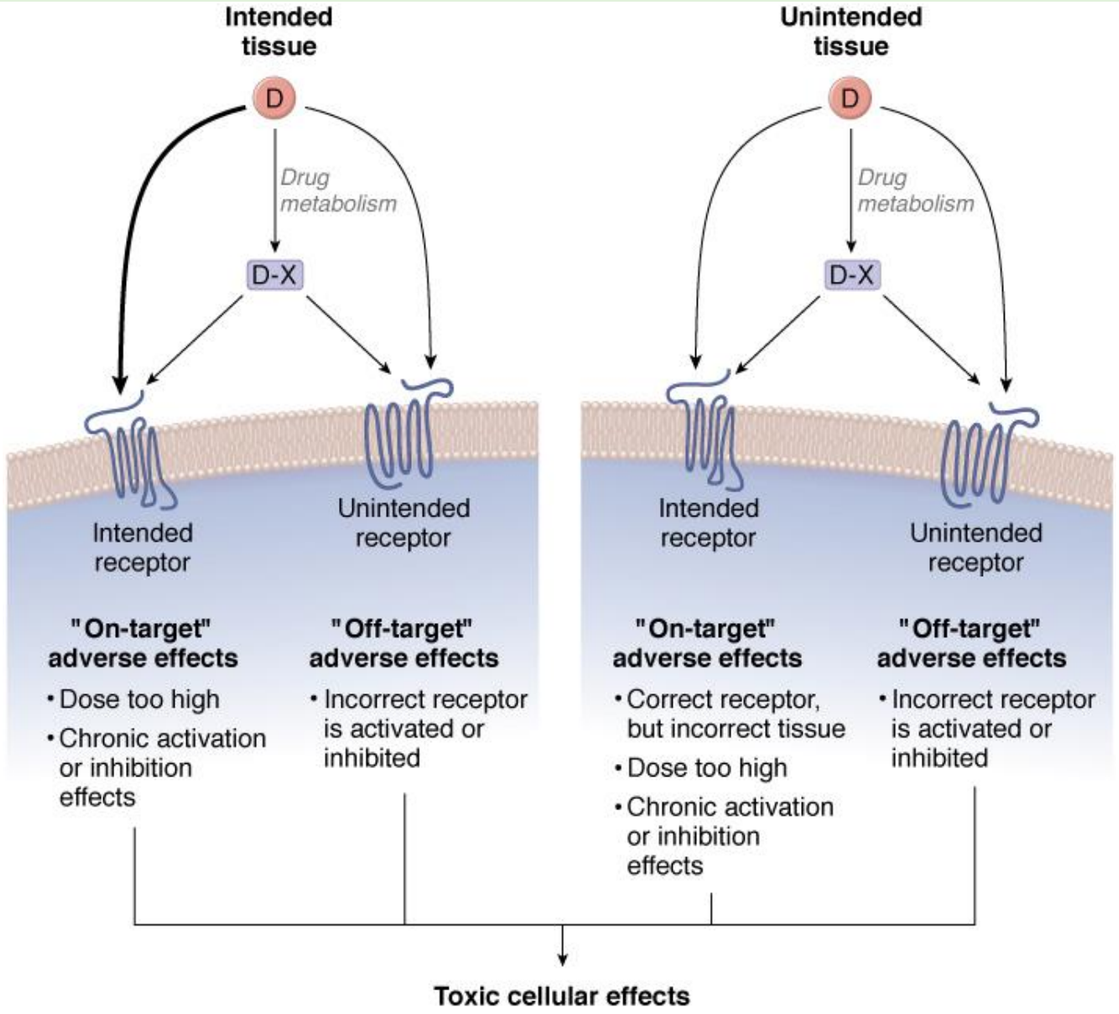
In addition to learning the terminology, be able to recognize, explain in your own words to a friend or relative, and apply the following:

- 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.

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)

Slide adapted by LG

Toxic effects may be acute, delayed, or cumulative

Adverse effects may cause …

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Local reactions

Systemic reactions

Immunogenic reactions

- Hypersensitivity reactions
- Mechanism-related immune system upregulation

  Example: anticancer immune checkpoint inhibitors

Photosensitivity

Fetal toxicity

Cellular toxicity

- Apoptosis
- Necrosis

DNA damage

- Mutagenesis:

  Gene mutations give rise to altered proteins.
- Carcinogenesis

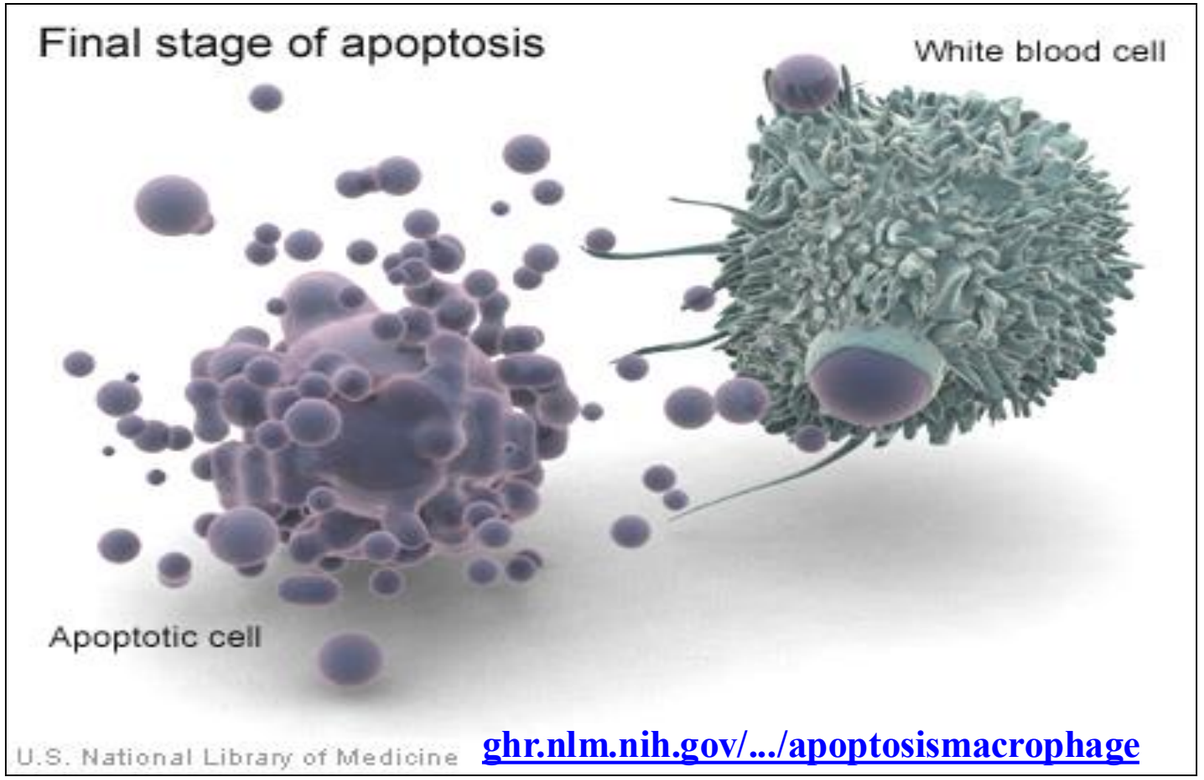
  Mutations in genes that regulate cell growth may lead to induction of cancer.

Organ toxicity

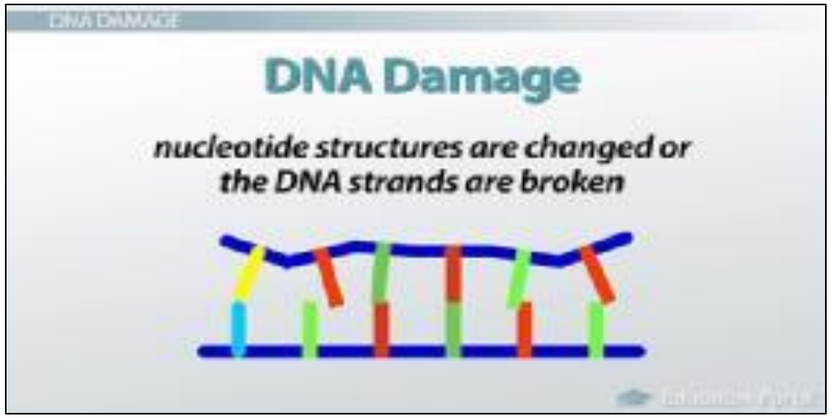
- Liver
  - Hepatitis / necrosis
  - Cirrhosis
- Kidney
  - Glomerular nephropathy
  - Tubular necrosis
  - Interstitial nephritis
- Nerves
  - Neuropathy
  - Seizures
  - Coma
- Bone marrow toxicity
  - Neutropenia
  - Anemia
  - Thrombocytopenia

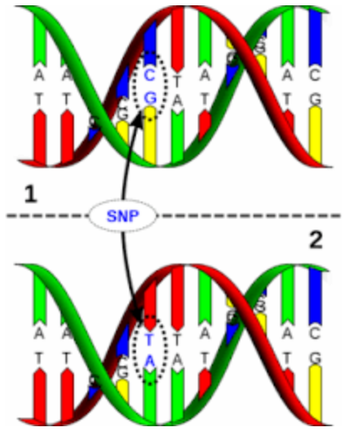
Effects may be reversible or irreversible.
Effects may range from minor discomfort to significant morbidity and mortality.

