Drug and Nutrient Interactions

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WHY DRUG AND NUTRIENT INTERACTIONS?

Have you ever stopped to think about...?

- How do prescription medications work?
- Whether diet impact effectiveness of prescription medications?
- We know some prescription medications indicate "Take with food", but why does this matter? And, why does it matter whether meds are taken in the morning versus at nighttime?

Drug and Nutrient Interactions is an online course and eBook developed to pursue questions at the intersection nutritional sciences and pharmacology. A 2013 Mayo Clinic survey estimates that 7 out of 10 Americans are on at least one prescription drug, and more than half take two. Despite prominent use of prescription medications, issues related to nutrition because of prescription use – and vice versa – how nutrition can affect drug action – are not typically explored.

Section I introduces readers to pharmacology terms and

concepts underlying drug and nutrient interactions. Mechanisms underlying drug and nutrient interactions with drug administration, absorption, distribution, metabolism and excretion are also described.

Section II describes the impact of drugs on nutrient status and conversely, the effect of nutrient status/nutrition on pharmacotherapy.

Section III considers the role of the Food and Drug Administration (FDA) on foods versus drugs, and the regulatory framework underlying pharmaceuticals, dietary supplements, foods and food products.

Review Questions

Use review questions to confirm your comprehension. Practice answering review questions with a friend, family member or classmate for an extra challenge. Explaining terms, concepts and connections to another person helps to solidify your understanding.

PART I
INTRODUCTION TO PHARMACOLOGY AND FOOD + DRUG INTERACTIONS

A. PHARMACOLOGY AND DRUG ACTIONS

Pharmacology is the study of drugs and their effects. A **drug** is a substance or chemical agent which can affect living processes – and can be a natural product, chemical substance, or pharmaceutical preparation for administration to a human or animal. Most drugs are used to treat the sick or a health condition; thus, pharmacology is a part of the broad science of medicine[1]. More broadly, pharmacology is concerned with the mode of action of drugs on the human body, and the use of drugs in therapies. (Not to be confused with pharmacy – the science and profession concerned with preparing, storing, dispensing and proper use of drug products). Toxicology is the branch of pharmacology that generally deals with the undesirable effects of drugs on biological processes[2].

1. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
2. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

Table 1.1 Two subdivisions of pharmacology: pharmacokinetics and pharmacodynamics

Pharmacokinetics	Study of what the body does to the drug	Refers to the movement of a drug going into, through, and out of the body; processes that determine the concentration of drugs in body fluids and tissues over time: drug absorption, distribution, metabolism and excretion
Pharmacodynamics	Study of what the drug does to the body	Refers to how drugs work and how they exert powers or effects on the body via target receptors and tissues: receptor binding, signal transduction, dose-response

Pharmacology includes two main subdivisions: pharmacokinetics and pharmacodynamics.

Pharmacokinetics describes what the body does to the drug. In order for a drug to "work", it must enter the body and somehow reach a site of action. In most cases the site of action

is a **receptor** located in a target tissue.[3] A receptor is a cellular bound or unbound macromolecule with structural specificity. When a receptor becomes bound or activated by a drug, it undergoes a conformational change that alone or through a series of chain reactions can manifest an effect.[4] A drug effect could be increasing of a secretion, a change in metabolism, inhibition of an enzyme, and so on.

Pharmacokinetics is concerned with processes that bring about changes in drug plasma concentration and the concentration of drugs in tissues over time. The concentration of any given drug will fluctuate according to the rates of four processes: **absorption**, **distribution**, **metabolism** and **excretion**; thus, interactions with nutrients may involve enzymes and transporters that are implicated in any of these processes.[5]

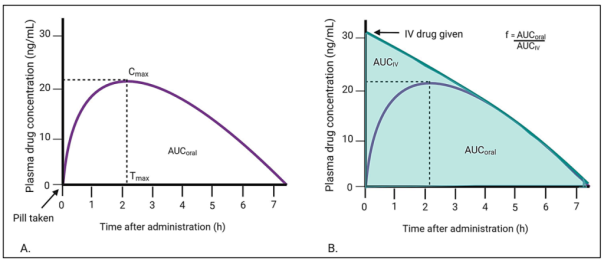
Pharmacodynamics describes what the drug does to the body, and involves the study of the actions of drugs on target receptors and tissues. As mentioned above, the majority of drugs bind to specific receptors on the surface or interior of cells; however, there are other cellular components and non-

3. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
4. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
5. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

specific sites which can serve as sites of drug action. Hydrogen and metal ions, enzymes, nucleic acids or macromolecular receptors can also be drug targets.[6]

Drug Plasma Concentration Curves

Following oral drug administration, plasma concentration typically increases over time. A standardized drug plasma concentration curve is shown in Figure 1.1 A below. In Figure 1.1, the y-axis is a linear scale of drug plasma concentration, often expressed in micrograms per milliliter or milligrams per liter, and the x-axis is a scale of time, usually expressed in hours. The maximal plasma drug concentration for a single dose of a drug given orally is known as maximum concentration (Cmax) and the time to time necessary to reach the Cmax is known as the Tmax, see Panel A.[7]



Created with BioRender.com

6. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
7. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

Figure 1.1. Plasma drug concentration and drug bioavailability[8]

Drug plasma concentration curves help us understand concepts such as bioavailability, which is defined as the fraction (f, in Figure 1.1.B) of the administered dose of a drug that reaches the systemic circulation in an active form. By definition, an intravenously administered drug has 100% bioavailability. The oral availability of a drug is determined by dividing the AUC of an orally administered dose of the drug (AUCoral) by the AUC of an intravenously administered dose of the same drug (AUCIV).[9]

8. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
9. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

B. MECHANISMS OF DRUG AND NUTRIENT INTERACTIONS

There are several mechanisms by which drugs may impact nutrient status and vice versa. The outcome of a drug-nutrient interaction may involve altered disposition of a drug or nutrient (modified absorption, distribution or elimination) – or altered effect of the drug and/or nutrient due to modified actions at the cellular level. Clinical outcomes of a drug-nutrient interaction can range from compromised nutrition status to altered therapeutic response.[1]

This section will describe opportunities for drug and nutrient interactions that may occur during processes of drug ingestion or administration, absorption, distribution, metabolism and excretion. Section C will define specific examples.

1. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Table 1.2 Processes that permit drug and nutrient interactions.[2]

Ingestion/ Administration	• Drug ingestion can cause changes in appetite and nutrient intake.
Absorption	• Mechanical effect – Both food and drugs can have a mechanical effect, via binding or absorption, that can increase or decrease drug and nutrient absorption. • Motility – Drugs can increase or decrease gastrointestinal motility, thereby increasing or decreasing nutrient absorption. • Chemical factors & pH – pH of the stomach contents is important to neutralize bacteria and critical for digestion. Drugs that influence (raise) stomach pH may have a negative impact on digestion of foods and absorption of various nutrients.
Distribution	• Drugs are distributed to organs and tissues via the circulation, diffusing into interstitial fluid and into cells from the bloodstream.

2. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Metabolism	• Drug-nutrient interactions take place predominantly during processes of drug metabolism. • Drug metabolism is divided into two general phases: Phase 1 and Phase 2. Each phase involves different sets of enzymes that function to process and "dispose" of a foreign substance (i.e., a drug). • Major classes of drug-metabolizing enzymes that may interact with nutrient or food components: ◦ Cytochrome P450 (CYP) ◦ Uridine diphosphate glucuronosyltransferases (UGT) ◦ Glutathione S-transferases (GST)
Excretion/ Elimination	• Excretion refers to disposal of a drug and/or its metabolites from the body; drugs and nutrients can synergistically and/or competitively interact causing increased or decreased rates of excretion.

