Handbook of Drug–Nutrient Interactions
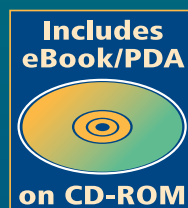
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HANDBOOK
OF DRUG–NUTRIENT INTERACTIONS

NUTRITION ◊ AND ◊ HEALTH
Adrianne Bendich, Series Editor

Handbook of Drug–Nutrient Interactions

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Due diligence has been taken by the publishers, editors, and authors of this book to assure the accuracy of the information published and to describe generally accepted practices. The contributors herein have carefully checked to ensure that the drug selections and dosages set forth in this text are accurate and in accord with the standards accepted at the time of publication. Notwithstanding, as new research, changes in government regulations, and knowledge from clinical experience relating to drug therapy and drug reactions constantly occurs, the reader is advised to check the product information provided by the manufacturer of each drug for any change in dosages or for additional warnings and contraindications. This is of utmost importance when the recommended drug herein is a new or infrequently used drug. It is the responsibility of the treating physician to determine dosages and treatment strategies for individual patients. Further it is the responsibility of the health care provider to ascertain the Food and Drug Administration status of each drug or device used in their clinical practice. The publisher, editors, and authors are not responsible for errors or omissions or for any consequences from the application of the information presented in this book and make no warranty, express or implied, with respect to the contents in this publication.

Series Editor's Introduction

The *Nutrition and Health* series of books have an overriding mission to provide health professionals with texts that are considered essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers in their respective fields; (3) extensive, up-to-date, fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters, but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient/health professionals' questions that are based on the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter as well as in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research- and practice-oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed *de novo*, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

The *Handbook of Drug–Nutrient Interactions*, edited by Joseph I. Boullata and Vincent T. Armenti, is a critical addition to the *Nutrition and Health Series* and fully exemplifies the goals of the series. Both editors are internationally recognized leaders in the field of nutrition and drug therapy. Both are excellent communicators and have worked tirelessly to develop a book that is destined to be the benchmark in the field because of its extensive, in-depth chapters covering the most important aspects of the complex interactions between diet and its nutrient components, health status, developmental stage, growth, and aging and the effects of drugs. The editors have chosen 41 of the most well-recognized and respected authors from around the world to contribute the 26 informative chapters in the volume. Key features of this comprehensive volume include more than thirty extensive tables and figures that provide the reader with excellent sources of detailed information about drug–nutrient interactions.

The editors clearly understand the seriousness of the issue of drug–nutrient interactions. They have stated that "In the care of patients, both drug therapy and nutritional therapy are critical. The potential for drugs and nutrients to interact with each other is significant, but unrecognized by many clinicians. These interactions may result in therapeutic failure or adverse effects of the drug, or alterations in the nutritional status of the patient—in either case impacting the patient's outcome."

The book chapters are logically organized to provide the reader with all of the basics of both drug metabolism and nutrition in the first section, Overview of Drug–Nutrient Interactions. Unique chapters in this section include an introductory chapter that describes the basics of drug metabolism followed by a more in-depth chapter that includes a thorough discussion of the drug-metabolizing enzymes in the critical chapter that includes 325 references. There is also a comprehensive review of the basics of the metabolism of the major dietary nutrients.

Part II contains two chapters that examine the effects of either under- or overnutrition (obesity) on drug disposition and their effects. Specialized topics in the third section include the effects of concomitant consumption of foods and a drug and include a detailed description of Food and Drug Administration requirements for conducting a clinical study on a fasted or fed state. Non-nutritive components of the diet such as herbs, caffeine, charcoal broiling of foods, and alcohol also affect drug efficacy and these effects are presented in extensive tables that organize the data clearly for the reader. The effects of grapefruit juice, garlic, ginkgo and other key herbs as well as nutrient–nutrient interactions are reviewed in separate, comprehensive chapters.

Cutting-edge discussions of the roles of the major drugs used by patients are covered in individual chapters and related to the dietary factors that can either interfere with or enhance efficacy. Drugs affecting the cardiovascular system and the nervous system, with emphasis on antiepileptics, are reviewed in depth. Specific emphasis is given to the effects of dietary minerals on drug pharmacokinetics and pharmacodynamics depending on whether the individual is deficient in the specific mineral. Likewise, supplementation with various dietary factors including folate, vitamin D, vitamin K, and calcium is also included.

Of particular relevance to clinicians are the chapters in Part V that examine drug nutrient interactions by life stages. Chapters include infancy and childhood, pregnancy and lactation, and the elderly, stages that have special considerations when examining the types of drugs used by the different groups and the varied nutritional requirements of these life stages.

The final section looks at drug–nutrient interactions in individuals who have either chronic diseases or special needs for certain classes of drugs. The chapter on cancer patients is particularly sensitive to the potential for drugs to affect the precarious health balance in these patients. Transplant patients also have unique needs and this chapter contains a valuable table that provides details about the nutrient requirements of transplant patients posttransplant. Several chapters examine the effects of chronic infections including HIV, tuberculosis, and hepatitis. Another concentrates on the effects of autoimmune diseases including rheumatoid arthritis, diabetes, and lupus, the drugs used in treatment, and the interactions of the disease, drug, and nutritional status. The final chapter looks at the role of enteral nutrition in affecting drug delivery, disposition, and clearance, another important clinically focused chapter.

Of great importance, the editors and authors have provided chapters that balance the most technical information with discussions of its importance for clients and patients as well as graduate and medical students, health professionals, and academicians. Hallmarks of the chapters include complete definitions of terms with the abbreviation fully defined for the reader and consistent use of terms between chapters. There are numerous

relevant tables, graphs, and figures as well as up-to-date references; all chapters include a conclusion section that provides the highlights of major findings. The volume contains a highly annotated index and within chapters, readers are referred to relevant information in other chapters.

This important text provides practical, data-driven resources based on the totality of the evidence to help the reader evaluate the critical role of nutrition, especially in at-risk populations, in optimizing drug efficacy. The overarching goal of the editors is to provide fully referenced information to health professionals so they may have a balanced perspective on the value of foods and nutrients that are routinely consumed and how these can help to assure that drugs can deliver their maximum benefits with minimal adverse effects. Finally, it must be noted that all of the authors and the editors agree that much more research is required to be able to give the best advice to patients with regard to drug–nutrient interactions.

In conclusion, *Handbook of Drug–Nutrient Interactions* provides health professionals in many areas of research and practice with the most up-to-date, well-referenced, and easy-to-understand volume on the importance of nutrition in optimizing drug efficacy and avoiding adverse effects. This volume will serve the reader as the most authoritative resource in the field to date and is a very welcome addition to the *Nutrition and Health Series.*

Adrianne Bendich, PhD, FACN
Series Editor

Foreword

Although there is a great deal of literature regarding drug–nutrient interactions (DNIs), there are limited sources of up-to-date comprehensive information. The *Handbook of Drug–Nutrient Interactions* admirably fills this gap. The editors, Dr. Joseph I. Boullata and Dr. Vincent T. Armenti, have a wealth of experience in this therapeutic area and have assembled a fine cadre of chapter authors who have individually contributed their high level of expertise.

As treatment for many diseases becomes increasingly complex with multiple drug therapies scheduled at varying times, the need to identify clinically significant DNIs is an essential part of medication management. This is a shared responsibility between health care professionals to interpret available data and individualize an approach to therapy that is compatible with the patient's disease state, life stage, and dietary intake.

Awareness of the significance of drug–food interactions is generally lacking. Although many texts contain lengthy lists of possible interactions, few data are provided for the clinician to gain an understanding of the mechanism of action of the interaction and subsequently apply the information to a particular patient or group of patients. For example, in the management of patients with HIV-AIDS who are taking complex prescribed drug regimens, herbal products, and nutritional supplements, many of which are affected by dietary intake, careful attention to DNIs is a critical component of therapy. Clinicians need to take account of not only the well-documented interactions between drugs and nutrients, but also the less obvious effects on drug–nutrient disposition and metabolism. The current text provides the reader with this valuable insight.

Designing a regimen that is both safe and effective for the patient is an important part of collaborative drug therapy management. As such, this comprehensive handbook will serve as a resource for pharmacists, dietitians, nurses, and physicians as they partner to enable better drug therapy adherence and therapeutic outcomes for their patients. In addition, the *Handbook of Drug–Nutrient Interactions* will serve as an excellent resource for both educators and students in raising the level of awareness and knowledge of the mechanisms of DNIs such that their consideration is given a level of importance similar to that of drug–drug interactions, which are more consistently reviewed.