Apoptosis: Programmed cell death

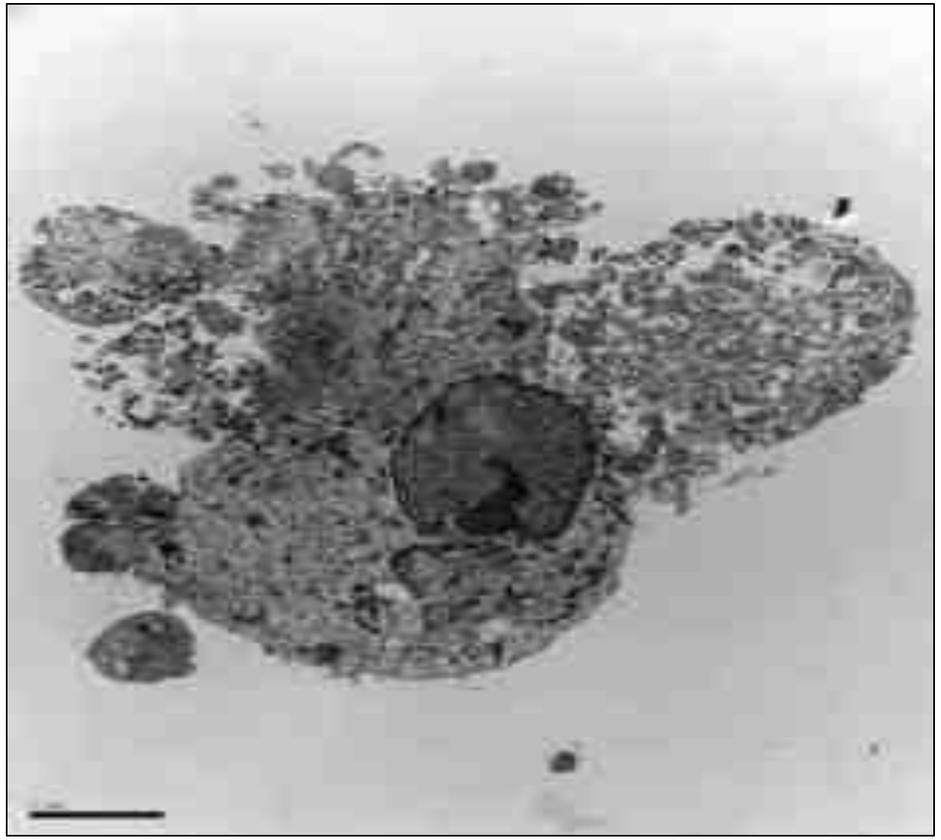


ghr.nlm.nih.gov/.../apoptosismacrophage





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



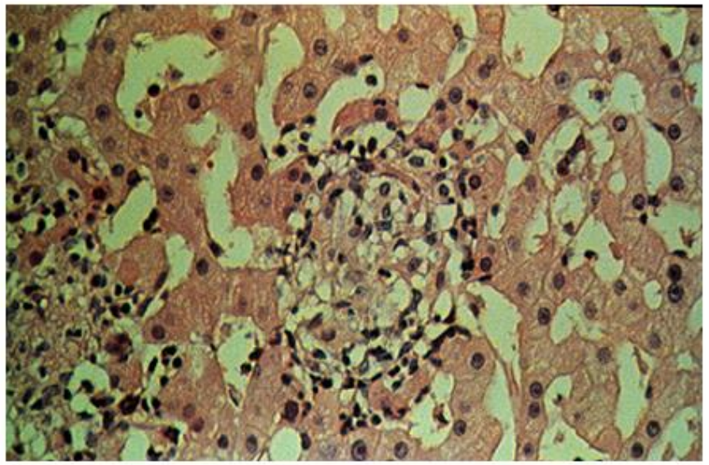
Francis Ka Ming Chan PhD
http://profiles.umassmed.edu/profiles/display/133299

Necrosis: Traumatic cell death

Electron micrograph of a necrotic cell exhibiting extensive loss of plasma membrane integrity.

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



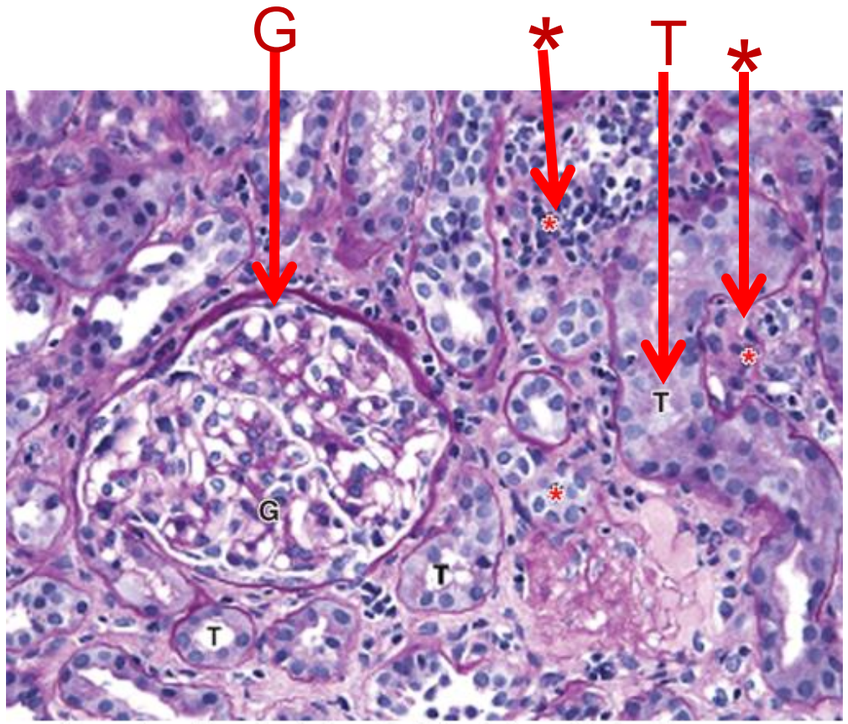
High power view of a liver biopsy shows a noncaseating granuloma and perigranulomatous mononuclear cell inflammation with hepatic necrosis.

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.

UpToDate Graphic 64126 version 1.0

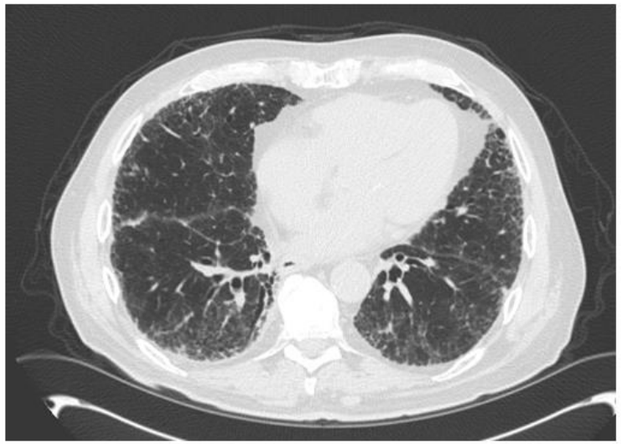


Source: Joseph Loscalzo, Anthony Fauci, Dennis Kasper, Stephen Hauser, Dan Longo, J. Larry Jameson: Harrison's Principles of Internal Medicine, 21e

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)

Harrison's Principles of Internal Medicine Figure 316-2

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.

UpToDate Graphic 90390 version 2.0

Pregnancy and Lactation (Drug) Labeling Rule

Labeling to facilitate prescriber counseling for patients of reproductive potential.