Ingestion/Administration

The mode of a drug's administration will directly impact its pharmacokinetics. A drug may enter the body in a variety of ways: as an oral liquid, pill or capsule; inhaled as a vapor or aerosol; absorbed through the skin; injected into muscle, subcutaneous tissue, spinal fluid, or directly into the bloodstream.[3] Drug ingestion can cause changes in appetite, food intake and absorption (e.g., taste disorder, nausea, vomiting, diarrhea), thereby indirectly altering nutrition status.[4]

Absorption

For a drug to "work", it must be absorbed into the circulation to reach a site of action. Most drugs are absorbed by passive diffusion across a biological barrier (such as a cell membrane) and into the circulation.[5] The rate of absorption is proportional to the drug concentration gradient across the barrier, and the surface area available for absorption at that site;

3. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
4. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
5. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

this is known as Fick's law (i.e. the higher the concentration, the higher concentration of drug absorbed).[6] Drugs may be absorbed passively through cells either by lipid diffusion or by aqueous diffusion, depending on their solubility. Lipid diffusion is a process by which the drug dissolves in the lipid components of cellular membranes, this process is facilitated by a high degree of lipid solubility of a drug. Aqueous diffusion occurs by passage through aqueous pores in cell membranes. Aqueous diffusion is restricted to drugs that have low molecular weights, many drugs are too large to be absorbed by this process.[7]

A few drugs require energy or a specialized carrier to be absorbed. Drugs that are absorbed by active transport require a specialized "carrier" molecule and a form of energy, provided by hydrolysis of the terminal high-energy phosphate bond of adenosine triphosphate (APT).[8] In the previous paragraph the process of passive diffusion was described. Passive diffusion does not require energy; drug molecules move "down" a concentration gradient (i.e. from a higher to lower concentration). However, active transport can transfer drugs

6. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
7. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
8. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

against a concentration gradient. Facilitated diffusion also requires a carrier molecule; however, no energy is required.[9]

Oral administration (PO). When a drug is swallowed, it must be absorbed from the gastrointestinal (GI) tract into the portal circulation. Many drugs are well absorbed from the GI tract.[10] However, there are a number of drug classes that cannot be administered orally. Biologics (i.e. antibodies) are usually too large, and protein drugs are destroyed in the digestive process. The rate and range of drug absorption by the GI tract is a function of physiochemical properties of the drug (water or lipid solubility), its formulation (tablet, capsule, liquid, time-release) and physiological environment (pH of the stomach).[11] With oral administration, foods and nutrients can impact the absorption of a drug by binding to it or by changing its environment (e.g., pH of the stomach). Food ingestion releases digestive enzymes that can inactivate certain drugs.[12] Oral administration is the route by which most drug and nutrient interactions occur. Interestingly, the bioavailability of some drugs is increased with food, and for

9. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
10. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
11. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
12. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

others, decreased. The variance is due to differences in drug solubility, molecular size and other chemical characteristics.[13]

Certain classes of antibiotics (e.g. tetracyclines and fluoroquinolones) bind divalent and trivalent cations to form a nonabsorbable complex, so taking them at the same time that you take certain dairy products, or iron/calcium supplements should be avoided.[14]

The *intravenous (IV)* route of drug administration delivers the drug directly into the bloodstream, to the heart and on to the general circulation.[15] This route bypasses challenges facing absorption from the GI tract and first pass metabolism and allows for quick adjustment of dose to effect. **First pass metabolism** (or the first pass effect) refers to the rapid uptake and metabolism of a drug by the liver, before it reaches the systemic circulation. First pass metabolism reduces the bioavailability of a drug to less than 100% when processed by the liver before reaching circulation.[16]

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13. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
14. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
15. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
16. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Other modes of drug administration include intramuscular, subcutaneous, inhalation, transdermal and topical routes. *Intramuscular (IM)* drug injection/ administration results in rapid drug absorption because of the high vascularity of muscles. *Subcutaneous (SC)* administration involves drug delivery into tissue beneath the skin and its subsequent intro into the blood perfusing the tissue.[17] Absorption following SC administration is generally rapid. Inhalation is a rapid route for drug absorption because of the large surface area and high vascularity of the lungs.[18]

Distribution

Drugs are distributed to target organs, tissues and cells via the circulation by diffusing into interstitial fluid and cells from the bloodstream. The extent of any given drug's distribution is dependent on these factors: lipid solubility and molecular size of the drug, organ blood flow/perfusion and plasma protein binding.[19] Patients with a higher BMI (body mass index) could require differential dosing and it may be expected based on

17. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
18. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
19. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

body composition that lipophilic drugs have a larger volume of distribution in obese patients.[20] While beyond the scope of this course, it is worth mentioning that a notable restriction to drug distribution is the blood brain barrier (also called BBB). The blood brain barrier is a network of blood vessels and tightly packed cells which functions to keep out bacteria, some drugs and other harmful substances. It allows water, oxygen, carbon dioxide, and general anesthetics to pass into the brain.[21]

Metabolism

Metabolism gradually decreases plasma drug concentration over time. **Metabolism** describes the chemical reactions that convert drugs into compounds which are easier for the body to eliminate and excrete.[22] Drug metabolism is also known as **biotransformation** and is a key step toward eliminating or disposing of a drug. Drug metabolism could be viewed as a detoxification process and ultimately makes a drug more water

20. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
21. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
22. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

soluble so that excretion processes (e.g. biliary, renal) can finish disposing of it.[23]

It should be noted that all organisms are constantly (and unavoidable) exposed to xenobiotics including man-made and natural chemicals such as drugs, plant alkaloids, microorganism toxins, pollutants, pesticides, and other industrial chemicals.[24] Biotransformation – or metabolism – of these compounds are generally subdivided into phase I and phase II metabolic reactions. These may or may not occur in "sequential" order. In many cases, phase 1 enzymatic reactions can create or unmask a chemical group that is required for a phase 2 reaction. However, drugs may bypass phase 1 and go directly to phase 2 metabolism. Some phase 1 metabolites are pharmacologically active; however, most phase 2 metabolites are inactive.[25]

Drug excretion is the removal of drugs from body fluids and occurs primarily in the urine. Other routes of excretion from the body include in bile, sweat, saliva, tears, feces, breast milk,

23. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
24. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
25. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

and exhaled air.[26] Drugs are handled by the kidneys in the same manner as are endogenous substances, undergoing processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.[27]

Phase 1 metabolism, or biotransformation, involves oxidative, reductive and hydrolytic reactions.[28] Microsomal cytochrome P450 (CYP) enzymes found in the endoplasmic reticulum of liver and intestinal mucosa cells are critical to the metabolism of endogenous and exogenous chemicals (drugs). These enzymes are also important for many diet-drug and drug-drug interactions. Many drugs can either inhibit or induce one or more of these enzymes and can influence the clearance of other drugs.[29] CYP enzymes have been extensively studied, cloned, and their role in drug metabolism is well established. CYP enzymes and isozymes (two or more enzymes with identical functions but different structures) are divided into three families: CYP1, CYP2 and CYP3. Each CYP

26. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
27. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
28. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
29. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

enzyme is denoted by a numeral designating the family (e.g., CYP1), a letter indicating the subfamily (e.g., CYP1A), and a number representing the individual enzyme (e.g., CYP1A2) (1). Up to fifty percent of prescription drugs are metabolized by CYP3A4.