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Preface

Although the influence of nutrition on health is obvious, its critical role in the care of patients is not as widely recognized. In caring for patients, more attention is often paid to the role of drug therapy. The field of clinical nutrition actually overlaps with the field of pharmacotherapy at several points, but none more clearly than at the interaction of drug and nutrient. A drug–nutrient interaction is considered the result of a physical, chemical, physiologic, or pathophysiologic relationship between a drug and nutrient(s)/food that is deemed significant when the therapeutic response is altered or the nutritional status compromised. We felt that a current reference book on this subject was long overdue, so we have put together this *Handbook of Drug–Nutrient Interactions*.

The handbook is intended for use by physicians, pharmacists, nurses, dietitians, nutritionists, and others, in training or in clinical practice, to better manage drug–nutrient interactions in their patients. This topic is particularly timely with so much attention being paid to the issue of patient safety in the current health care delivery system. Although a number of manuals exist that provide extensive lists of documented and potential drug–nutrient interactions, this handbook takes a scientific look behind many of those interactions, examines their relevance, gives recommendations, and suggests specific areas requiring research. This handbook provides clinicians with a guide for use in understanding, identifying, or predicting, and ultimately preventing or managing significant adverse drug–nutrient interactions to optimize patient care. We hope this handbook challenges clinicians to become more aware of potential drug–nutrient interactions, document them regularly, and carry out research projects to clarify their mechanisms and clinical significance. Much more needs to be known about drug–nutrient interactions than is currently appreciated. Some topics have yet to amass enough information to allow inclusion in a chapter; others are as yet unanticipated. For example, how long will it be before genetic engineering allows relatively inexpensive production of certain pharmaceuticals by plants? Without placing a value judgment on that notion, it becomes clear that the issue of drug–nutrient interactions has moved past the problems of how to time drug administration around meals.

The book begins with a perspective on the topic (Chapter 1), and is followed by overviews of drug disposition, nutrient disposition, and enzyme systems involved in both drug and nutrient metabolism (Chapters 2–4). These chapters allow the reader, regardless of discipline, to gain a sense of the topic and the underlying foundation that is needed in the remainder of the book. Two chapters discuss the effect of nutritional status on drug disposition and effect (Chapters 5–6), a topic often overlooked. The next group of chapters discusses the influence of food, nutrients, and non-nutrient dietary components on drug disposition and effect (Chapters 7–12). Given the widespread use of dietary supplements, interactions with drugs and with nutrients by this diverse group of substances—some of which behave more like drugs than nutrients—these chapters are most relevant. The influence of medications on nutrient status is presented both generally and in regard

to specific groups of drugs or nutrients (Chapters 13–17). Another set of chapters discusses drug–nutrient interactions that are relevant to various stages of the life cycle or to specific patient groups or conditions (Chapters 18–26).

There is no one best way to approach drug–nutrient interactions, and we have included some topics not typically considered in such a presentation. Clearly, not every documented drug–nutrient interaction identified in vitro, ex vivo, in animal models, or in human studies is covered. Not discussed are the sequential interactions between nutrients, disease and drugs (e.g., micronutrients impacting HIV disease, which then influences drug disposition). One multifaceted topic deserving of discussion, but not included, is the set of interactions involving parenteral nutrition, in terms of both the effect on drug disposition and the impact of each nutrient or combination of nutrients on each other and on concurrently infused drugs. However, parenteral drug–nutrient interactions could fill an entire book. Overlap is almost unavoidable in a book on drug–nutrient interactions, but we have tried to avoid major sections of redundancy. For example, although the chapter on interactions involving folate mentions the antiepileptics, a chapter entirely devoted to antiepileptic interactions follows. Similarly, the interactions involving grapefruit juice are touched on in several chapters, but a more in-depth discussion is reserved for the chapter dedicated to that topic. The more detailed chapter on the elderly is in part related to the historic relevance of drug–nutrient interactions in this group.

What we have attempted to provide is a bit more than a listing of common interactions. The authors, some having spent many years with their subject matter, provide a framework for understanding many of the more common, and some less common, drug–nutrient interactions, including the mechanisms and clinical approaches to their management. We hope that this *Handbook of Drug–Nutrient Interactions* helps make the case that the issue of drug–nutrient interactions is a significant one for clinicians and researchers alike. We are grateful to the authors for their work, and excited about this compilation, although we are looking forward to new information on drug–nutrient interactions as it continues to emerge. We would welcome comments from readers that will help improve the breadth, depth, and quality of this book and the care of patients.

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I

OVERVIEW
OF DRUG–NUTRIENT INTERACTIONS

1 A Perspective on Drug–Nutrient Interactions

Joseph I. Boullata and Jacqueline R. Barber

1. SCOPE OF THE ISSUE

There are so many drugs available for use in the human condition, with continued approval of new agents, and expanded indications for existing ones *(1)*. Likewise spending on pharmaceuticals in the United States continues to increase by 10–15% each year, driven by increased utilization as well as increased cost per prescription *(1)*. According to a recent report, close to $141 billion of the estimated $1.4 trillion spent on health care annually in the United States are accounted for by prescription drugs *(2)*. Beyond prescription medication, the wide availability of over-the-counter (OTC) pharmaceuticals and dietary supplements together with the increasing emphasis on self-care among people further increases consumption patterns of pharmacologically active substances. Recent estimates are that about 80% of Americans use medication, whether prescription, OTC, or dietary supplement products *(3)*.

Although dietary intake may not be recognized in similar terms of increasing discoveries, it should be recognized that food intake habits have changed along with advances in nutrition and food sciences *(4–6)*. Furthermore, our understanding of food components included in the diet, whether nutrients or phytochemicals, has expanded *(7,8)*. This makes for an ever-widening potential for interactions between drugs and food, food components, or specific nutrients. The potential for interactions becomes that much more complex when patients with any underlying alteration in nutritional status are included. The working definition of a drug–nutrient interaction (DNI) used throughout this volume is that which results from a physical, chemical, physiologic, or pathophysiologic relationship between a drug and a nutrient, multiple nutrients, or food in general. The interaction is considered significant from a clinical perspective if therapeutic response is altered or nutritional status is compromised.

The potential number of interactions and permutations seems infinite. But it remains unclear what proportion of these have actually been identified, and more to the point, what number of the identified subset may be considered clinically significant. Clearly, if one is not looking for a DNI, one will not find it. For those interested in identifying specific interactions, a number of books over the years have dedicated some or all pages to DNIs *(5,9–29)*. Some lists of DNIs are so brief they seem to question the legitimacy of the topic, others are so extensive one wonders how an interaction could ever be

avoided. With this mixed message, many clinicians simply discount the relevance of DNIs to their practice. A recent survey of health care providers found their knowledge of common DNIs to be wanting (30). This may in part explain why so few health care providers provide DNI counseling to the majority of their patients (31). These findings occur at a time when regulatory agencies expect DNIs to be addressed by clinicians in institutionalized settings. What is needed is a rational approach to evaluating the scientific basis and clinical relevance of existing DNIs to allow for appropriate recommendations. At the same time, this approach should set up a framework on which to build a database for the many interactions yet to be identified, evaluated, and documented. Although much has been done over the years, much more still needs to be accomplished.

2. HISTORICAL PERSPECTIVE

Through the ages, the use of food combinations or the addition of medicinal remedies to food were employed to preserve health or to manage disorders. Time has not slowed down either our penchant for food or the advancement of therapies used to manage disease. But more important than a historic review of the entire topic, is the evolution in relative importance placed on clinically relevant DNIs.

That disease and therapy could precipitate malnutrition was barely mentioned in a lengthy clinical review on nutritional assessment many years ago (32). A few decades later, the only clinically recognized DNIs were the more obvious intraluminal interactions between drug and food (33). It was still several years until the first major review recognizing the impact of food on drug absorption was published, finally stimulating clinical interest (34). As a result, any identified interactions between a drug and food were then treated with caution. The appreciation that not all interactions were clinically relevant developed more slowly. Even then, the idea that clinically relevant DNIs may involve more than simply physical interactions between food and drug also evolved slowly. This limited clinical focus occurred despite much earlier work on the impact of specific nutrients on drug metabolism (35) and the effect of drugs on nutrient metabolism (36,37). At about the same time, the overlap of heredity on the interaction between drugs and nutrients was recognized (38), and the effects of nutritional status on drugs began to be explored as well (39,40). Over the intervening decades, DNIs have been studied and discussed more formally, and presented in practical formats.