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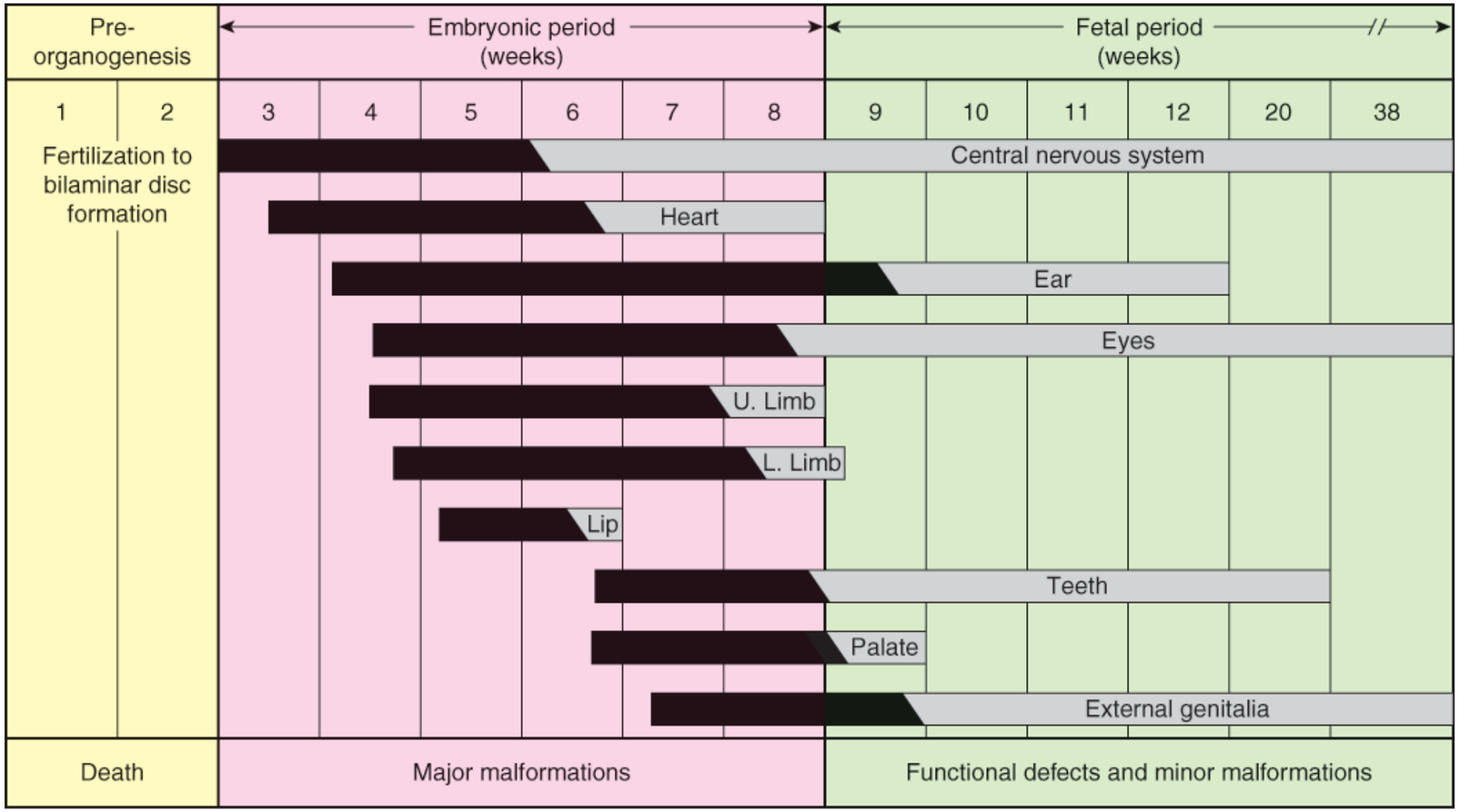
Three subsections:

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

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

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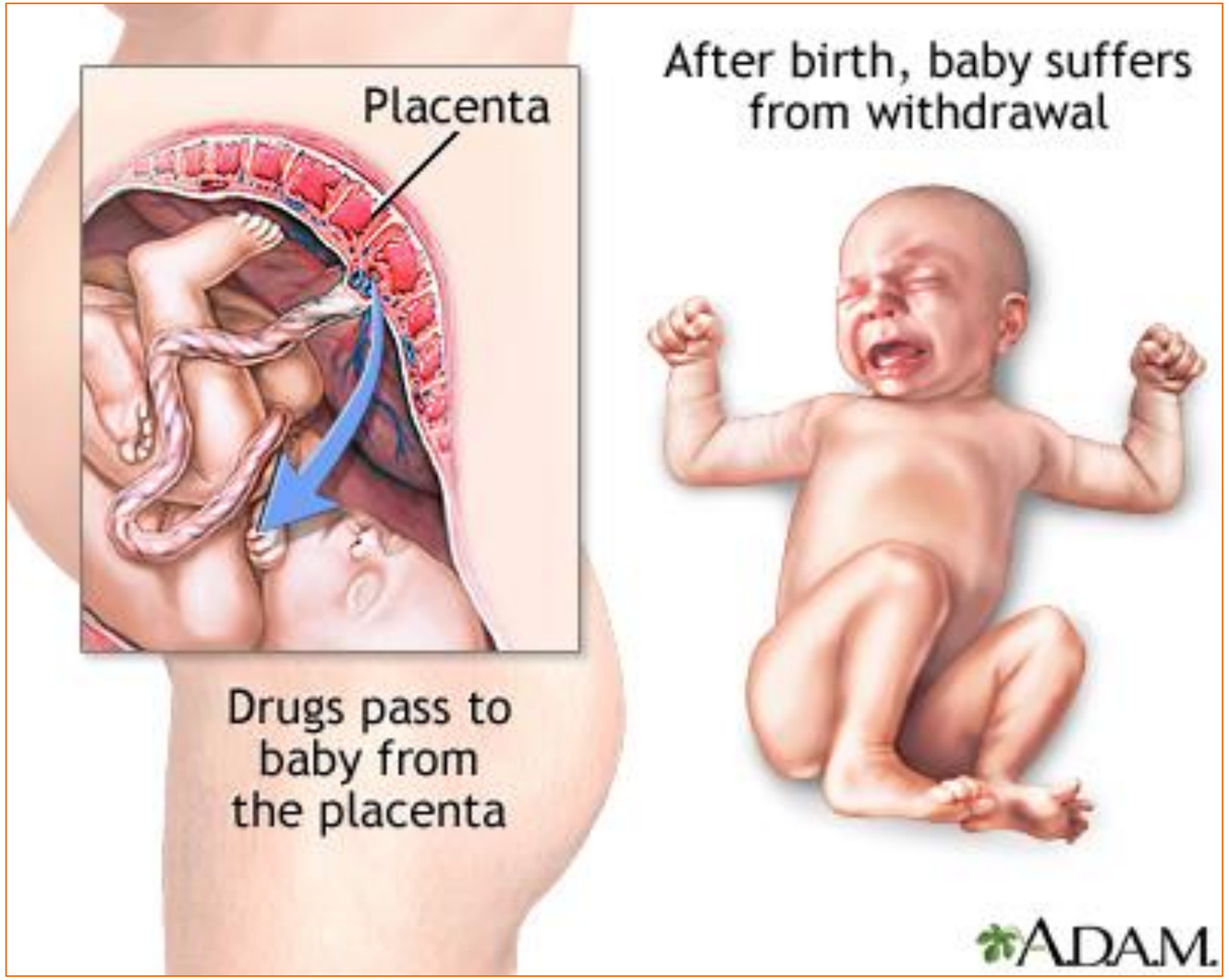
Fetal effects

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

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- 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?

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.

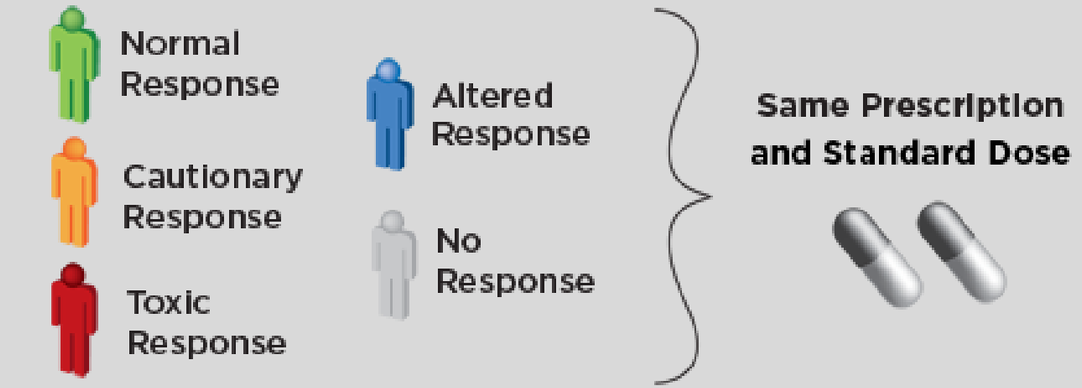
Pharmacogenomics:

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.