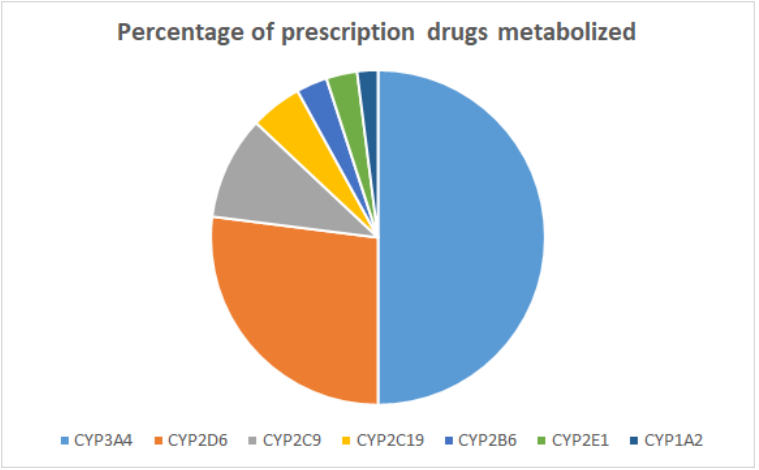

Figure 1.2. Relative contribution of enzymes involved in drug metabolism[30]

Therefore, inhibition of CYP enzymes or isozymes prevents their action on a drug compound, causing its plasma concentration to rise.[31]

Phase 2 metabolism, or biotransformation, involves conjugation reactions that make partially metabolized drug

30. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
31. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

compounds more water soluble, thereby promoting excretion.[32] On the other hand, these conjugations also can play an essential role in the toxicity of many chemicals due to the metabolic formation of toxic metabolites such as reactive electrophiles. Gene polymorphism of biotransformation enzymes may often play a role in various pathophysiological processes. Phase II metabolism, or conjugation reactions, attach small hydrophilic molecules (i.e., acetate, glucuronic acid, sulfate, or glycine) to create more water-soluble compounds, allowing for eventual elimination.[33]

Glucuronidation, carried out by UDP-glucuronosyltransferases (UGTs) belong among key enzymes of metabolism for various exogenous and endogenous compounds.[34] Conjugation reactions catalyzed by the superfamily of these enzymes serve as the most important detox pathway for a broad spectrum of drug, dietary chemicals, carcinogens and environmental chemicals. Glucuronide formation is the most common conjugation reaction (40-70% of clinically used drugs) and uses glucuronosyltransferases to

32. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
33. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
34. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

conjugate a glucuronate molecule with the parent drug molecule.[35]

Sulfoconjugation (or sulfonation) catalyze the conjugation of several drugs and endogenous compounds. The enzyme family mediating sulfoconjugation reactions are called sulfotransferases (SULTs). Acetaminophen as well as dopamine undergo sulfonation.[36]

Acetylation is accomplished by N-acetyltransferase enzymes that use acetyl coenzyme A (acetyl CoA) as a source of the acetate group.[37] Compared to sulfonations and glucuronidations, acetylations are modest in terms of the number and variety of substrates. Acetylation reactions are characterized by the transfer of an acetyl moiety, the donor generally being acetyl coenzyme A, and the accepting chemical group is a primary amino function.[38] Drugs and other foreign compounds that are acetylated in intact animals are either

35. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
36. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
37. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
38. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

aromatic amines or hydrazines, which are converted to aromatic amides and aromatic hydrazides.[39]

Conjugation reactions are a key mechanism for maintaining homeostasis during exposure to various xenobiotics, such as drugs, industrial chemicals, or food procarcinogens.[40] In humans and many other mammals, the liver is a major site of expression of xenobiotic-metabolizing enzymes, but extra-hepatically localized enzymes also are of great importance. In the intestines, several drug metabolizing enzymes decrease the bioavailability of orally administered drugs or activate environmental carcinogens.[41]

Excretion

Excretion, or elimination, refers to the removal of drugs from the body. The biological effects of exogenous substances (i.e., synthetic or natural compounds) are terminated by the processes of metabolism and excretion. Multiple factors affect the rate and extent of excretion, and accumulation occurs if the rate of absorption and distribution of a drug or a nutrient

39. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
40. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.
41. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.

exceeds the rate of excretion. The kidneys are the major route for excretion of many drugs; body fluids and occurs primarily in the urine. Other routes of excretion from the body include in bile, sweat, saliva, tears, feces, breast milk and exhaled air. Drugs are handled in the kidneys in the same manner as are endogenous substances, undergoing processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption.[42]

42. Brenner GM, Stevens CW. Pharmacology. Fifth edition. ed. 1 online resource (579 pages) p.; Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

C. FOOD-RELATED PRESCRIPTION WARNINGS

Many prescription medications contain warning labels to avoid consumption of specific beverages, foods or supplements within a range of time around dosing. This section expands warning information with mechanisms underlying common warnings.

Take with food/ Take without food

The most common food-related prescription warnings you may notice are related to taking drugs with or without food. Some drugs should be taken with food to help improve adherence to a therapeutic plan, to avoid GI upset, or to improve drug absorption. Interestingly, taking medication with food can increase or decrease its bioavailability, depending on a drugs' lipid solubility and other factors.[1] Some drugs

1. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

should always be taken without food in order to be properly absorbed from the GI tract; some generic examples include Zithromax, Flagyl, Lasix and Ambien.[2]

Grapefruit juice

Grapefruit juice is perhaps the best-known drug-food interaction. Grapefruit juice contains furanocoumarins and other substances that inhibit CYP3A and other CYP isoforms.[3] As discussed in part B, CYP enzymes hold primary responsibility for processing/metabolizing drug compounds during Phase 1 metabolism. As a result, drugs that are absorbed by the intestines and metabolized by CYP3A can be significantly affected by grapefruit juice. Grapefruit juice that is reconstituted from frozen concentrate or diluted from concentrate have also been shown to interact.[4] Segments from unprocessed grapefruit are also reactive. In short, any form of grapefruit should be considered to produce a drug interaction. Importantly, even small amounts of grapefruit or grapefruit juice (200 mL, or less than 1 cup) is sufficient to produce

2. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
3. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
4. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

this effect.[5] The drug interaction caused by grapefruit juice has a lengthy duration. For example, grapefruit juice consumed today could impact the oral bioavailability of a drug administered tomorrow. As a result, it is recommended that grapefruit juice consumption should best be avoided entirely during pharmacotherapy, rather than within hours of drug administration.[6] A patient's pre-existing medical conditions affects susceptibility to grapefruit juice and drug interactions. For example, dihydropyridines produce a blood pressure-lowering effect that is dependent on pretreatment blood pressure. (They are known L-type Calcium channel blockers, used in the treatment of hypertension.) The greatest reduction in blood pressure occurs in patients with the highest pretreatment blood pressure.[7] Age is also a concern that can affect susceptibility to drug interactions. Elderly patients have demonstrated an enhanced antihypertensive effect to dihydropyridines compared to younger individuals. The elderly are most often prescribed medications and major consumers of grapefruit juice; as a result, the potential for

5. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
6. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
7. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

an unwanted grapefruit juice – drug interaction in this population is substantial.[8]

A formal clinical study involving patients with untreated borderline hypertension established the grapefruit juice and CYP3A reaction. The peak concentration (Cmax) and area under the plasma drug concentration -time curve (AUC) of felodipine (a dihydropyrine, mentioned in the above paragraph) were essentially three-fold to the same measurements when dosed with orange juice or water.[9] This pharmacokinetic drug-nutrient interaction is only seen with orally dosed medications. In the clinical study mentioned above, intravenously (IV-) administered felodipine with grapefruit juice was unaffected. The mechanism underlying this drug-nutrient interaction is reduced activity of felodipine metabolism, which is mediated by CYP3A4, during first-pass.[10] Researchers have noted that administration of just 250mL of grapefruit juice causes a mean 62% reduction of enterocyte CYP3A4 protein content. Liver CYP3A4 activity was not altered. This provides clear evidence for the

8. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
9. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
10. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

gastrointestinal (GI) tract as a central site of drug metabolism.[11]

Cruciferous vegetables

Cruciferous vegetables are rich sources of a variety of interactive dietary components. Classic examples are Vitamin K-rich kale, cabbage and Brussels sprouts. Other interactive dietary components in cruciferous vegetables include indoles, including indole-3-carbinol and indole-3-acetonitrile.[12] These vegetables and indoles have effects on the metabolism of environmental carcinogens such as aflatoxin B1 and binding of their metabolites to DNA. In other words, consumption of cruciferous vegetables has been shown to mitigate cellular damage associated with environmental contaminants and cancer-causing agents.[13] These findings led to research aimed at investigating the impact of cruciferous vegetables on drug oxidation and conjugation in normal, healthy patients on prescriptive diets.