Dr. Daphne A. Roe was once referred to as the founder and "godmother" of the DNI issue (41). This noted physician spent a good portion of her tremendous professional energies in the arena of DNIs. She clearly understood that it was the responsibility of all clinicians to understand DNIs, and provided guidelines that included clinical aspects of DNIs. Besides contributing to the primary literature (42–46), she authored handbooks (10,20,21) and texts (13,14,17) on the subject. She also served as the editor of a journal dedicated to the topic—*Drug–Nutrient Interactions: A Journal of Research in Nutrition Pharmacology and Toxicology* (*Drug–Nutr Interact*), first published in 1982. A quick review of the periodical for its topics and authors reveal the breadth of original research activity and the quality of investigators in the field of nutritional pharmacology, many of whom remained active. They represented departments of nutrition, food science, and pharmacology in schools of medicine, pharmacy, and varied universities. The studies in the journal were supported by a variety of government and industry sponsors, as well as

individual academic institutions, in the United States and abroad. The contents of some of the published papers set the stage for the current understanding of DNIs. There were studies that teased apart mechanisms, and involved human subjects as well as animal models. Negative studies were included to allow for clarification of issues. Although papers seemed to answer some of the questions of the day, they certainly opened the doors to further questions. From a clinical perspective, the work published in *Drug–Nutr Interact* began to scratch the surface. Some of the studied drugs are no longer in use, but considering the number of drugs that enter the marketplace each year, so many more have yet to be evaluated for their DNI potential. In fact, in recent years the re-emergence of herbal remedies and complex dietary supplements have increased awareness of, if not identified weaknesses in, DNIs and their relevance. Much of this type of literature is now published across various disciplines in the clinical and scientific journals of food science, medicine, nutrition, pharmacology, and pharmacy.

But much is left undone or unstudied. Each potential DNI needs to be investigated, and those with clinical relevance need to be documented by clinicians, and examined mechanistically by researchers. From a practical standpoint, the focus of surveillance should be on the most commonly used chronic medications, particularly those that influence homeostasis, having a narrow therapeutic index, and active metabolites, in populations at greatest risk. High-risk populations would include the elderly, the critically ill, and those requiring nutrition support. We need to be able to identify additional factors (e.g., gender, genetics, other disease states, etc.) and then predict relevant interactions. Genetic markers of susceptibility and outcome need to be explored further. Research goals considered appropriate at an international conference in 1984 are still relevant in 2004 *(46)*. They included reporting DNIs, understanding their cause, predicting likelihood of outcomes, assessing subpopulation risk factors, and educating health care professionals.

Given the early descriptions of interactions as impacting predominantly on absorption, it is not difficult to understand how many clinicians have come to dismiss or trivialize all but a few of the documented or potential interactions. Another barrier to overcome is the lack of consideration given to nutrients as being "drug-like." Each nutrient is an organic structure or inorganic element, with unique properties, that require absorption, distribution, metabolism, and elimination from the body, and in fact elicit a dose-related physiologic response from that body following administration. An interaction could potentially occur at any point in nutrient disposition or effect.

A recent approach based on scientific rigor could lead to a more comprehensive examination of the broad range of DNIs *(47)*. It specifically recognizes that more research and clinically relevant information about DNIs is needed *(47)*. Toward a rational approach to generating and presenting data on DNIs, it seems reasonable to classify existing DNIs, generate new data, recognize the complexity of individual interactions, appreciate the breadth of the topic, and identify sources for clinical application.

3. APPROACH TO DNIs

3.1. Classification

The classification of DNIs can be approached in a variety of ways—by drug, by nutrient, by patient type, by outcome (clinical manifestations), by mechanism (chemical or physiologic), or by location (ex vivo, gastrointestinal [GI] tract, circulation, and site

of effect). A classification system based on the location and mechanism of an interaction, with both an identified precipitating factor and an object of the interaction may help to more easily design management strategies, and focus research efforts. Such a classification system for clinically identified DNIs as recently described *(47)* could fit into a single, broad, and inclusive approach (Table 1). Such an approach would allow DNIs to be described or examined based on five general categories:

1. The impact of nutritional status on drug disposition and effect.
2. The impact of food on drug disposition and effect.
3. The impact of specific nutrients on drug disposition and effect.
4. The impact of drugs on nutritional status.
5. The impact of drugs on the disposition and effect of specific nutrients.

Within each of the five categories, a specific precipitating factor would have a defined location and/or mechanism of interaction with the object that is affected by the interaction. Keep in mind that the precipitating factor could be multifaceted, including the interplay of disease and genotype.

3.2. Mechanisms

Why certain drugs and nutrients interact with each other and not with others, relates to physicochemical factors of the medication, food or nutrient, as well as to individual physiology whether normal or disordered. But the clinical consequences often relate to altered disposition and/or effect. Disposition includes steps that influence bioavailability, distribution, metabolism, and excretion. Effect refers to pharmacological or physiological consequences of a drug or nutrient interacting directly or indirectly with cellular targets.

Malnutrition, from starvation to obesity, can influence drug absorption, distribution, elimination, and effect. Food in general, the type of meal, a specific food, or even non-nutritive food constituents can impact on the absorption, elimination, and effect of various drugs. At the level of the GI tract, interactions may be due to physicochemical reactions, as well as altered enzyme or transporter function. Nutrients found in food, or those delivered in pharmaceutical dosage forms can interact with drugs as well. The complexity of enteral and parenteral nutrition regimens and the patients who require them creates opportunity for numerous interactions. This would include specific physicochemical reactions for ex vivo interactions involving the mixture of medication with food or with nutrition support products. Mechanistically, DNIs may occur ex vivo as reactions between drugs and nutrients in a delivery vehicle, at the site of drug and nutrient absorption to alter bioavailability, and systemically in drug or nutrient distribution, storage, metabolism, or elimination *(47)*. Specific drugs may alter nutrient intake, absorption, storage, metabolism, and excretion. Non-nutrient agents (herbals and other dietary supplements) have the same potential to alter nutritional status and nutrient disposition. Systemic interactions may involve effects on distribution, biotransformation, elimination, or organ, tissue, cell membrane, or subcellular function.

3.3. Impact of Nutritional Status and Food Intake on Medications

Both protein-calorie malnutrition and obesity are known to influence drug disposition and effect *(48,49)*. Several micronutrients including riboflavin and ascorbic acid are active components in microsomal enzyme systems used for drug metabolism with capac-

Table 1
Approach to Drug–Nutrient Interactions

Precipitating Factor	Object of Interaction	Scientific Basis	Clinical Management Strategy
Altered nutritional status	Drug	Identify mechanism	Aim to minimize treatment failure or drug toxicity
Food or food component	Drug	Identify mechanism and location	Aim to minimize treatment failure or drug toxicity
Nutrient	Drug	Identify mechanism and location	Aim to minimize treatment failure or drug toxicity
Drug	Nutritional status	Identify mechanism	Aim to maintain or improve nutritional status
Drug	Nutrient	Identify mechanism and location	Aim to maintain or improve status of individual nutrient

ity reduced in deficiency *(50,51)*. Although vitamin A deficits may slow drug metabolism in animal models, this remains poorly defined in humans *(52)*. However, it may not even require a clinically apparent alteration in nutritional status for dietary changes to influence drug response *(38)*, particularly when underlying gene polymorphism plays a role.

The known polymorphism of methylenetetrahydrofolate reductase (MTHFR) can be important in terms of determining appropriate nutrient dosing (vitamin B_6, vitamin B_{12}, folic acid, riboflavin) *(53,54)*. Genetic variants in vitamin metabolism can likely mean more individualized requirements. It may also be important in terms of the drugs that impact on the associated pathways. For example, methotrexate toxicity may be manifest differently depending not only on folate status but also on MTHFR genotype *(55)*. For example, cases of hematologic toxicity associated with low-dose methotrexate as used in rheumatoid arthritis patients have been reported. These occurred in patients not receiving folic acid. The reports describe serum folate (but not erythrocyte folate), but then barely mention the issue of folic acid supplementation let alone genotype *(56,57)*, despite recommendations to include folic acid in methotrexate regimens *(58)*. The value of folic acid supplementation during treatment with methotrexate should be evaluated prospectively while also taking MTHFR genotype into account.

Meals, specific foods, or specific compounds in foods can impair drug absorption and bioavailability *(59)*. For example, carbohydrates may enhance, and protein may reduce phenytoin absorption *(60)*. Foods containing hydrolyzable or condensed tannins (e.g., black tea, coffee) can cause precipitation of medications (e.g., phenothiazines, tricyclic antidepressants, propranolol, hydralazine, histamine receptor antagonists) even in diluted form at intestinal pH *(61)*. Drug metabolism is also influenced by the diet *(62)*. Use of drug cocktails (e.g., midazolam, caffeine, chlorzoxazone, and debrisoquin) and metabolite ratios can help predict cytochrome P450 (CYP)-mediated interactions, includ-

ing those posed by dietary supplements, while taking individual phenotype into account *(63)*. Supraphysiologic doses of the various vitamin E isoforms may play a role in drug interactions *(64)*.