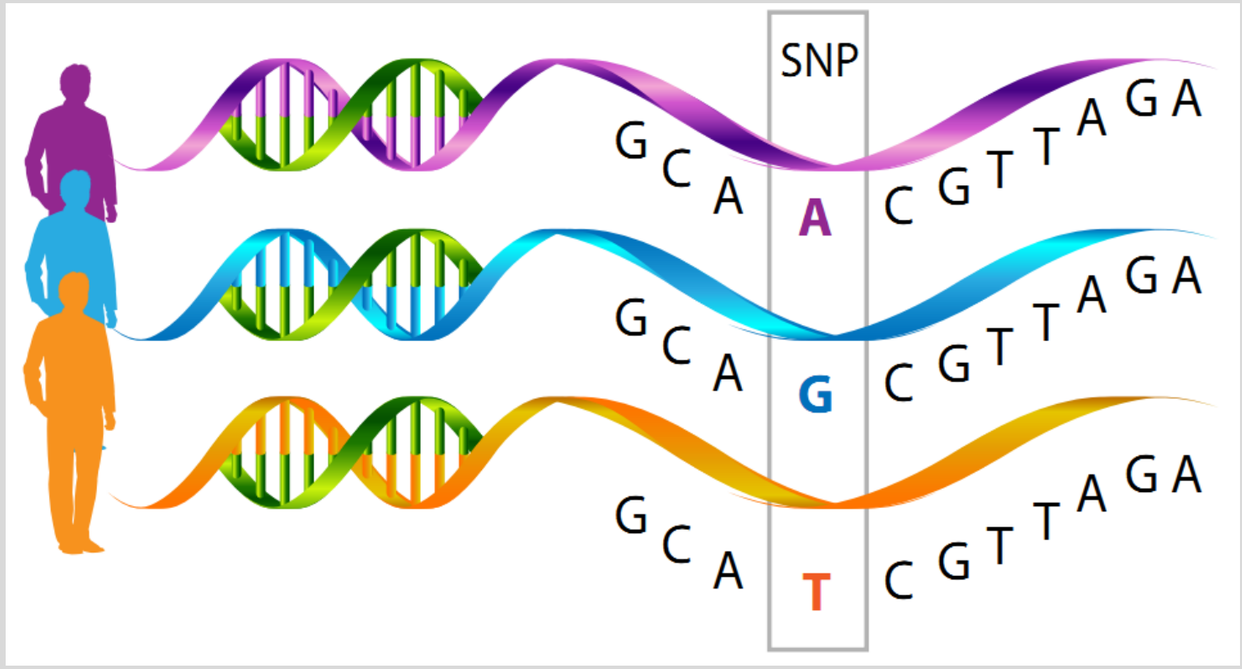
http://www.admerahealth.com/pharmacogenomics-physicians/

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.

NIH National Institute of General Medical Sciences: Pharmacogenomics
https://www.nigms.nih.gov/education/fact-sheets/Pages/pharmacogenomics.aspx

Single Nucleotide Polymorphism (SNP)



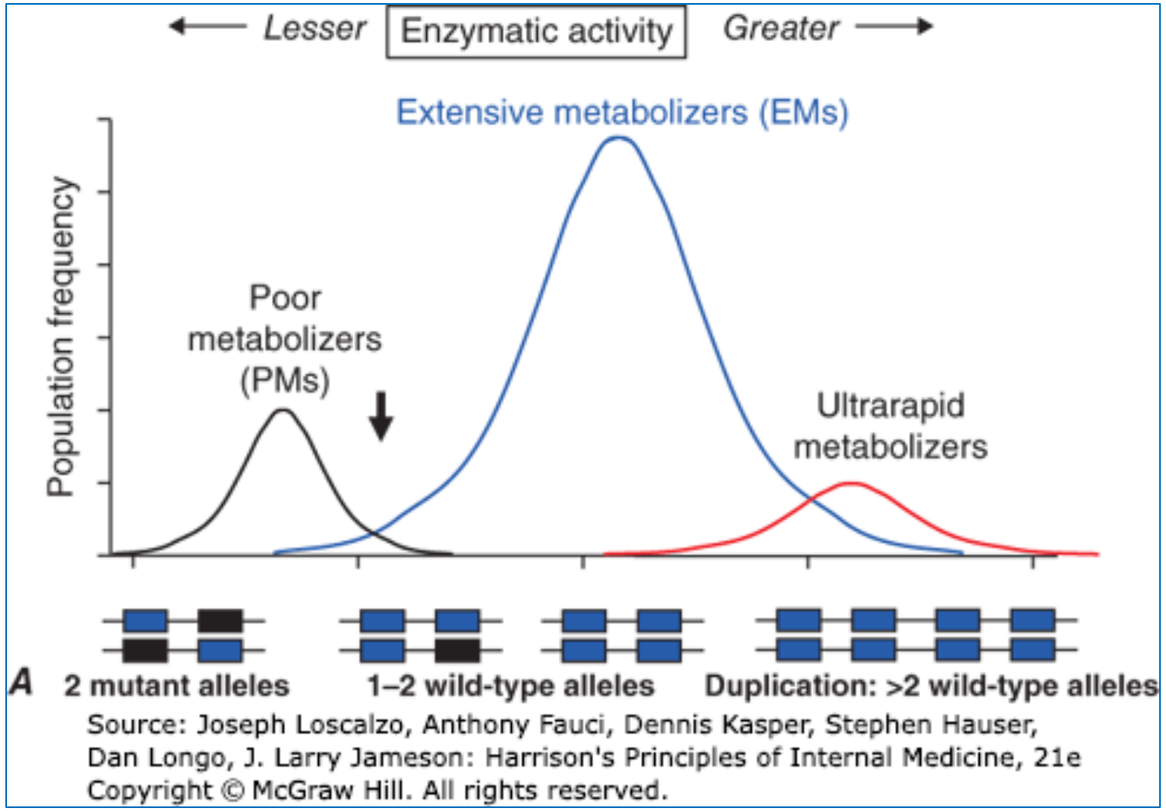
Single Nucleotide Polymorphisms are a single nucleotide changes in an area of an organism's DNA that is different in more than 1% of the population. SNPs occur in the DNA in **1 out of every 300 nucleotides**. In the human genome, this means that there are at least 1 million SNPs in the human's 3 million-nucleotide 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/

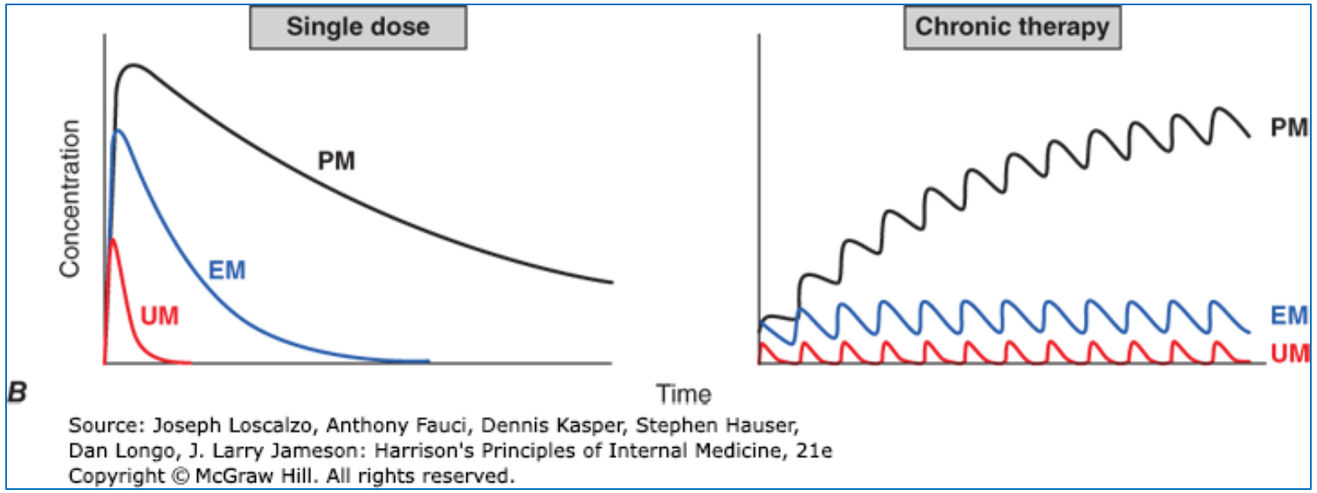
Pharmacogenomics looks at variations in genes for proteins, such as metabolic enzymes, drug transporters, and drug targets.