Clinical research studies investigating the capacity of

11. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
12. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
13. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

cruciferous vegetables to impact drug metabolism have demonstrated that cruciferous vegetables (Brussels sprouts and cabbage) significantly enhance the oxidative metabolism of antipyrine, phenacetin, and the conjugation of acetaminophen.[14] Watercress is also a cruciferous vegetable and contains a glucosinolate precursor of phenethyl-isothiocyanate, which can impair CYP2E1 activity and the metabolism of drugs such as chlorzoxazone.[15] In clinical research studies investigating watercress and drug metabolism, a single ingestion of watercress increased the area under the chlorzoxazone plasma concentration time curve by 56% and prolonged the chlorzoxazone elimination half-life by 53%.[16] The magnitude of this effect is similar and somewhat greater, respectively, compared to those seen with an established CYP2E1 inhibitor, isoniazid. Watercress has also been shown to reduce peak plasma concentration and area under the plasma concentration-time curve for oxidative metabolites of acetaminophen (the active ingredient in Tylenol).[17]

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14. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
15. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
16. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
17. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Alcohol

You may have noticed prescription warnings "Avoid or limit alcohol consumption" on labels and drug information. Specific drugs can elicit mild to severe adverse drug reactions when taken with or during alcohol use. One extreme examples of alcohol-drug interaction are seen in tetraethylthiuram disulfide (disulfiram).[18] Adverse reactions develop soon after alcohol is consumed in patients taking disulfiram. As a result, disulfiram is used to treat chronic alcoholism. The drug has been used in alcohol treatment programs as an adjunctive means of encouraging alcohol abstinence.[19] Unpleasant manifestations of the alcohol-disulfiram reaction include flushing, headache, nausea, vomiting, weakness, vertigo, blurred vision and seizures. Disulfiram inhibits the enzyme aldehyde dehydrogenase, which oxidizes acetaldehyde that is derived from alcohol.[20]

Cephalosporin antibiotics are also known to interact with alcohol. These antibiotics have differing effects on liver alcohol dehydrogenase and circulating acetaldehyde levels.

18. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
19. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
20. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Cephalosporin drugs reported to cause disulfiram-like reactions include cefoperazone, moxalactam, ceftriaxone, cefonicid, and cefmetazole.[21] All of these except ceftriaxone have been pulled from the US market because of these issues. Metronidazole (Flagyl) might be the most prominent antibiotic in this family that remains available, with a disulfiram-like reaction. The mechanism underlying this drug reaction is not enzyme inhibition, but reactive metabolites. Drugs with a very specific chemical structure are associated with this type of unfavorable reaction (drugs with a N-methyl-tetrazole-thiol side chain in the 3'-position).[22] Moreover, drugs with this type of structural feature can also inhibit vitamin K epoxide reductase (VKOR) and cause coagulopathies (hypoprothrombinemia and bleeding), particularly in patients with vitamin K deficiency. Vitamin K supplementation can prevent this drug-induced condition.[23]

Caffeine

Caffeine is a common, natural, non-nutritive methylxanthine

21. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
22. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
23. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

component of foods and several beverages such as coffee and tea. It is also added to many popular carbonated beverages. Caffeine is extensively metabolized by CYP enzymes. When caffeine is taken regularly, it can accumulate and influence drug metabolism.[24] Caffeine's effects on drug metabolism are complex and may involve saturation, inhibition, or induction of liver enzymes that metabolize methylxanthines and other drugs and chemicals.[25]

Clozapine is metabolized by CYP1A2 enzymes (similarly to caffeine) and is used in the treatment of schizophrenia. In a clinical research study evaluating the impact of caffeine withdrawal on clozapine treatment, it was found that clozapine concentrations were lower after changing to a caffeine-free diet for 5 days.[26] Therefore, habitual caffeine intake can alter the metabolism of clozapine. As a result, caffeine intake should be medically supervised and clozapine levels monitored when this medication is prescribed for schizophrenic patients.

24. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
25. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
26. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

PART I. REVIEW QUESTIONS

1. Define “drug”.
2. How is pharmacology different from pharmacy?
3. Compare and contrast pharmacokinetics and pharmacodynamics.
4. What factors impact the absorption of drugs?
5. Compare Phase I versus Phase II metabolism.
6. List common examples of foods that can elicit drug-nutrient interactions.
7. What is a CYP and which one is predominantly involved in drug metabolism?

PART II
EXPLORING DRUG-NUTRIENT INTERACTIONS

EXPLORING DRUG-NUTRIENT INTERACTIONS

Nutrition can have a critical impact on the way in which drugs affect the body. In addition, drugs can alter the body's nutritional requirements. A **drug-nutrient interaction** is defined as an "interaction resulting from a physical, chemical, physiological, or pathophysiologic relationship between a drug and a nutrient, multiple nutrients, food in general, or nutritional status."[1] The outcomes of drug-nutrient interactions are typically associated with changes to the metabolism and/or the effect of the drug or nutrient, which can pose a serious threat to patient health. Individuals more at risk for drug-nutrient interaction complications are primarily those taking multiple medications including individuals with chronic disease conditions, the elderly, and individuals who may be immune or nutritionally compromised.[2]

1. Santos CA, Boullata JI. An approach to evaluating drug-nutrient interactions. Pharmacotherapy. 2005;25(12):1789-800.
2. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Drugs Impact on Nutrients and Nutritional Status

Many drugs can impact the overall nutritional status of an individual through alterations in appetite, gastrointestinal absorption, and nutrient metabolism. Drugs that alter appetite are either classified as **orexigenic** or **anorexigenic**, meaning increasing or decreasing appetite, respectively.[3] Therefore, a common listed side effect of specific drugs falling into these categories may be weight gain or weight loss. Patients should be informed when taking drugs with these potential side effects so that they can monitor and adjust dietary intake as needed.