3.4. Impact of Drugs on Nutritional Status

The impact of drugs on nutritional status or on the status of a specific nutrient has been well recognized *(36,37,65,66)*. Many such realizations occurred as synthetic drug development proliferated. Drugs can influence nutrient synthesis, absorption, distribution, metabolism, and excretion. However, a few situations account for most clinically common nutrient depletions—when a drug causes significant anorexia or malabsorption, when nutrients are involved in multiple pathways (e.g., folic acid, vitamin B_6), or when a drug, by its structure and function, is a vitamin antagonist (e.g., methotrexate). Even the anti-vitamin effects of a medication may be due to one or more factors—reduced absorption or reduced conversion to active form, interference with vitamin-dependent pathways, or increased vitamin clearance (metabolism or excretion). These are each more likely to occur when used chronically, and in patients with marginal nutritional status. The biochemical or functional or clinical manifestation will depend on the degree of deficit and the tissue compartment most affected. Stretching the definition would also include drugs that could induce pancreatitis and thereby alter nutrient disposition. Of course by implication, DNIs are assumed to play negative roles in patient outcome, but some interactions can improve therapeutic outcome. In fact, the action of certain drugs (e.g., warfarin) are by their very nature the result of a DNI.

There may be as yet unrecognized adverse nutritional effects to a given drug. Recognized drug effects can include a reduction in appetite or absorption, alteration of nutrient metabolism, and increased urinary losses, whether used for a short or longer duration. These only account for drug-related factors; the patient variables are also important. These might include altered physiological nutrient requirements, a marginal diet, malabsorption, a chronic or catabolic disease, altered organ function, concomitant ingested substances (drugs, dietary supplements, drugs of abuse) or environmental exposures (or lack of ultraviolet light in the case of vitamin D), and pharmacogenetic variability.

The influence of drugs on nutritional status may begin with impeding the ability to gather, prepare, and ingest food. The next logical step of interference would be nutrient absorption, which was documented early in the case of mineral oil *(67)*. This could occur because of physicochemical interactions within the lumen as well as via mucosal damage, altered bile salt availability, or pancreatic exocrine function *(68,69)*.

Micronutrient deficits need to be examined along a spectrum from normal status to overt classic deficiencies. For example, vitamin B_6 deficits following treatment with isoniazid (iso-nicotinic acid hydrazide) may manifest as neuropathic, anemic, or pellagrous findings. Quite a number of drugs are known to alter vitamin B_6 status given the reactivity of the compound *(70)*. Folic acid deficits secondary to phenytoin or methotrexate therapy may present with hypersegmented neutrophils, anemia, GI symptoms, and weight loss. Several drug groups impact on vitamin B_{12} status by reducing absorption (e.g., biguanides, bile acid sequestrants, proton-pump inhibitors), or inhibiting coenzyme synthesis (nitrous oxide). These losses would be expected to occur over time eventually leading to classic signs or symptoms of deficiency, but should be identified (or better yet prevented) long before that degree of deficit has been reached. Theophylline, for example,

is a pyridoxal kinase antagonist at therapeutic concentrations that could induce vitamin B_6 deficits. It is possible that some patients taking the drug chronically may require vitamin B_6 supplementation to limit nervous system side effects, particularly tremor seen at therapeutic concentrations *(71)*.

The cause and even the diagnosis of drug-induced vitamin D deficiency are likely often overlooked. Given the complexities of vitamin D formation, activation, and metabolism, not to mention polymorphism of the vitamin D receptor, drugs can interfere with vitamin D status at several levels. OTC sunscreen products that provide a barrier to ultraviolet light may reduce vitamin D formation in the skin. Bile acid sequestrants could reduce the absorption of ingested vitamin D. Mineral oil and cholestryramine can reduce absorption of vitamin D (and vitamin A) by acting as a solvent or by binding needed bile salts. This is unlikely to lead to overt clinical deficits in vitamin A replete patients. Hepatic enzyme inducers (e.g., phenobarbital, phenytoin, carbamazepine) could accelerate vitamin D metabolism to inactive forms, among other effects, and otherwise result in low levels of the active hormone. Regimens of broad-spectrum antibiotics may reduce intestinal floral production of vitamin K_2, although this is unlikely to lead to clinical deficits given the minor role that this source of the vitamin plays in humans. However, pharmacological doses of vitamin E can induce manifestations of vitamin K deficiency *(72)*.

Other potential interactions have not yet been well evaluated. For example, the initial steps of vitamin E metabolism requires the CYP enzyme system, although metabolic rates for each individual tocopherol and tocotrienol may differ *(73,74)*. Inhibition or induction of these pathways by drugs, including ethanol, could alter the clearance of vitamin E forms or vitamin E status. Ethanol competes with retinol at a common initial step in their metabolism, while increasing CYP activity, both of which create deficits of retinoic acid, which in turn may account for ethanol-induced hepatic injury *(75)*.

Mineral status can also be influenced by medications. This relates both to macrominerals (electrolytes) and microminerals. Consider, for example, the drug-induced syndrome of inappropriate antidiuretic hormone secretion leading to hyponatremia. The antidepressants have been reported to be one cause *(76)*. This is especially true for the serotonin reuptake inhibitors *(77)*, although unlikely to be linked to CYP genotype *(78)*. Diuretics can cause true sodium depletion, as well as potassium losses. Laxative abuse and high-dose corticosteroids may also cause hypokalemia *(79,80)*. Aminoglycosides and amphotericin B can also induce hypokalemia. Alcohol abuse leads to depletion of magnesium stores. Neomycin and colchicine can induce intestinal malabsorption of calcium *(81)*. The proton pump inhibitor lansoprazole, used for significant gastroesophageal reflux disease, may cause severe symptomatic hypocalcemia *(82)*.

Antinutrient, metabolic effects of a drug are typically acutely manifest (e.g., warfarin, isoniazid), whereas those that interfere with intake, absorption, or clearance may take longer to develop (e.g., cholestyramine, diuretics). If not being looked for, it is easy to see how few clinicians recognize the importance of DNIs. Although the use of cholestyramine may reduce vitamin absorption (e.g., folic acid, vitamin D), clinically significant nutritional deficits may not occur in the nutrient-replete patient with adequate intake. This is not to say it will not occur in a patient with marginal status or poor intake. The point being that a clinically significant outcome is patient-specific, not necessarily just drug-specific. Anecdotally, patients with the best adherence to therapeutic regimens are those more likely to develop nutrient deficits. A complex case of drug-induced

nutrient deficits leading to disease provides the opportunity to explain the cause *(83)*. It is interesting that few would question the value of providing pyridoxine therapy pharmacologically to patients receiving isoniazid, for example, but many would consider it strange to evaluate similar strategies for other medications that pose risks to nutritional status (e.g., folic acid to patients receiving phenytoin).

Although some of these interactions may be reasonably well recognized today, the impact of medications on subclinical states of nutrient deficit may not be. The use of analytic laboratory techniques to identify functional deficits may be valuable in assessing the impact of a drug on nutritional status *(45)*. The balance between requirements and supply determines an individual's nutrient status. Although nutrient requirements vary with age, gender, and health status, the supply of nutrients is determined by food habits, dietary restrictions, socioeconomic status, food processing and preparation, among other factors. Recent surveys indicate marginal nutrient status in high-risk groups even if using supplements *(84)*. The poor ability of many clinicians to identify micronutrient deficiency, whether clinically obvious or not, may limit the wider recognition of drug-induced nutritional deficits. A nutritionally focused patient history and physical exam is important in order to correctly identify nutrient deficits and differentiate them from the "usual suspects" *(85,86)*.

3.5. Adverse Drug Effects Following Nutrient Losses

The idea that some adverse effects of medications are directly related to their influence on nutrient status is not new. Several examples have already been described in the previous section. In other words, adverse effects of medication may occur through an alteration of nutrient status.

So, drug-induced nutritional deficits may be considered as a subclass of adverse drug effects, whether identified as dose-related, duration-related, or idiosyncratic in nature. For example, valproic acid hepatotoxicity, teratogenicity, and antifolate activity may each be related by a common mechanism involving drug-induced alteration in the methionine cycle *(87)*. Management through nutrient replacement may not always prove corrective. Nucleoside reverse transcriptase inhibitor-induced hepatotoxicity may be partly and indirectly related to nutrient status, but a nutrient supplementation regime will not necessarily improve the clinical manifestations *(88)*. Also, nonsteroidal anti-inflammatory drugs can irritate the GI tract leading to blood and iron loss, fluid and sodium retention with weight gain, and possibly hyperkalemia—all of which are considered as drug-induced nutritional effects.

Antiepileptic agents are likely to alter the status of several nutrients, including folic acid and biotin. The interaction between folate and phenytoin has been examined little by little over time *(89–93)*. Our understanding of this two-way interaction is still not sufficient to assure a consistent management approach. Epileptic patients receiving anticonvulsants, especially individuals with a specific MTHFR mutation, may have a higher folate requirement based on homocysteine levels *(94)*. Carbamazepine, among other agents, can reduce the GI absorption of biotin and increase its metabolic clearance *(95,96)*. The metabolic consequences may be a reduced clearance of endogenous compounds that are known to be neurotoxic. This could play a role in the adverse effects of carbamazepine *(96)*. Exploring the possibility that drug effects may have a nutritional basis allowed someone to establish that the teratogenic effects of D-penicillamine were likely related to copper deficits *(97)*.