- 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



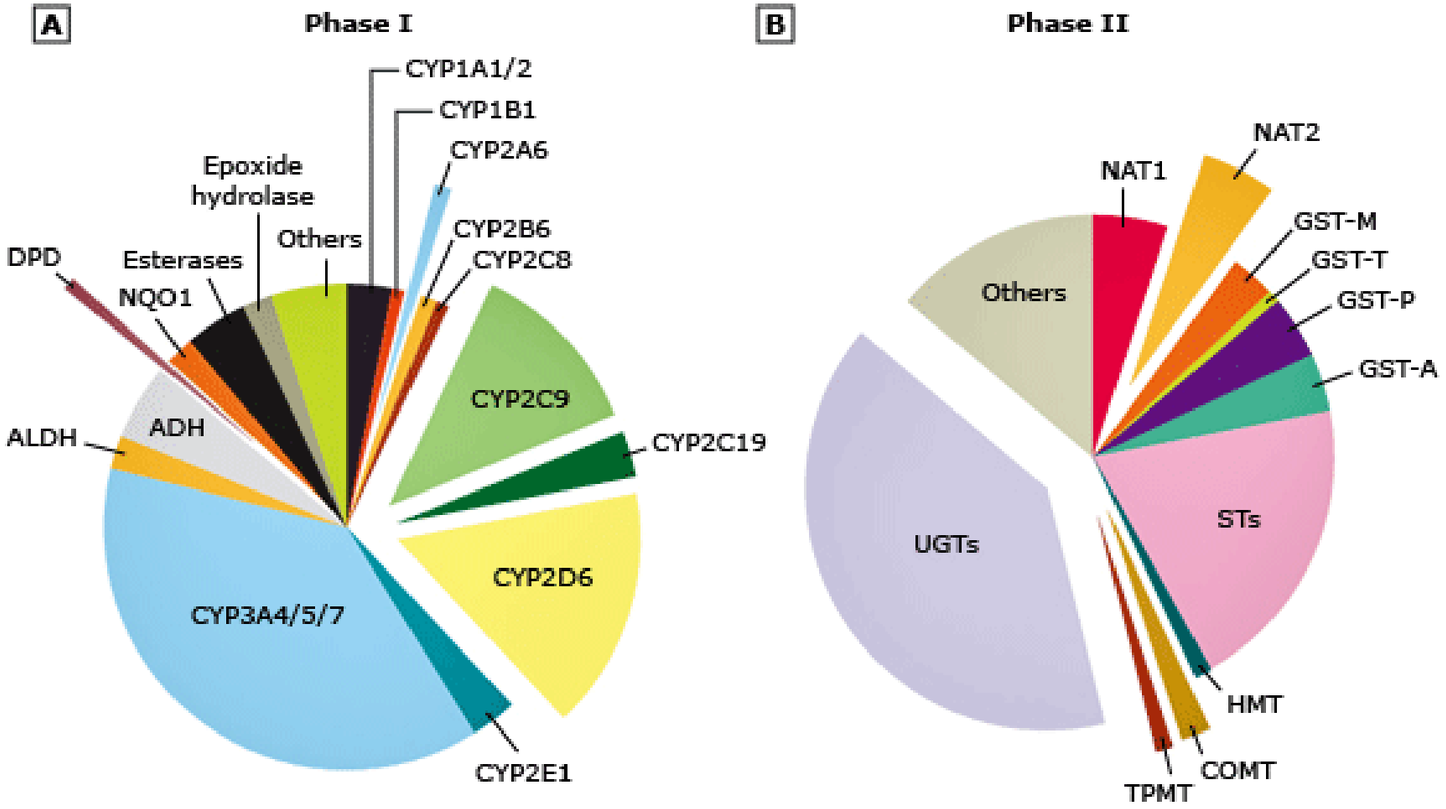
A. Distribution of CYP2D6 metabolic activity across a population. The heavy arrow indicates an antimode, separating poor metabolizer subjects (PMs, black), with two loss-of-function CYP2D6 alleles (black), indicated by the intron-exon structures below the chart. Individuals with one or two functional 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).

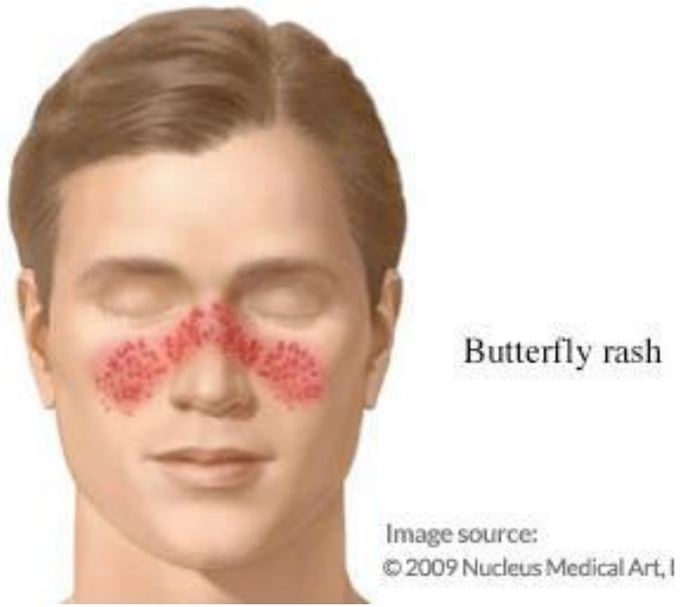
Citation: Chapter 68 Pharmacogenomics, Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson J. *Harrison's Principles of Internal Medicine, 21e;* 2022, figure 68-1.
Available at: https://accessmedicine.mhmedical.com/content.aspx?bookid=3095&sectionid=259857147 Accessed: May 30, 2023



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.



Butterfly rash

Image source:
© 2009 Nucleus Medical Art, I

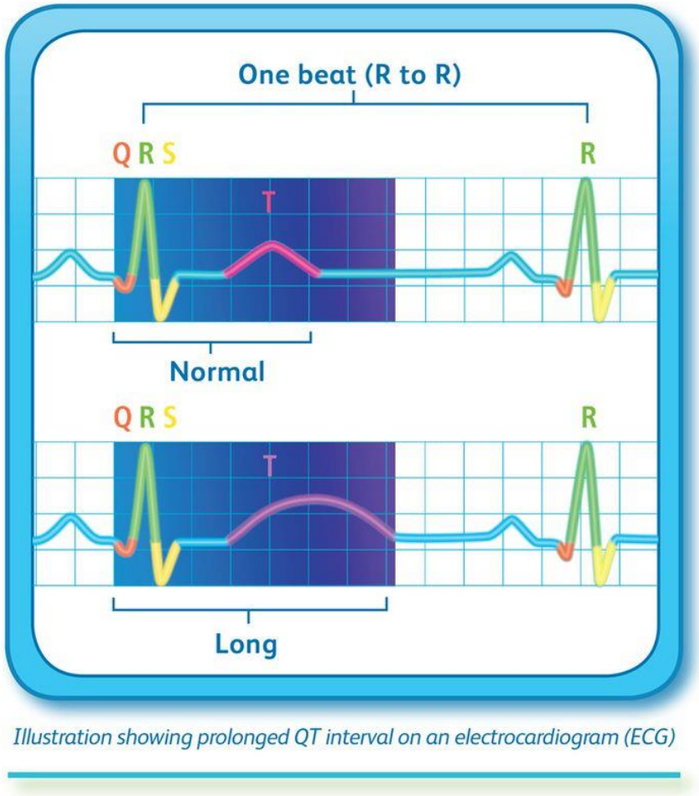
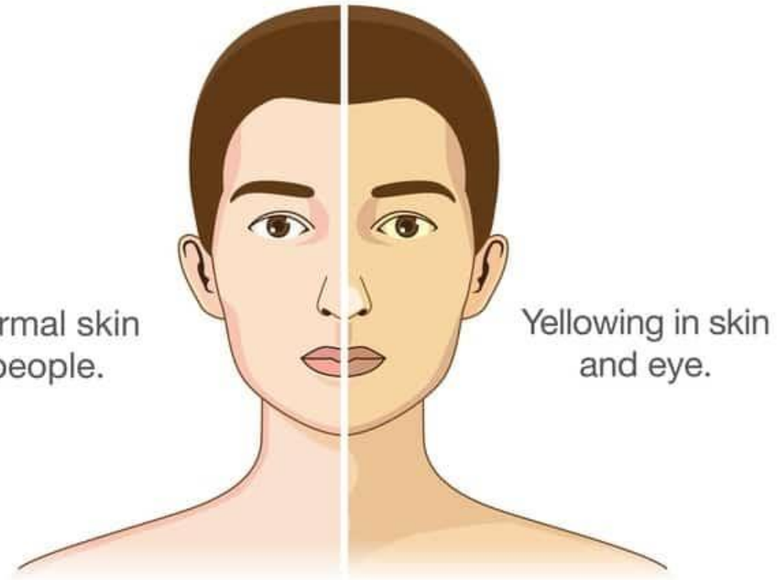