Additionally, drugs can also impact the absorption, metabolism, or levels of the three **macronutrients** in the body: carbohydrates, fats, and proteins. Unlike drugs with orexigenic or anorexigenic side effects, drugs that impact macronutrients typically are utilized for these specific purposes.[4] This is best represented by classes of antidiabetic drugs, which aim at maintaining blood glucose levels (carbohydrate) through various mechanisms. Furthermore, to manage blood lipid (fat) levels, drugs can be taken that either

3. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
4. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

decrease fat absorption in the small intestine, or facilitate metabolism and excretion of blood lipids.[5] Protein seems to be minimally affected by drugs; certain antibiotics' mechanism of action is interference with bacterial protein synthesis. There is no evidence that this interference translates to mammalian cells.[6]

Vitamins and minerals, also known as **micronutrients**, play important roles in overall health and assist in several key metabolic and enzymatic processes in the body. Therefore, the effects that drugs may have on the actions and/or levels of these micronutrients is critical to understand. From a broad perspective, many drugs can alter the levels of vitamins and minerals in the body by interfering with absorption of these micronutrients in the gastrointestinal tract, distribution, metabolism, or excretion through urine or feces.[7]

Vitamins are classified into two main categories, water soluble and fat soluble. **Water soluble vitamins** include all of the B vitamins and vitamin C. These vitamins are absorbed in the small intestine through energy-dependent and energy-independent transport mechanisms. Due to the water-soluble

5. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
6. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
7. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

nature of these vitamins, they are excreted fairly rapidly through the urine if an individual is sufficient and thus do not pose a great risk of toxicity.[8] Drugs that increase urinary excretion such as a diuretic or antihypertensive pose the highest risk for affecting water soluble vitamin levels (see Table 2.1 for more detail).[9] **Fat soluble vitamins** include vitamin A (retinol), E (tocopherols and tocotrienols), D (calciferol), and K (phylloquinone and menaquinone). This class of vitamins are absorbed in a similar mechanism to lipids and are not as readily excreted as water soluble vitamins, so toxicity is a considerable risk.[10] Therefore, drugs that influence or interfere with lipid absorption pose the highest risk to fat soluble vitamin status. An example of this interaction is bile acid sequestrants which interfere with bile acid absorption in the ileum, promoting the excretion of bile acids as well as fat soluble vitamins.[11]

8. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
9. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).
10. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).
11. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).

Importantly, any clinical manifestation of a drug-nutrient interaction may be patient-specific, as much as drug-specific. Development of an overt and severe micronutrient deficiency due to prescription drug use would be extremely rare. Instead, a lesser degree of micronutrient deficit(s) may be associated with clinical outcomes.[12] Some examples of established drug-induced nutrient interactions include antibiotics and diuretics. Antibiotics are well understood to interfere with the absorption of iron from foods and thus individuals taking antibiotics frequently are at greater risk for development of iron deficiency anemia. Diuretics are commonly used to manage fluid levels in patients with edema or congestive heart failure by increasing urinary excretion of fluid. However, many electrolytes are excreted along with the fluid which can lead to dangerously low levels of key electrolytes such as sodium and potassium.[13]

Many drug interactions with vitamins and minerals are due to interference with absorption or increases in excretion, leading to reduced levels of these micronutrients. However,

12. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).
13. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010; Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).

there are some examples where drugs can increase the level of vitamins/minerals and may even be therapeutic. For example, HMG-CoA reductase inhibitors (i.e. statins), a drug class used to treat elevated blood cholesterol, may improve vitamin D levels in the body through mechanisms that are still not fully understood.[14] An overview of common drugs and their known impacts on vitamin and mineral status' is depicted in table 2.1 below.

14. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

Table 2.1 Common Drugs and Their Impact on Vitamin/ Mineral Status[15]

Drug / Drug Class	Nutrient	Effect on Nutrient Status or Function
Proton Pump Inhibitors	Cobalamin (B12)	*Decrease*
	Vitamin C	*Decrease*
	Iron	*Decrease*
	Calcium	*Decrease*
	Magnesium	*Decrease*
	Zinc	*Decrease*
	B-carotene	*Decrease*
Aspirin	Vitamin C	*Decrease*
	Iron	*Decrease*
Diuretics / Antihypertensives	Calcium	*Increase/Decrease*
	Magnesium	*Decrease*
	Thiamin (B1)	*Decrease*
	Potassium	*Decrease*
	Folate (B9)	*Decrease*
	Sodium	*Decrease*
Statins	Coenzyme Q10	*Decrease*
	Vitamin D	*Increase*

	Vitamin E	*Increase/Decrease*
Hypoglycemics (Biguanides/ Thiazolidinediones)	Cobalamin (B12)	*Decrease*
	Calcium	*Decrease*
	Vitamin D	*Decrease*
Selective Serotonin Reuptake Inhibitors (SSRIs)	Calcium	*Decrease*
	Vitamin D	*Decrease*
Glucocorticoids	Calcium	*Decrease*
	Vitamin D	*Decrease*
	Sodium	*Increase*
	Potassium	*Decrease*

Nutrients and Nutritional Status' Impact on Drugs

A person's nutritional status can also alter the impact of drugs. The most common example of this would be whether a drug is to be taken with or without food. If the prescription states to take with food, the drug likely is better absorbed with food and/or has adverse gastrointestinal side effects that are reduced

15. Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).

when taken with food. On the contrary, prescription drugs may be taken without food if absorption is reduced in the presence of food.[16] Foods high in fiber and other bulking components can interfere with the drug reaching the intestinal absorptive cells and thus the drug ends up being partially absorbed and partially excreted.[17] There are two main types of fiber: soluble and insoluble. Both types interact with the gastrointestinal environment and its contents differently, causing alterations in GI function. **Soluble fiber** binds water and other hydrophilic compounds, slowing transit time through the intestine and adding bulk to stools. Because of its affinity for water, soluble fiber is commonly recommended for individuals dealing with diarrheal conditions.[18] However, hydrophilic drugs may also bind soluble fiber, preventing complete absorption of the dose taken. **Insoluble fiber** acts differently because it doesn't attract water and thus it speeds up transit time through the intestine. This means that drugs taken in the presence of insoluble fiber may have less time to

16. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
17. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
18. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

be absorbed, which can result in lower bioavailability of the drug.[19]

Aside from whether medication is taken with or without food, pre-existing nutrient deficiencies can also impact the way in which drugs interact with the body. For example, severe energy and protein malnutrition reduce enzyme levels involved in drug metabolism thereby reducing or altering their functions.[20] Furthermore, overall dietary balance of macronutrients may influence drug action and efficacy. Clinical research studies have compared the effects of high-carbohydrate, high-fat, and high-protein diets on drug metabolism. In one clinical research study, three test diets were isocaloric and drug clearance of antipyrine and theophylline were analyzed for six normal male subjects.[21] These drugs were utilized because of their dependence on liver CYP enzymes. Metabolic clearance for antipyrine and theophylline were significantly increased during the high-protein dietary period than during the other two diets. Conclusion of these studies indicated that substitution of protein for either dietary fat or carbohydrates can increase drug oxidation rates, whereas

19. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
20. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
21. Kappas A, Anderson KE, Conney AH, Alvares AP. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther. 1976;20(6):643-53.

exchanging carbohydrate and fat has no major effect.[22] Studies have also examined the effect of protein supplementation on drug clearance and demonstrated similar findings: higher protein loads are associated with increased rates of drug metabolism. Differences in dietary fat and carbohydrate intake do not confer similar effects.[23]

The precise mechanism by which increasing dietary protein accelerates drug oxidation is unknown. Interestingly, this effect of protein can be leveraged within specific disease states. As an example, Parkinson's patients may benefit from adhering to a low-protein diet.[24] In Parkinson's patients eating a high-protein diet, large neutral amino acids can inhibit the transport of levodopa across the blood-brain barrier, leading to reduced brain dopamine formation from exogenous levodopa.[25] However, a "protein-redistribution diet", where protein is restricted during the day and unrestricted near bedtime has been found to be beneficial in clinical studies.