Bone marrow hypoplasia seen in severe malnutrition includes an anemia that responds specifically to riboflavin administration. This appears due to secondary adrenal failure or an indirect effect on erythropoeitin production or release *(98,99)*. This could possibly be one mechanism to explain how drugs might induce erythroid hypoplasia or aplastic anemia.

The previous discussion of an approach to DNIs included brief reference to a small number of examples. The story of a single nutrient in more depth may be informative.

4. ASCORBIC ACID

Vitamin C is a required nutrient for humans and other primates, as well as for the guinea pig, each of which is unable to synthesize the molecule. With its own absorption, distribution, and elimination now reasonably well described, ascorbic acid's physiological roles continue to be explored. It is an essential cofactor in numerous biochemical reactions, including the indirect provision of electrons to enzymes, which require prosthetic metal ions in reduced form for their activity. Although rare, cases of the classic deficiency state, scurvy, continue to be reported *(85,86)*. Deficits of ascorbic acid in the absence of scurvy are much more common, however, existing in close to half of elderly hospital admissions *(100)*. In addition to reduced intakes, some people regularly consume vitamin C supplements above the current Recommended Dietary Allowance. This diversity in vitamin C status is important because ascorbic acid is involved in drug disposition and effect, and may itself be influenced by drugs. What follows is an overview of these findings, which also highlight some of the confounding factors that impact on any potential interactions. Much remains to be unraveled in the complexity of interactions involving just this single nutrient. The same can be said for others and for nutrient combinations and varied food matrices as seen in the clinical situation.

4.1. Role in Drug Metabolism

4.1.1. Ascorbic Acid Deficits

Ascorbic acid's role in drug metabolism was recognized early when vitamin C deficiency was shown to impair pentobarbital metabolism and prolong its effect in a guinea pig model *(35)*. Antipyrine and caffeine are additional markers often used in studies of hepatic drug metabolism. Antipyrine half-life also increases in guinea pigs with vitamin C depletion *(101)*. Although a change in half-life may also be a consequence of altered volume of distribution, drug half-life was often used alone as a marker of clearance in these older studies. Repletion of vitamin C in this model returned drug half-lives back to normal *(101)*. In a set of depletion–repletion studies, ascorbic acid did not appear to influence antipyrine clearance in a primate model *(102)*.

A chronically vitamin C-deficient diet resulted in lower clearance and longer half-lives of caffeine in a young group of adult guinea pigs *(103)*. This was associated specifically with hepatic microsomal metabolism of these drugs, although not consistent with ascorbic acid possessing a direct cofactor role *(51)* and recognized as likely influencing the activity of select CYP isoenzymes *(104)*. These reductions in drug metabolism were also found to occur in subclinical states of deficit *(105)*. The effect of vitamin C deficits is most pronounced as hepatic concentrations fall below 30% of normal *(106)*. The activity of several hepatic enzymes is reduced in guinea pigs without scurvy but never-

theless deficient in the vitamin *(107)*. Although they help to identify mechanisms, findings from animal models are not necessarily relevant to the clinical situation. The half-life of caffeine in the guinea pig is about 10 h compared to about 5 h in man, and even less in rodents. Conversely, the half-life of antipyrine is longer in humans (~10 h) than it is in the guinea pig (~2 h). Assuming that these differences relate predominantly to clearance, and not to differences in volumes of distribution, they may be accounted for by variability in the population, density, and activity of the various CYP enzymes. Of course, interspecies differences do occur, and some data has since been derived in humans.

Similar findings in humans have been reported using antipyrine, whose low clearance in patients with poor vitamin C status increased following vitamin C repletion *(100,108,109)*. This was demonstrated particularly in those elderly patients with subclinical deficiency, but not in those without any obvious vitamin C deficits *(100)*. These findings have not always been confirmed in controlled human depletion trials, which may be explained in part by different responses to acute compared with chronic deficits *(110,111)*. Chronic deficits and long-term repletion studies support the alteration in antipyrine clearance with vitamin C status *(109)*.

4.1.2. ASCORBIC ACID SUPPLEMENTATION

Given the wide use of both vitamin C supplements and vitamin C-enriched food products, patients may more commonly consume amounts of ascorbic acid above the current dietary recommendations. This pharmacologic dosing of ascorbic acid may have an impact on drug metabolism as well. In a guinea pig model, the chronic administration of high-dose ascorbic acid significantly increased the elimination of caffeine compared to the normal vitamin C group with an accompanying half-life reduction *(103)*. Interestingly, this was best seen in younger but not in older animals *(103)*. Hepatic enzyme activity is increased when large doses of ascorbic acid are administered above that in a normal diet *(107)*. High ascorbic acid levels, or vitamin C status in general, in part differentiates the effect of age on caffeine pharmacokinetics. In a rodent model, large ascorbic acid doses reduced hepatic, but not lung, CYP1A1 gene expression induced by cigarette smoke exposure *(112)*. In ascorbic acid-depleted but asymptomatic monkeys, there was no change in antipyrine clearance compared with the repleted state except in those further supplemented with isoascorbic acid (an isomer with similar redox potential) in which clearance increased significantly *(102)*.

The limited findings on drug metabolism in humans appear as varied following ascorbic acid supplementation as with vitamin C deficits. Human studies have found that doses of up to 1–4.8 g daily for 7 or more days may either increase or have no effect on antipyrine clearance *(113,114)*. At an ascorbic acid dose of 300–4800 mg daily for 1–2 wk there was no influence on antipyrine clearance following a single oral dose *(113)*. Ascorbic acid did not affect the pharmacokinetics of antipyrine in elderly men *(115)*. Again, the chronicity of supplementation may play a role. Chronic consumption (12 mo) of ascorbic acid 500 mg daily did increase elimination of antipyrine in hypercholesterolemic patients, but the variability in total body clearance effect was considerable *(109)*. What determined the variability—age, gender, genetics, dose—remains unclear. It should be kept in mind that these human studies did not evaluate confounding factors such as ascorbic acid levels, genotypic differences in CYP isoenzymes, or other medications.

Based on this discussion, it can be appreciated that vitamin C can potentially influence the disposition or action of medications in clinical use. Although these involve ascorbic acid's role in metabolism, the vitamin may also potentially influence drug absorption, distribution, and excretion. The interactions are not necessarily detrimental in all cases. Conversely, drugs can influence ascorbic acid status as evaluated predominantly by static tests (e.g., total body pool, tissue or fluid concentrations) rather than functional tests (e.g., enzyme activity).

4.2. Influence of Vitamin C on Drug Disposition

By way of example, patients are known to ingest large doses of vitamins in attempts to prevent adverse effects from chemotherapeutic agents. In vitro data suggest that vitamin C at different concentrations may alter cytotoxicity of doxorubicin in several cell lines *(116)*. Evaluation of human lymphocytes indicate that ascorbic acid may reduce the number of chromosomal aberrations caused by cisplatin *(117)*. Ascorbic acid at a low concentration (0.1 mmol/L) induces oxidative stress in platelets similar to the effect of cisplatin, however, at higher concentrations (3 mmol/L), vitamin C had a protective effect on cisplatin-induced oxidative stress *(118)*. However, in vivo data from animal models suggest that high-dose ascorbic acid does not improve and may worsen cisplatin-induced nephrotoxicity and genotoxicity *(119)*.

Beyond chemotherapeutic agents, ascorbic acid may alter disposition or adverse effects of other drugs. Modulation by vitamin C of a tobacco-specific nitrosamino to a less active metabolite could reduce the toxin's carcinogenic potential *(120)*. Repeated doses of ascorbic acid may reduce the impact of hepatotoxins like carbon tetrachloride *(121)*. Ascorbic acid may limit the potential for digoxin to induce lipid peroxidation, a means of mediating drug toxicity *(122)*. Lipid peroxidation induced by ceftizoxime was reduced by ascorbic acid *(123)*. Ascorbic acid has been used in the treatment of nucleoside reverse transcriptase inhibitor-related mitochondrial toxicity *(88)*. Consider how much of the variability in adverse effects attributed to a medication may have a direct or indirect nutritional explanation.

In vitro findings cannot necessarily be extrapolated to in vivo or clinical situations. Ascorbyl palmitate reversibly inhibits CYP3A4 in vitro, exhibiting strong competitive inhibition of nifedipine oxidation, but this is not supported by in vivo data during a single-dose study *(124)*. Ascorbic acid is noted to increase the absorption and overall bioavailability of co-trimoxazole, not otherwise predicted by in vitro study *(125)*.