Illustration showing prolonged QT interval on an electrocardiogram (ECG)



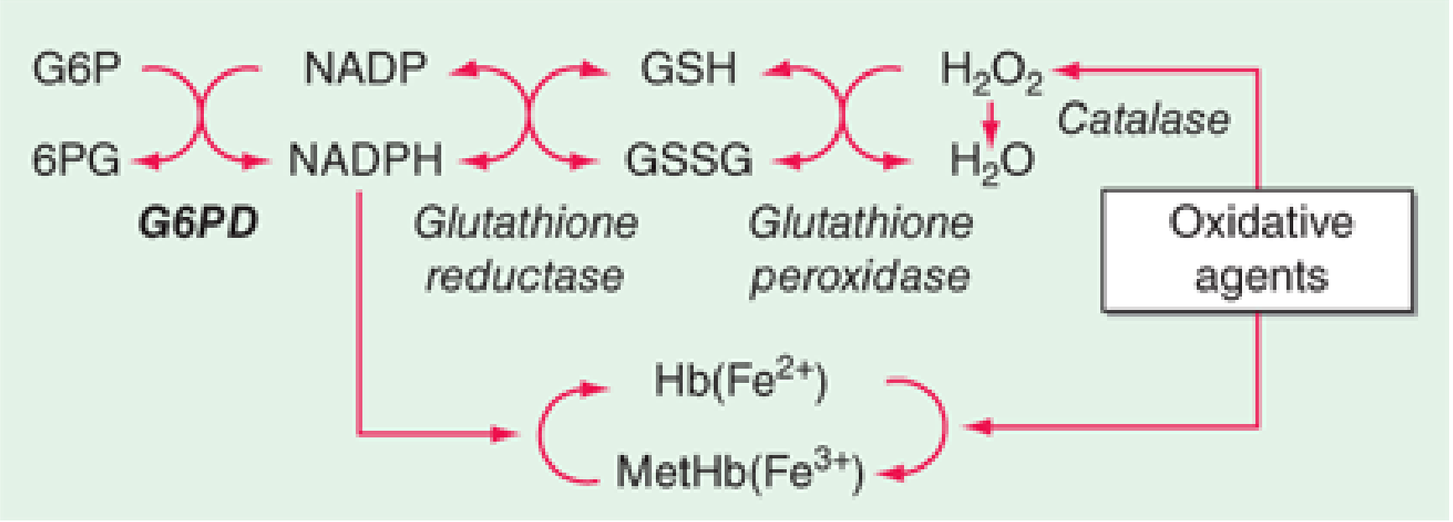
https://www.pinterest.com/icedraspberries/prolonged-qt/ https://andrea-digestive-clinic.com/gilberts-syndrome/

NAT2 PMs
Lupus-like syndrome (immune reaction)

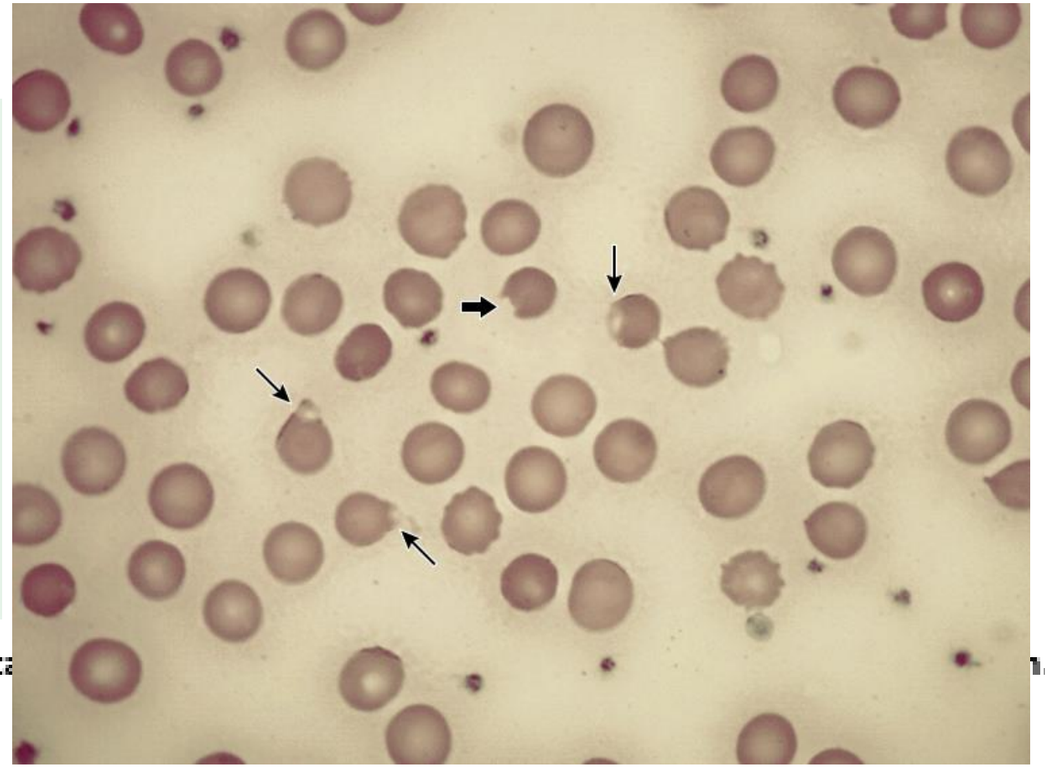
CYP PMs
QT interval prolongation can lead to ventricular arrhythmia
Decreased CYP metabolism of drugs that ↑QT interval or patients with ∗long QT syndrome∗

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.

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



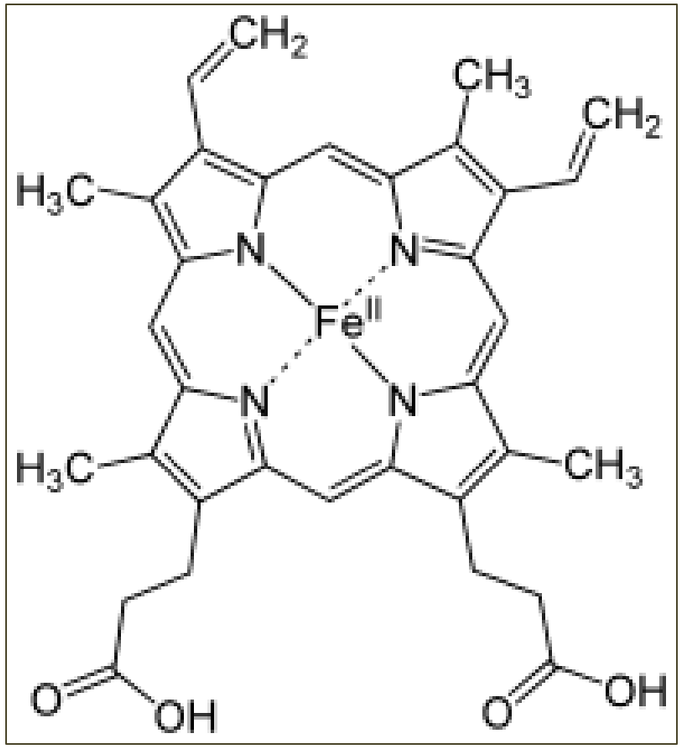
Left: Harrison's Principles of Internal Medicine, 19e, 2015; Figure 129-5