22. Kappas A, Anderson KE, Conney AH, Alvares AP. Influence of dietary protein and carbohydrate on antipyrine and theophylline metabolism in man. Clin Pharmacol Ther. 1976;20(6):643-53.
23. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
24. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
25. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

This is an example whereby dietary modifications augment pharmacological efficacy for a particular disease state.[26]

From a micronutrient perspective, certain vitamins and minerals can alter drug metabolism and detoxification enzymes. Many vitamin deficiencies and incidences of excess levels have been shown to alter hepatic phase 1 and phase 2 drug metabolism through various mechanisms.[27] While there are still many interactions that are not fully understood, some examples of known effects and mechanisms of these interactions are listed in Table 2.2 (Adapted from Raiten[28])

26. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
27. Raiten DJ. Nutrition and pharmacology: general principles and implications for HIV. Am J Clin Nutr. 2011;94(6):1697S-702S.
28. Raiten DJ. Nutrition and pharmacology: general principles and implications for HIV. Am J Clin Nutr. 2011;94(6):1697S-702S.

Table 2.2 Impact of nutrients on drug metabolism enzymes

Nutrient	Effect on drug metabolism	Potential mechanisms
Vitamin B6 (Pyridoxine):	*Excess*: not known	—
	Deficiency: ⇩ phase 1 drug metabolism	Reduced synthesis of heme and potential impairment in protein synthesis
Vitamin C:	*Excess:* ⇧ cytochrome P450 activity	Increased expression of CYP isozymes
	Deficiency: ⇩ phase 1 drug metabolism	Decreased expression of CYP isozymes
Vitamin E:	*Excess*: not known	—
	Deficiency: ⇩ phase 1 drug metabolism	Potential reduction in antioxidative mechanisms
Vitamin B1 (Thiamine):	*Excess:* ⇩ activity of reductase and cytochrome P450	Potential reduction or interference with substrate binding
	Deficiency: ⇧ activity of cytochrome P450	Potential increased activity of P450 isozymes and other enzymes, but the mechanism is unknown.
Iron:	*Excess:* ⇧ microsomal lipid peroxidation	Can lead to damage of the phase 1 system as a whole

	Deficiency: ⇧ and ⇩ phase 1 drug metabolism	Mechanisms not fully known

Aside from broad effects on phase 1 and phase 2 drug metabolism, certain vitamins and minerals can also impact specific drug actions through interplay in pathways in which the drug is targeting. One of the most well-known examples of this is the effect of vitamin K on Warfarin (also known as Coumadin and Jantoven). Warfarin is an anti-coagulant agent used to prevent blood clots.[29] Conversely, vitamin K's primary function is to facilitate blood clotting, preventing wounds from bleeding excessively. Therefore, patients who are taking warfarin or other blood thinners should be advised to maintain a consistent vitamin K intake while taking this drug, as changes in vitamin K levels can disrupt the drug action and efficacy.[30] Interestingly, vitamin K is a recognized antidote for warfarin-induced bleeding. Another example of a vitamin that alters drug action is vitamin B6's effect on levodopa. Vitamin B6 supplementation can enhance the peripheral conversion of levodopa to dopamine by dopa-decarboxylase so that less

29. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.
30. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010.

levodopa is able to cross the blood brain barrier and be converted to active dopamine there.[31]

While many of the nutrient-drug interactions discussed above are detrimental, there are some instances where nutrition and medicine can be utilized together to improve outcomes. Selective Serotonin reuptake inhibitors (SSRIs) are a commonly used class of drugs used to treat depression/anxiolytic conditions. Previous research identified an association between low levels of folate and depression and that individuals with low folate levels were less likely to respond favorably to SSRI therapy.[32] Interestingly, several studies have found that addition of folate supplementation (via L-methylfolate) to SSRI treatment significantly improved self-reported depression symptoms and greater satisfaction ratings of medication treatment.[33] While the mechanism behind these improvements remains to be fully elucidated,

31. Boullata JI, Armenti VT, SpringerLink (Online service). Handbook of drug-nutrient interactions. New York, NY: Humana Press; 2010; Mohn ES, Kern HJ, Saltzman E, Mitmesser SH, McKay DL. Evidence of Drug-Nutrient Interactions with Chronic Use of Commonly Prescribed Medications: An Update. Pharmaceutics. 2018;10(1).
32. Shelton RC, Sloan Manning J, Barrentine LW, Tipa EV. Assessing Effects of l-Methylfolate in Depression Management: Results of a Real-World Patient Experience Trial. Prim Care Companion CNS Disord. 2013;15(4).
33. Shelton RC, Sloan Manning J, Barrentine LW, Tipa EV. Assessing Effects of l-Methylfolate in Depression Management: Results of a Real-World Patient Experience Trial. Prim Care Companion CNS Disord. 2013;15(4).

these findings highlight an important interaction where nutrition modification and medication work synergistically to improve quality of life and overall health for patients.

PART II. REVIEW QUESTIONS

1. What are some factors that may increase an individual's risk of experiencing a drug-nutrient interaction?
2. Why is there a higher risk of fat-soluble vitamin toxicity, as it relates to drug and nutrient interactions?
3. Describe a mechanism by which nutrients or food components can impact drug efficacy.
4. Define the terms: orexigenic and anorexigenic.
5. How does dietary fiber affect drug metabolism?

PART III

FDA'S ROLE IN PHARMACEUTICALS, DIETARY SUPPLEMENTS AND FOODS

FDA'S ROLE IN PHARMACEUTICALS, DIETARY SUPPLEMENTS AND FOODS

History of the FDA

The Food and Drug Administration or FDA is the oldest consumer protection agency within the US government. The FDA's origin began in 1906 with the passage of the **Pure Food and Drugs Act**, a law that prohibited interstate commerce in adulterated and misbranded (i.e. containing additives that were not listed clearly and/or potentially hazardous) food and drugs.[1] However, the FDA didn't officially become known as such until the 1930. In 1938, President Franklin Delano Roosevelt signed the **Food, Drug, and Cosmetic Act** (FD&C Act) into law, increasing federal regulatory authority over drugs through implementation of a premarket review of

1. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.

safety and a ban on false therapeutic claims.[2] This law, although amended numerous times, remains as the foundation of the FDA's regulation standards today.

The present mission of the FDA is *to protect the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation*.[3] While the FDA is responsible for all of the categories listed above, for the purpose of this book, the scope will be limited to drugs and food products.

2. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.
3. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.

Table 4.1 Key Acts of the FDA[4]

Year	*Piece of Legislature*	*Purpose*
1906	Pure Food and Drug Act	Banned foreign interstate traffic in adulterated or mislabeled food and drug products
1938	Federal Food, Drug, and Cosmetic Act	Gave the FDA authority to oversee the safety of food, drugs, medical devices, and cosmetics
1958	Food Additives Amendment	Amendment to the Federal Food, Drug, and Cosmetic Act that was created in response to concerns about the safety of food additives. This amendment established the classification of "generally recognized as safe" (GRAS).
1966	Fair Packaging and Labeling Act	Requires labels on consumer products to state: 1. the identity of the product 2. the name and place of business of manufacturer 3. the net quantity of contents
1987	Prescription Drug Marketing Act	Established legal safeguards for prescription drug marketing and sales to ensure the safety and effectiveness of drugs.
1990	Nutrition Labeling and Education Act	Gave the FDA authority to require nutritional labeling of most foods and ensure that nutrient content and health claims meet FDA regulations

1994	Dietary Supplement Health and Education Act	Defines and regulates dietary supplements; regulates for good manufacturing practices (GMP)
2011	FDA Food Safety Modernization Act	Set regulations to improve the safety of the food supply and prevent foodborne illness.