The bioavailability of an oral contraceptive containing ethinyl estradiol and levonorgestrel was not enhanced when 1 g ascorbic acid was taken 30 min prior in a group of young women, despite the idea that competition for sulfation would allow for that to occur *(126)*. However, 1 g ascorbic acid daily has been reported to cause heavy break-through bleeding during several cycles in a patient taking ethinyl estradiol/levonorgestrel, that resolved when vitamin C was not used during a subsequent cycle, suggesting increased drug clearance *(127)*.

Although high-dose "pretreatment" (1 g timed-release ascorbic acid, five times daily for 2 wk) did not influence circulating lactate-pyruvate ratios or impaired intellectual function following acute oral administration of ethanol (0.95 g/kg), it did increase serum triglycerides and enhance ethanol clearance in the otherwise healthy volunteers *(128)*. There was significant variability in the degree of enhanced clearance (1–74% increase),

whereas several subjects had slight decreases or no change at all in ethanol clearance. This tended to support a previous finding of ascorbic acid-dependent ethanol oxidation via catalase. The greatest increase in clearance occurred in those with the slowest clearance during the placebo phase. The highest increase in clearance following ascorbic acid pretreatment occurred in an Asian subject, leading to the suggestion of phenotypic confounding as well (as Asians are more likely to possess atypical forms of alcohol and acetaldehyde dehydrogenase). Pharmacological doses of ascorbic acid are also reported to reduce acute alcohol-induced hepatotoxicity *(129)*.

In terms of inducing metabolism of misonidazole, a radiosensitizing agent used with radiation therapy, 2 g ascorbic acid daily for 2 wk in healthy humans did not compare to 1 wk of treatment with phenytoin or phenobarbital *(130)*. Although phenytoin and phenobarbital each induced misonidazole metabolism, thereby increasing total body clearance and reducing area under the curve, ascorbic acid did not.

Although 1 g of vitamin C may not be problematic, higher doses of ascorbic acid may interfere with the activity of warfarin when taken together *(131–133)*.

4.3. Influence of Drugs on Vitamin C Status

It appears from an animal model that aspirin may influence ascorbic acid distribution by inhibiting its uptake into leukocytes and hence result in an increased urinary excretion of ascorbic acid *(134)*. This is an example of a medication worsening the status of a nutrient. Both aspirin and ethanol may reduce tissue ascorbic acid saturation *(135)*. Although speculative, the reduction in tissue saturation may occur in part by a change in the function of ascorbic acid transporters or the expression of transporter genes. Oral contraceptive users appear to have a more rapid turnover of ascorbic acid *(136,137)*. Cigarette use can worsen ascorbic acid status. Although it is known that tobacco smokers have a higher metabolic turnover of vitamin C *(138)*, the environmental exposure to tobacco smoke may also reduce ascorbic acid concentrations in nonsmokers, including children, even after adjusting for dietary intake *(139,140)*.

Additional human studies of DNIs involving ascorbic acid need to be undertaken, while controlling for genetics, nutritional status, and other factors, in order to develop a better handle on the clinical significance of identified interactions and to design appropriate recommendations.

5. APPLICATION TO PRACTICE

5.1. Patient Care

Minimizing adverse outcomes and maximizing benefits of medicines includes reducing the prevalence of DNIs. Although once limited predominantly to dietitians, it has become the purview of other clinicians as well (e.g., pharmacists, nurses, and physicians). In order to be competent in preventing or managing clinically significant DNIs, it is necessary for clinicians to be able to recognize and identify them first. This comes as part of a thorough assessment of a patient's presenting history and physical examination. Examining patients with a chronic disorder often turns up interesting dietary habits as well as patterns of medication use. Clinicians should not be content just knowing that antidepressants may cause weight gain, diuretics may cause hypomagnesemia, or that

poor anticoagulation with warfarin could result from changes in dietary vitamin K. Questions need to be posed by curious clinicians to identify the less well-known or as yet unknown DNIs.

Nutritional status of patients needs to be routinely evaluated, and if malnutrition is identified, one of the questions that needs to be asked is whether it is drug-induced. Similarly, if an alteration in the status of a specific nutrient or group of nutrients is suspected, one should question the contribution of the patient's drug regimen. If the therapeutic effect of a drug is other than expected, whether subtherapeutic or toxic, the question needs to be asked whether the effect is nutritional status-, diet-, food-, or nutrient-induced.

One-on-one counseling with patients about DNIs needs to be focused and include supporting patient education materials. Counseling materials and programs have been developed *(141)*. Patient-focused information on select DNIs is even made available by the Clinical Center at the National Institutes of Health, based on the work of a task force (www.cc.nih.gov/ccc/patient_education/drug_nutrient/). More than just a list of drugs and nutrients that interact, material can make targeted efforts at specific patient subgroups likely to be using many medications. The materials need to be available in all care settings and to all health care providers. Adverse consequences of DNIs—reduced efficacy, increased toxicity, altered nutritional status—do not discriminate by care setting. Clearly, the issue of patient counseling on DNIs should cover all patients in acute, chronic, or ambulatory care settings. Reporting of suspected cases of DNIs is still to be encouraged.

Up until about the 1980s, what we knew about DNI causes, effects, and preventive measures came mostly from observation, personal investigation, or reading the limited literature—often largely anecdotal. The emergence of computer technology has allowed for the creation of databases to explore these interactions. An early system of spreadsheets took into account the specific attributes of DNIs such as those causing lactose intolerance and flushing reactions *(42)*.

How can one assure safe use of drugs with respect to nutritional status? Identification of risks is paramount to prevention or minimization of DNIs. Certainly, altered nutritional status, chronic drug use, and age serve as risk factors for DNIs. In the same way that every medication is expected to have adverse effects of one degree or another, it could be expected that there are potential effects on nutritional status unless proved otherwise. Patients may be at risk for drug-induced malnutrition (global or nutrient-specific) based on genetics, age, poor diet, malabsorption, organ dysfunction, or substance abuse.

Sources of answers include individual case reports, drug-surveillance reporting systems, and case-control and cohort studies. Some of these data are found in more convenient summary format.

5.2. Resources for Point of Care

Resources for information on DNIs are varied and continually evolving. Traditionally, information could be accessed through research of references including but not limited to textbooks, handbooks, journal articles (pharmacy, medicine, dietetics, nursing, and nutrition literature have all been useful resources), as well as Joint Commission on Accreditation of Health Care Organizations (JCAHO) manuals and publications. Assembling information in this manner and adapting it for use in various settings could be time-consuming. Along with these types of references, more commonplace are examples of

nutrition and DNI screening programs incorporated into the hospital or health system computer package(s). These computer programs promise the advantages of providing more consistency while greatly streamlining the process of making the information more readily available to clinicians and ultimately, to patients.

Newer mechanisms for clinician-friendly, point-of-care resources include programs that can be accessed via the internet or CD-ROM, and downloaded or installed into personal digital assistants (PDAs), such as the PalmOS or Pocket PC-based devices. On PDAs, they are carried along for immediate use during the course of clinical activities. Two specific resources that offer various options in each of these categories are listed in Table 2. Reference tools such as these offer the advantage of being updated regularly, in some cases multiple times in the course of a calendar year, making it easier to remain current with new data. Other internet-based resources include the various search engines, Medline® resources, Micromedex®, listservs for clinical nutrition or hospital organizations, and web sites of related professional groups (JCAHO, American Society for Parenteral and Enteral Nutrition [ASPEN], American Dietetic Association, American Pharmacists Association, American Society of Health-System Pharmacists, American Nurses Association).

Finally, one should not underestimate the experience of colleagues and other institutions and organizations when attempting to develop and refine programs of this nature.

5.3. JCAHO

The JCAHO has defined the role of hospital clinicians in identifying and preventing DNIs. The JCAHO requires a level of sophistication in documenting and managing these DNIs in organized health care settings in the United States. Specifically, it is stipulated that "patients are educated about potential drug-food interactions, and provided counseling on nutrition and modified diets" *(142)*. Although it is mandated that patient education regarding potential DNIs shall take place, it is not specifically described how this is to be done within each organization. Rather, it is left up to the individual setting to assess the needs of its patient population and resources of staff in order to design an appropriate plan. Institutions vary greatly in the types of patients served, nature of drug and supportive therapy delivered, and staff available to conduct this type of patient education. It is not specifically delineated which health care providers are to be involved, although this responsibility may typically involve physicians, dietitians, pharmacists, and often, the primary nurse for the patient *(143)*. Surveyors may also differ in emphasis placed on evaluation of different programs. Information from various institutions that have recently prepared for and undergone JCAHO review may be accessed through internet search engines as well as via organizations such as ASPEN through their web site (www.nutritioncare.org) and listserv services available to members. The current JCAHO accreditation manual, their website (www.jcaho.org), and various other JCAHO publications may also be helpful *(144)*.