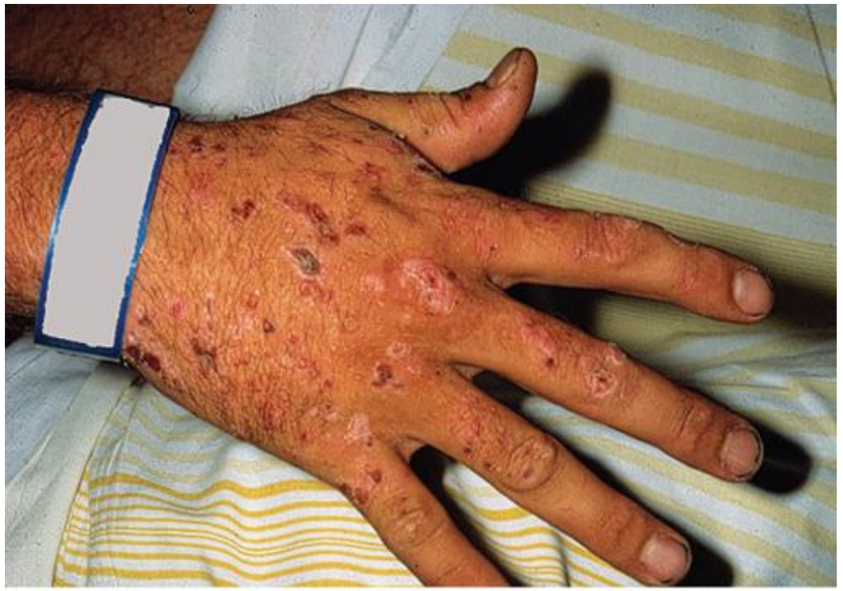
Examples of a bite cell (thick arrow) and blister cells (arrows) in a patient with G6PD deficiency.

UpToDate Graphic 117737 version 1.0

Certain drugs can precipitate porphyria attacks.

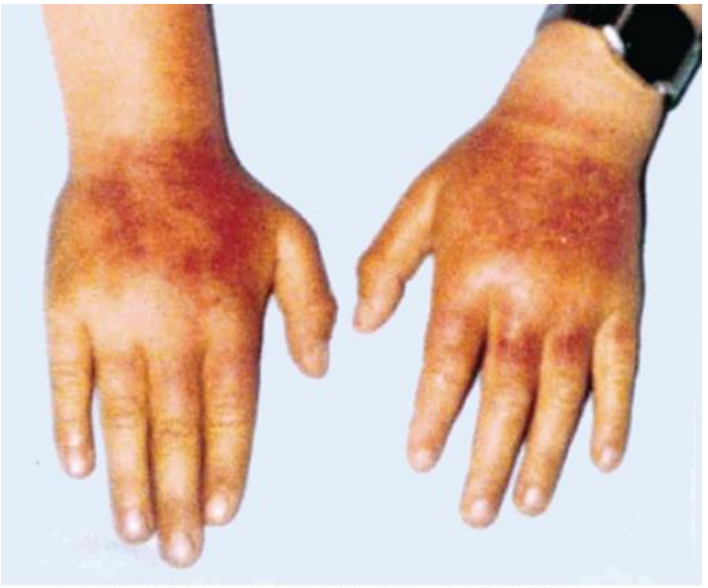


Heme biosynthesis involves eight enzymatic steps in the conversion of glycine and succinyl-CoA to heme. The eight enzymes are encoded by nine genes as the first enzyme in the pathway is encoded by two genes.



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.

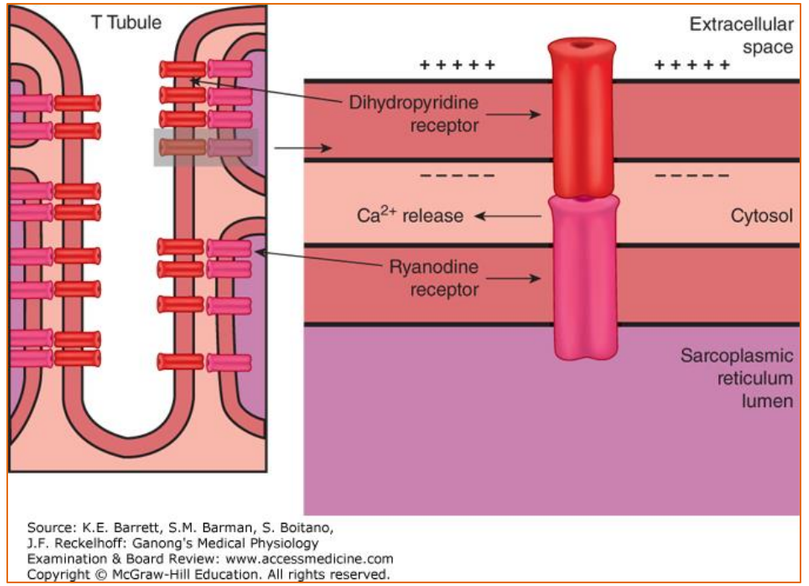
Harrison's Principles of Internal medicine, 21e Figure 416-3



Erythema and edema of the hands due to acute photosensitivity in a 10-year-old boy with erythropoietic protoporphyria

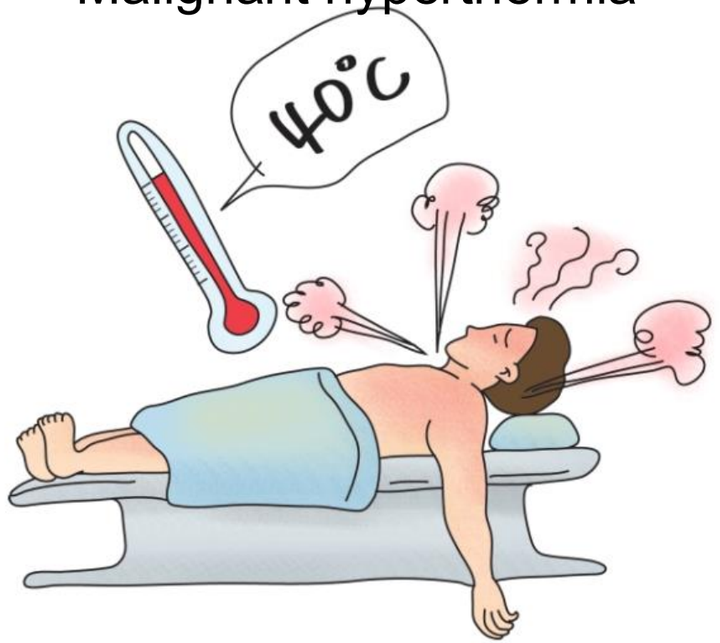
Harrison's Principles of Internal medicine, 21e Figure 416-4:

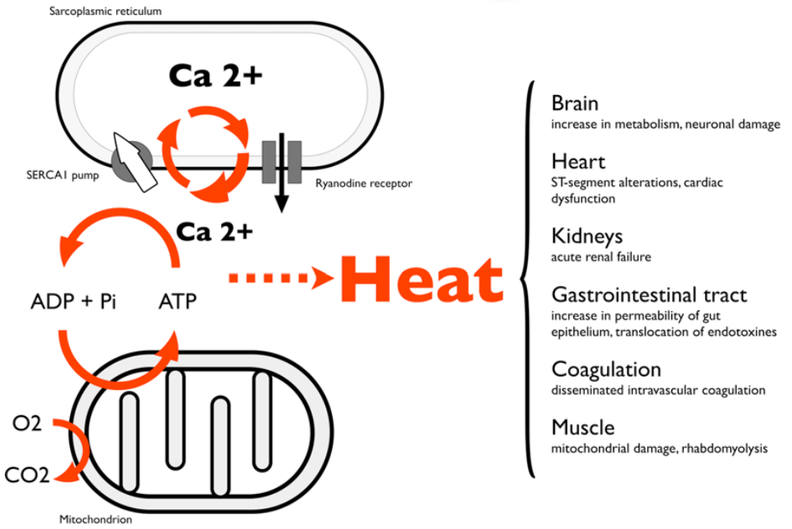
The porphyrias are metabolic disorders, each resulting from a deficiency of increased activity of a specific enzyme in the heme biosynthetic pathway. Certain drugs can precipitate attacks.