FDA's Role in Pharmaceuticals

To market any prescription drug in the US, the manufacturer must first obtain FDA approval. To do this, the manufacturer must demonstrate the drug's safety, **efficacy**, and **effectiveness**.[5] The FDA measures safety by 1) testing the toxicity of a drug to determine the optimal dose needed to achieve desired result or the highest tolerable dose and 2) identifying potential adverse effects of the use of the drug. Efficacy is determined based on how a drug performs over placebo or other intervention when tested in a tightly controlled situation, such as a clinical trial. Effectiveness examines how the drug works in a real-world situation and considers interactions with other medications the patient may

4. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.
5. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.

be taking and other comorbidities that the patient may have that might alter how the drug acts.[6] These parameters are examined in Phase I, II, and III clinical trials. Prior to initiation of clinical development and clinical trials, the manufacturer must submit an "Investigational New Drug Application" (IND) which details information about proposed clinical study designs, animal test data that shows safety and efficacy, and qualifications of the lead investigators.[7]

6. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.
7. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.

Table 4.2 Phases of Clinical Trials[8]

Phase	Objective	Length; Number of people
I	To determine safety and highest dose without adverse side effects. To identify acute side effects; to document metabolism and excretion pathways. About 70% of drugs pass this phase.	Several months to 1 year; 10-30 people
II	To test drug effectiveness, sometimes compared to different treatments. Randomized and typically double blinded clinical trials. About one-third of drugs successfully complete this phase.	About 2 years; up to several hundreds of people

8. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.

III	Large-scale randomized and double-blind testing to determine whether the new drug works better than current drugs. Approximately 70-90% of drugs that reach this phase make it to market and obtain FDA approval.	Several years; hundreds to thousands of patients

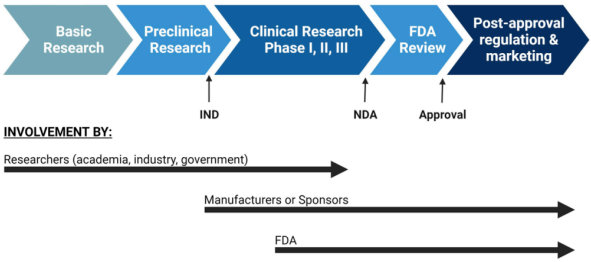
After clinical trials, the manufacturer has to submit a "New Drug Application" (NDA) to the FDA's Center for Drug Evaluation and Research. The NDA contains information about clinical trial results as well as information about manufacturing processes and facilities that are utilized for drug production.[9] When reviewing an NDA, the FDA examines three main parameters:

1. Evidence for the drug's safety and effectiveness; whether benefits of use outweigh the risks
2. Appropriate and complete proposed labeling information
3. Manufacturing methods that maintain drug quality,

9. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.

and/or preserve its structure and purity

Once drugs are approved, the FDA remains responsible for managing and regulating them on the market. This is referred to as "post-approval regulation" and is overseen by the Office of Surveillance and Epidemiology (OSE).[10] Post-approval regulation involves monitoring safety and adverse outcomes, continuously reviewing relevant literature, and comparing similar drugs on the market to predict potential issues. Overall, the role of the FDA in drug regulation is to ensure the safety of human consumption through regulation of quality, manufacturing, and marketing.



Created with BioRender.com

Figure 4.1. Overview of drug development[11]

10. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.
11. Dabrowska A, Thaul, S. How the FDA Approves Drugs and Regulates Their Safety and Effectiveness. In: Service CR, editor. 2018.

FDA's Role in Foods

The FDA defines food as *"articles used for food or drink for man or other animals, chewing gum, and articles used for components of any such article"* (56). This is intentionally vague in order to allow the FDA to determine what exactly constitutes food and created standards at which to evaluate foods. Standards for commercially available food in the US are outlined in Chapter IV of the Federal Food, Drug, and Cosmetic Act (FD&C Act) which identified two main categories of food that violates these standards: "adulterated" and "misbranded" food.[12]

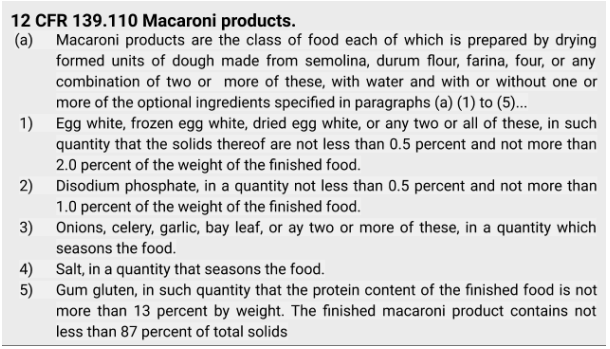
Adulterated food is defined as a food that *"bears or contains any poisonous or deleterious substance which may be rendered injurious to health"*. Foods may also be considered adulterated if they are manufactured in unsanitary conditions, produced from a diseased or improperly slaughtered animal, packaged in unsafe materials, or irradiated outside of guidelines set in place in the FD&C Act.[13] The FDA regulates this through inspections of manufacturing establishments, which may be unannounced. Results of inspections are used

12. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.
13. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.

to generate an Establishment Inspection Report (EIR) that details any issues or problems noted.[14]

Misbranded food is considered as such if *"its labeling is false or misleading in any particular way"*. The FDA determines this through inspection of any containers/ wrappers utilized for packaging as well as any pamphlet or booklet that may accompany an item. One example of how the FDA regulates branding is through setting standards of identity for foods.[15] This is a description that describes what exactly must be in a specific food for it to be labeled under a certain name, setting minimum and maximum requirements, optional ingredients, and prohibited ingredients. The FDA currently has over 300 identity standards in 20 categories of foods. An example of a typical standard of identity is in Figure 3.2.

14. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.
15. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.



12 CFR 139.110 Macaroni products.

(a) Macaroni products are the class of food each of which is prepared by drying formed units of dough made from semolina, durum flour, farina, four, or any combination of two or more of these, with water and with or without one or more of the optional ingredients specified in paragraphs (a) (1) to (5)...

1) Egg white, frozen egg white, dried egg white, or any two or all of these, in such quantity that the solids thereof are not less than 0.5 percent and not more than 2.0 percent of the weight of the finished food.
2) Disodium phosphate, in a quantity not less than 0.5 percent and not more than 1.0 percent of the weight of the finished food.
3) Onions, celery, garlic, bay leaf, or ay two or more of these, in a quantity which seasons the food.
4) Salt, in a quantity that seasons the food.
5) Gum gluten, in such quantity that the protein content of the finished food is not more than 13 percent by weight. The finished macaroni product contains not less than 87 percent of total solids

Figure 4.2. Specific criteria, or standards, for a category of food as identified by the FDA (ex. macaroni products)

The FDA does not monitor and regulate advertising of foods, as this regulation falls under the scope of the Federal Trade Commission (FTC).[16] Health claims on food labels are included within regulations enforced by the FTC. The FDA does not regulate meat, poultry, and certain egg products; regulation of these products falls under the scope of the United States Department of Agriculture (USDA).

FDA's Role in Dietary Supplements

Dietary Supplement Health and Education Act of 1994

16. Borchers AT, Hagie F, Keen CL, Gershwin ME. The history and contemporary challenges of the US Food and Drug Administration. Clin Ther. 2007;29(1):1-16.

was enacted to define and regulate dietary supplements and also to regulate good manufacturing practices (GMP) of companies producing the supplements to ensure the safety of the public.[17]

The definition of a **dietary supplement** under the DSHEA is *"a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or any combination of the aforementioned ingredients."*[18]

Under the DSHEA, dietary supplements must also abide by labeling guidelines. To meet FDA standards, a dietary supplement label must include the following:[19]

- Statement of identity that contains the words "dietary supplement" or use the dietary ingredient to replace the word "dietary".
- Net quantity of contents

17. Swann JP. The history of efforts to regulate dietary supplements in the USA. Drug Test Anal. 2016;8(3-4):271-82.
18. Swann JP. The history of efforts to regulate dietary supplements in the USA. Drug Test Anal. 2016;8(3-4):271-82.
19. Swann JP. The history of efforts to regulate dietary supplements in the USA. Drug Test Anal. 2016;8(3-4):271-82.