Several approaches have been employed in the development of DNI education programs in hospital and health care settings in response to JCAHO stipulations that such education for patients be implemented *(145,146)*. One example of such an approach includes targeting certain patient groups as being more likely predisposed to DNIs, such as newly diagnosed diabetics, transplant patients receiving high-dose corticosteroids, patients taking pancreatic enzymes, or other patient groups that may require specific

Table 2
Examples of Resources for Drug–Nutrient Interactions in Multiple Formats

Resource	Handbook	CD-ROM (Windows)	Palm/Pocket PC PDA (Software Programs)	On-line Format (Subscription)
FMI[a]	YES	YES	NO	NO
Lexi-Comp[b]	YES	YES	YES	YES

[a]Food-Medication Interactions, website: www.foodmedinteractions.com

[b]Lexi-Comp: a series of specialty medical and drug-related databases that include drug–nutrient information, website: www.lexi.com

and/or multiple pharmacotherapies, and so on. Another popular approach is to instead target certain "high-risk" drugs, examples of which may include warfarin, monoamine oxidase inhibitors, selected antibiotics, phenytoin, lithium, theophylline, digoxin, alendronate, cyclosporine, lansoprazole, isoniazid, drugs that may interact with grapefruit juice, drugs significantly affected by meals and feeding, and other combinations that may cause potentially dangerous interactions. Identification of target drugs within a health care setting may largely be based on two factors: degree of risk associated with use of certain drugs, and frequency of use within that facility or health care system. Additions to the formulary would typically be reviewed for propensity to induce clinically relevant DNIs. Specialty services may develop their own list of drugs that require counseling about potential food and drug interactions in their respective patients.

In most institutions, DNI education programs are, by nature, and in practice, interdisciplinary, and as such, a team effort. Examples of responsibilities of individual departments may be assigned as follows *(145,147–149)*:

1. The pharmacy may generate a daily list of patients receiving drugs targeted for DNI attention through the use of the hospital computer system and patient medication profiles. Cautionary labels or stickers may be utilized to draw attention to such drugs in the patient's chart, drug bin, or in the automated dispensing systems (e.g., Pyxis machine). Protocols for standardized medication administration times with relation to food may also be developed and implemented with the collaboration of nursing units. Pharmacy personnel may also be involved with instruction of patients using written materials as necessary with appropriate documentation in the patient's medical record.

2. Nutrition and food services can use the list generated by the pharmacy to make modifications in diet choices and snacks in order to avoid certain DNIs. Dietitians may document changes, identify food restrictions for individual patients, and also provide patient counseling.

3. Nursing activities related to addressing DNIs in hospitalized patients often include maintaining readily available resources for patient instruction and information, checking for alerts or warnings related to drug therapy and possible interactions with foods, and assuring that appropriate standardized protocols for administration and timing of medications in relation to food and meals or nutrition support regimens are employed.

4. Outpatient care providers in various settings may also be involved in providing information and instruction to patients receiving prescriptions or therapy involving target drugs.

Experience has shown that JCAHO historically places significant emphasis on determining the existence of the DNI patient education program in a form appropriate to the setting, and that such activities are documented in the patient care record by the health care providers involved. This information must be made available for inspection on request. Although these points continue to be significant in audits, it is important to recognize that the specific focus during the survey is continually evolving, and subject to the discretion of the specific team of surveyors. The intent of surveyors in reviewing DNI practices within an institution is to ascertain that predetermined standards have been developed, a program for addressing DNIs is in place, and that resultant activities to meet those standards are employed, documented, re-evaluated on a regular basis, and improvements incorporated as indicated. In summary, the JCAHO wants to know how and why the institution or health system arrived at its existing policy regarding DNIs, how well the institution is meeting its defined objectives, and the current status of the overall plan *(150,151)*.

5.4. The Next Step?

Frankly, the number of professionals interested in this area with qualifications in both nutrition and pharmacotherapeutics has been limited, given so many other opportunities for these individuals. And given the potential scope of the problem, it could be viewed from a public health perspective that more should be done. Identifying cases in practice is even difficult when one considers that there is no one person looking specifically at nutritional aspects of drug use or vice versa. Dietitians may take very good diet histories, whereas pharmacists may do the same with drug usage, taking into account prescription, OTC, and supplement intake. However, whether a particular clinical manifestation as observed by the physician is integrated with the diet or drug history to conclude the possibility of a DNI seems infrequent. This may account for the poor documentation of DNIs in practice and the limited research in the area. What about the vast majority of the medication-consuming public seen rarely if at all by a dietitian, infrequently by a physician, and for only limited visits with a pharmacist—many who are not attuned to the potential for DNIs? Yet, it is this ability to identify a potential DNI that is required to set off the signal for further study. A case report or case series may lead to a hypothesis that can be tested. Several things could be tried to move the topic forward.

An organized, technology-based system would likely perform better than observation or voluntary case reporting alone. Surveillance data (e.g., Boston Drug Surveillance, phase IV drug study, National Health and Nutrition Examination Survey) may be useful for generating hypotheses as well by identifying poor drug outcomes by nutritional association, or poor nutritional status with drug intake. This may be more economically acceptable than performing DNI screening as part of the premarket drug safety process. But to make this work requires clinicians who recognize the potential for DNIs and who evaluate that potential with each contact with a patient. A scoring system to determine the probability that an adverse outcome is related to a DNI could be developed based in part on the Naranjo criteria for estimating the probability of an adverse drug reaction *(152)*. Quantitative systems that examine GI physiology as it affects drug bioavailability could be used to predict potential for DNIs *(153)*. Predicting interactions based on small intestine metabolic activity may become useful once genetic and gender variability is taken into account. Correspondence analysis could also be used to identify agents or

patients at risk for significant DNIs *(154)*. Pharmacogenomics technology could also be potentially useful in predicting susceptibility to DNIs *(155)*. Much work needs to be done with our colleagues in biomedical informatics as it pertains to pharmacogenomics *(156)*. In the wake of the human genome project, a systematic understanding of the genes that modulate drug response and more so the potential interplay of nutrients or nutritional status on the phenotypes (enzymes, receptors, postreceptor signaling) and ultimately on drug response (therapeutic or toxic) is important.

6. CONCLUSION

The impact of drugs on nutritional status or the effect of nutrition on drugs is rarely predicted from animal studies, and is not routinely assessed during the drug-approval process. Ideally, every new drug should be evaluated for potential DNIs prior to marketing. But given the poor likelihood of that occurring, clinicians should operate on the assumption that any variability in drug response is the result of an interaction with nutritional status, diet, food, or a nutrient unless proven otherwise. Variability from genetic, gender, and age factors would also need to be taken into account. Similarly, any change in nutritional status should be evaluated for drug-related causes.

It would be difficult to study high-risk populations such as the elderly and those with chronic conditions because of issues of consent or the time lapse involved in appreciating nutritional deficiencies. A further constraint is the limited funding available for nutrition-related research, particularly in this subject matter.

Having an approach to DNIs may improve classification of old interactions and development of an organized search for new ones, their mechanisms, and management options to address them. However, what still remains critical is the clinician's ability to recognize poor outcome of drug therapy and search for potential causes including nutrition-related factors. Just as important is the clinician's ability to recognize alterations in nutritional status, even single nutrient abnormalities, and seek drug-induced causes.

DNIs will obviously depend on the drug and the nutrient, but will also depend on the matrix of each, the model in which it is studied, the presence of disease or organ dysfunction, status of other nutrients, genetic polymorphism, and the like. Given all of this, clinically useful data concerning all the potential DNIs have hardly yet been explored. Additionally, research efforts to help refine existing recommendations are sorely needed.

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2 Drug Disposition and Response

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1. INTRODUCTION

The basis for this book is that a drug–nutrient interaction (DNI) is the result of a physical, chemical, physiologic, or pathophysiologic relationship between a drug and nutrient(s)/food that is considered significant if the therapeutic response is altered adversely or if the nutritional status is compromised. This chapter presents an overview of drug disposition and drug action that forms the basis for understanding such adverse interactions.

Pharmacokinetics is the term used to describe drug disposition, that is the absorption, distribution, metabolism, and excretion of the drug. *Pharmacodynamics* is the term used to describe drug action (i.e., its mechanism and effects).

2. PHARMACOKINETICS

Pharmacokinetics is important for understanding or predicting the magnitude or duration of an effect of a drug or nutrient. A substance can produce an effect only if it can reach its target(s) in adequate concentration. Several factors can affect the absorption and distribution of drugs and nutrients.

2.1. Absorption

The route by which a substance is introduced into the body affects its pharmacokinetics *(1,2)*. Hence, a review of the major characteristics of the more common routes of administration is warranted.