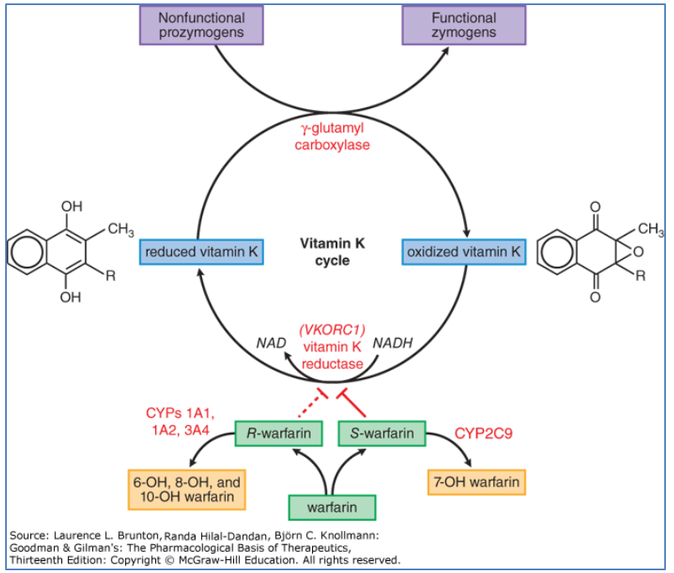


In skeletal muscle, the voltage-gated dihydropyridine receptor in the T tubule triggers Ca^{2+} release from the sarcoplasmic reticulum (SR) via the ryanodine receptor (RyR).
In patients with RyR1 channelopthy, succinylcholine and halogenated anesthetics can trigger CA2+ release in muscle cells, causing sustained contraction and heat production → **malignant hyperthermia.**

Malignant hyperthermia

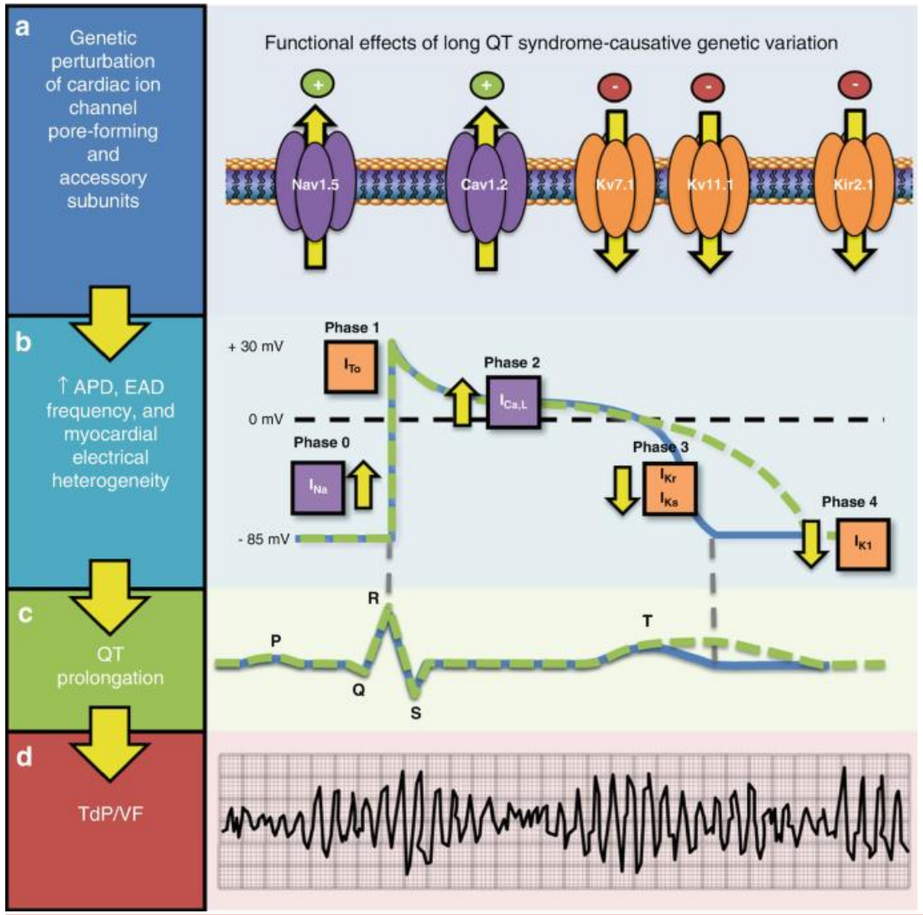






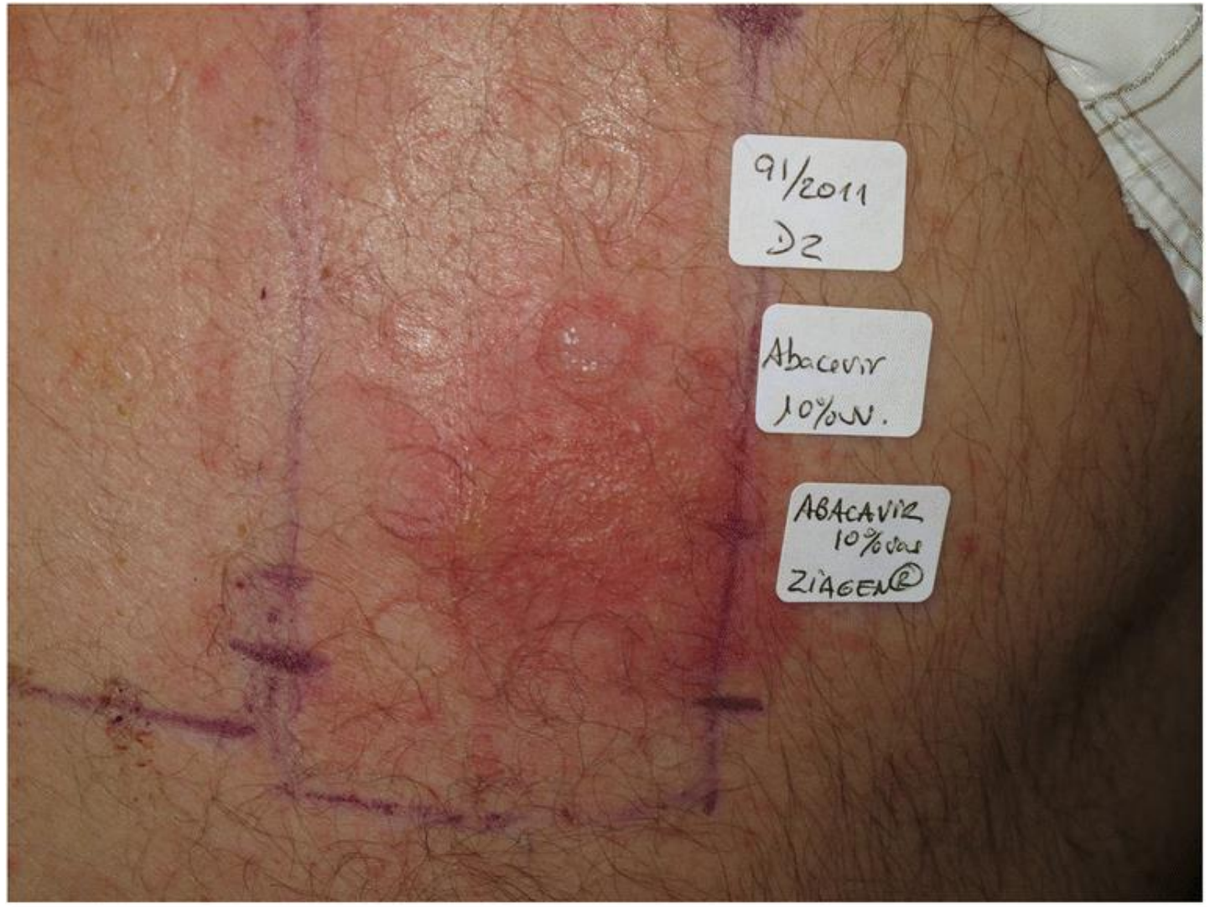
Vitamin K is a cofactor essential in the formation of the coagulation factors synthesized in the liver: II, VII, IX, X, protein C and protein S.
VKORC1: vitamin K epoxide reductase complex subtype 1 polymorphisms may increase sensitivity or resistance to standard warfarin doses.

Left: Barret, Barnum, et.al. Ganong's Medical Physiology Examination & Board Review, 2017; Figure 5-7
Middle: https://www.thinglink.com/scene/705211532971081729; Freiermuth & Iaizzo; https://www.researchgate.net/publication/259978859
Right: Goodman & Gilman *The Pharmacological Basis of Therapeutics*, 13e, 2018 Figure 32-6



Long-QT syndrome is a clinically and genetically heterogenous 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.

https://link.springer.com/chapter/10.1007/978-3-030-41967-7_33



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

NEW YORK INSTITUTE OF TECHNOLOGY
College of Osteopathic Medicine

- **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.

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