- Supplement Facts panel (serving size, amount, percent daily value, of each ingredient)
- If contains a proprietary blend, net weight and listing of ingredients in descending order of weight
- The part of the plant used, if an herb or botanical
- Complete list of ingredients by common or usual names in descending order
- Safety information about the consequences that may result from use
- Disclaimer "This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease"

An important distinction to make with the FDA's regulation of dietary supplements is that the FDA only regulates the manufacturing processes and labeling standards for the supplement. The FDA does not examine effectiveness, safety, and actual content of dietary supplements and only has a limited capacity to monitor adverse reactions from supplements. However, if there is ample proof that a supplement is dangerous or poses a "significant and unreasonable risk" the FDA may ban it.[20]

20. Swann JP. The history of efforts to regulate dietary supplements in the USA. Drug Test Anal. 2016;8(3-4):271-82.

PART III. REVIEW QUESTIONS

1. Compare and contrast a phase II and phase III clinical trial.
2. Define adulterated food.
3. Discuss the role of the FDA in the regulation of dietary supplements.
4. Define an IND (Investigational New Drug Application).
5. What three parameters does the FDA examine when considering a NDA (New Drug Application)?

GLOSSARY

Absorption

Movement of drugs from their site of administration into the vascular bed; influenced by many factors

Administration

Refers to route or method of drug delivery; examples include oral, intramuscular, subcutaneous, intravenous

Adulterated food

A food that "bears or contains any poisonous or deleterious substance which may be rendered injurious to health"

Anorexigenic

A factor that results in a reduction in appetite.

Biotransformation

The alteration of a substance (such as a drug), within the body.

Chrono-nutrition

The coordination of food intake and nutrients with the body's natural circadian rhythms

Chrono-pharmacology

The study of how drugs and their effects vary with biological timing and circadian periodization

Circadian rhythm

Biological processes displaying endogenous and entrain able oscillation of about 24h

Conjugation reactions

Refers to enzymatic reactions that generally occur in Phase 2 metabolism; these reactions add endogenous substances to partially metabolized drug compounds to ultimately facilitate excretion

Dietary supplement

A product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate,

metabolite, constituent, extract, or any combination of the aforementioned ingredients

Dietary Supplement Health and Education Act of 1994

Defines and regulates dietary supplements and also regulates good manufacturing practices (GMP) of companies producing the supplements to ensure the safety of the public.

Distribution, or Volume of Distribution

The volume in an organism throughout which a drug appears to have been distributed; the volume into which a drug appears to have been dissolved after administration to an organism

Drug

A substance or chemical agent, which can affect living processes - and can be a natural product, chemical substance, or pharmaceutical preparation for administration to a human or animal

Drug-nutrient interaction

The effect of a medication on food or a nutrient in food.

Effectiveness

A parameter that focuses on how a drug works in a real-world situation and considers interactions with other medications the patient may be taking and other comorbidities that the patient may have that might alter how the drug acts

Efficacy

The maximum effect of which the drug is capable. A potent drug may have a low efficacy, and a highly efficacious drug may have a low potency.

Enzymes

Proteins that enable and/or speed up the rate of a chemical reaction within a living organism; an enzyme can act as a catalyst for a specific set of reactants (called substrates) into specific products

Excretion

The process of eliminating a drug from the body; there are several routes for drug elimination from the body (sweat or skin; via kidney to urine; via liver to feces, etc.)

Fat soluble vitamins

Vitamins that are insoluble in water. Includes vitamin A

(retinol), E (tocopherols and tocotrienols), D (calciferol), and K (phylloquinone and menaquinone)

Fermentation

An anaerobic metabolic process used by bacteria to generate energy for growth from compounds and host-indigestible dietary components

Firmicutes to Bacteroidetes ratio

A parameter commonly examined in gut microbial research. A higher ratio is commonly associated with chronic inflammatory conditions.

First-pass metabolism

Also known as the first-pass effect; this refers to the rapid uptake and metabolism of a drug agent by the liver before it reaches systemic circulation

Food anticipatory activity

The time-specific arousal prior to feeding

Food entrain able oscillator

A circadian clock that controls food anticipatory activity

Food, Drug, and Cosmetic Act

A law passed in 1938 that gave the FDA authority to oversee the safety of food, drugs, medical devices, and cosmetics

Genetics

Study of individual genes, their role and function in health and disease, and their mode of inheritance

Genomics

Refers to an organism's entire genetic information, the genome, and the function and interaction of DNA with the genome, as well as with environmental or non-genetic factors, such as a person's lifestyle

Gut microbiome

Total population of microorganisms colonizing the gastrointestinal tract

Hydrolytic reaction

Hydrolysis is a chemical process in which a molecule of water is added to a substance

Insoluble fiber

Type of fiber that doesn't attract water and thus speeds up transit time through the intestine.

Macronutrients

Dietary components (fats, carbohydrates, protein) that are required in large quantities and contribute to energy.

Metabolism

The chemical reactions that convert drugs into compounds that are easier for the body to eliminate and excrete; also known as biotransformation

Microbial diversity

A measure of the richness and evenness of a bacterial community and is commonly associated with positive health outcomes.

Micronutrients

Dietary components, specifically vitamins and minerals, required by the body in small quantities to maintain health and prevent disease.

Misbranded food

A food where the "labeling is false or misleading in any particular way"

Nutrigenomics

Concerned with the impact of dietary components on the genome and how genetic variations affect the way we react to specific foods

Orexigenic

A factor that results in an increase in appetite.

Peripheral oscillators

Biochemical circuits outside of the central clock that cycle in a continuous phase and receive input from the SCN and external stimuli

Pharmacodynamics

What a drug does to the body

Pharmacogenomics

Concerned with how genes affect a person's response to drugs

Pharmacokinetics

What the body does to a drug

Pharmacology

The study of drugs and their effects

Phase 1 metabolism

Refers to the action of the cytochrome P450 (CYP) oxidative enzyme system; CYP monooxygenases are phase I enzymes.

Phase 2 metabolism

Refers to conjugation reactions that involve the addition of intracellular polar groups (glucuronate, glutathione, sulfate, and glycine) to the foreign molecules (partially metabolized drug compounds) and function to protect humans against chemical insult by facilitating excretion

Prebiotics

Selectively fermented ingredients that allow for alterations in both the composition and/or activity of the gut microbiota that in turn confers benefits on host health and well-being

Probiotics

Beneficial live microorganisms that when administered in adequate amounts can provide health benefits to the host.

Prodrug

The inactive form of a drug that must be modified in some way to become biologically active

Pure Food and Drugs Act

A law passed in 1906 that prohibited interstate commerce in adulterated and misbranded (i.e. containing additives that were not listed clearly and/or potentially hazardous) food and drugs

Receptor

Cellular bound or unbound macromolecule with structural specificity

Short chain fatty acids

Inorganic fatty acids produced by bacterial fermentation of indigestible carbohydrates

SNP (single nucleotide polymorphism)

DNA sequence variations that account for 90% of all human genetic variation

Soluble fiber

Type of dietary fiber that binds water and other hydrophilic compounds, slowing transit time through the intestine and adding bulk to stools

Suprachiasmatic nucleus

Small region of the hypothalamus that is responsible for controlling circadian rhythms

Time-restricted feeding

Broad term to refer to a protocol of eating at specific times and fasting the rest of the time

Water soluble vitamins

Vitamins that dissolve in water. Includes all of the B vitamins and vitamin C.

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