2.1.1. SYSTEMIC ROUTES

Systemic routes of administration are those that deliver the substance with the intent of producing a systemic (on the system) effect, rather than a local effect on, for example, the skin. A subdivision of systemic route of administration is parenteral, which refers to systemic routes other than oral, sublingual, buccal, or rectal, which are termed alimentary routes. Oral administration is generally the simplest, most convenient, safest (because of slower onset of drug effect and ability to reverse a mistake), and often most economical route of administration. Most drugs are well absorbed from the gastrointestinal (GI) tract. The rate and extent of absorption is a function of the physiochemical properties of the drug substance (e.g., hydrophilic, lipophilic), its formulation (e.g., tablet, capsule, liquid,

slow-release reservoir, or matrix), excipients, physiological environment (e.g., stomach pH), and any metabolism in the gut wall. Alteration of any of these features that occurs, for example, as a result of change in diet, lifestyle, age, or health status, can affect absorption. Nutrients and foodstuffs can affect absorption by direct binding or by altering the physiologic environment (e.g., pH of the stomach contents). The simple act of food ingestion, or even its anticipation, can release digestive enzymes that inactivate certain drugs, such as penicillins. The intravenous route of administration delivers drug substance directly into the bloodstream. With the exception of the portal circulation (see later), the drug is then delivered to the heart and from there to the general circulation. The intravenous route bypasses problems of absorption from the GI tract, allows for rapid adjustment of dose to effect, can be used even if the patient is unconscious, and avoids the "first-pass effect" (see later). Intra-arterial drug administration, although much less common clinically than intravenous administration, is advantageous when infusion of a high concentration into a specific target is desired, such as chemotherapeutic agents for treatment of certain cancers and vasodilators for the treatment of Raynaud's syndrome (a condition characterized by excessive vasoconstriction, particularly affecting the digits). Subcutaneous administration involves delivery of the drug into the tissue beneath the skin for subsequent entry into the vasculature. Absorption following subcutaneous administration is generally rapid, depending on the perfusion of a particular site, and the rate of absorption can be accelerated (e.g., by heating or vasodilators) or decelerated (e.g., by cooling, vasoconstrictors, or slow-release formulations). Intramuscular administration is generally rapid because of high vascularity and provides an opportunity for sustained-release formulations such as oil suspensions. Inhalation provides one of the most rapid routes of drug administration due to the large surface area and high vascularity of the lung. Other systemic routes include intraperitoneal, which is particularly useful for the administration of drugs to small animals because it provides a rapid, convenient, and reproducible technique due to the warm, moist environment and extensive vascularity of the peritoneum and the transdermal route, because of its convenience and control for extended drug delivery.

Systemic routes of administration provide an opportunity for drug and nutrient/food interactions at several levels, including: the rate at which drug substance or nutrient is available for absorption (e.g., dissolution rate, degree of ionization, adsorption, etc.); the extent of plasma protein binding; and the rate or route of metabolism.

2.1.2. Topical Routes

Topical routes of administration—such as direct application to the skin or mucous membranes—for the purpose of local action are not generally sites of interaction between drugs and nutrients/food. A possible exception is the reduction of ultraviolet light exposure by sunscreen lotions, thereby decreasing activation of vitamin D. However, if the skin is damaged (such as in serious abrasions and burns) or if transmucosal passage is significant, the drug does not remain localized to the site of application and administration is akin to systemic administration with the attendant opportunity for interaction.

2.1.3. Other Routes

Direct application of drugs for localized effects to the eye (opthalmic administration), ear (otic administration), nerves (intraneural administration), spinal cord (e.g., epidural or intrathecal administration), or brain (e.g., intracerebroventricular administration) do

not often lead to significant nutrient/food interactions, but any substance that alters the drug's access to specialized compartments (e.g., through the blood–brain barrier [BBB]) will alter the magnitude or duration of the drug effect.

2.1.4. Factors That Affect Absorption

The rate and extent of absorption is influenced by many factors related both to the characteristics of the drug or nutrient substance and the particular characteristics of the recipient at the time of administration *(3)*. For example, the product formulation generally determines the rate of dissolution under specific physiological conditions, but these conditions depend on the person's state of health and other factors, such as diet. The solubility of the administered substance, its dosage, and route of administration also affect absorption.

The absorption (and elimination) of substances generally follows either zero-order kinetics, that is, a constant amount is absorbed (or eliminated) per unit time (Fig. 1A) or first-order kinetics that is, a constant fraction is absorbed (or eliminated) per unit time (Fig. 1B). Most of the currently used drugs follow first-order kinetics.

2.2. Distribution

Whether a drug or nutrient is administered directly into the bloodstream, such as intravenously, or indirectly via another route of administration, once in the bloodstream it is subject to binding to plasma proteins, the extent of binding is dependent on the physiochemical properties of the drug. Additionally, the drug or nutrient usually must pass some biological barrier in order to reach its ultimate site of action. Because plasma-protein binding is reversible and competitive, and there is a finite capacity for binding, plasma-protein binding offers a potential site of drug and nutrient/food interaction.

2.2.1. Plasma-Protein Binding

Due to their physicochemical characteristics, drug molecules (D) can form weak, reversible physical and chemical bonds with proteins (P) such as albumin in plasma according to D + P ⇔ DP *(4)*. These drug–protein complexes (DP) have nothing to do with the drug's ultimate effect, but in some instances, can significantly influence the magnitude or duration of the drug's effect. This is because that protein-bound drug is generally inactive at its site of action and, because of size exclusion, is less likely to transverse the glomerulus into the kidney nephron and be excreted. Each drug binds to plasma proteins to a different extent. Drugs that bind avidly with plasma proteins are susceptible to interaction with other drugs and nutrients that bind to the same sites on plasma proteins. This is because plasma-protein binding is saturable (i.e., there is a finite number of such sites) and competition occurs among all substances that have affinity for such sites. The transfer from the "bound" to the "free" state can result in a significant change in effect magnitude or duration.

2.2.2. First-Pass Effect

The venous drainage system of the stomach and intestines differs from that of most other organs in a way that has implications for drug effects. The venous drainage of most organs goes directly to the heart, but venous drainage of the GI tract sends blood into the portal circulation, which delivers blood to the liver (hepatic venous drainage then goes to the heart). This is of clinical import because the liver is a site of active biotransforma-
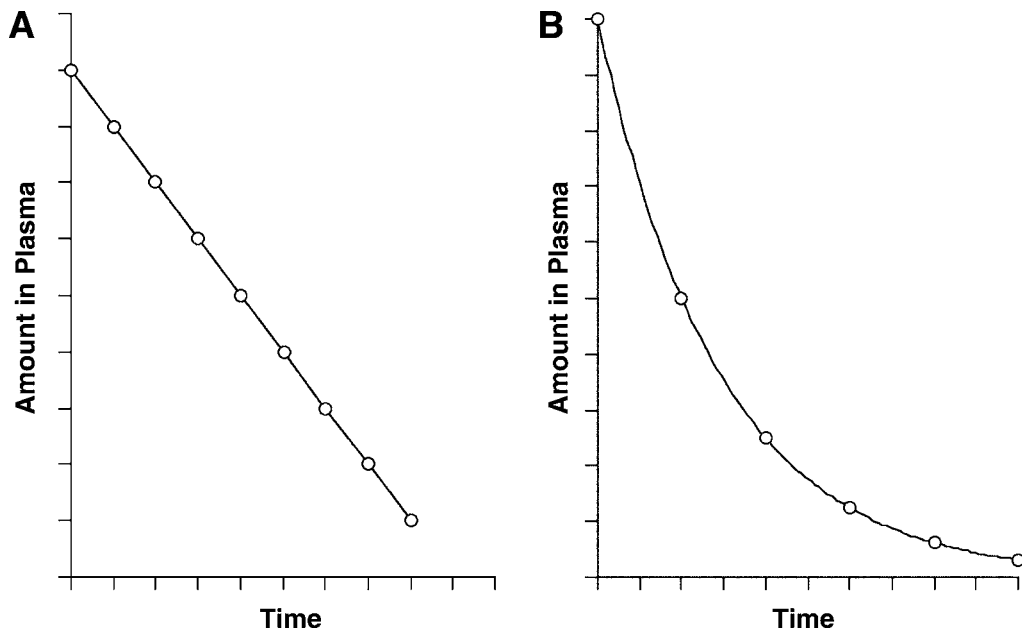
Fig. 1. (**A**) An example of zero-order relationship. (**B**) An example of first-order relationship.

tion (discussed later) and potential for drug interaction. Biotransformation (drug metabolism) in the liver can be extensive, accounting for more than 99% reduction of the parent drug substance for some commonly used drugs. In some cases, this biotransformation results in conversion of an inactive parent substance (prodrug) to its active metabolites. More often, the metabolites are less active than the parent substance. Once through the liver, the drug and metabolites follow the venous drainage to the heart and into the systemic circulation. All subsequent pharmacokinetics is the same as for any other systemically administered substance. Hence, the portal circulation introduces a special influence on drug distribution during the first pass into the circulation *(5)*. Drugs administered intravenously are not subjected to first-pass effect. Oral administration has the highest first-pass effect.

The extent of first-pass metabolism is an important consideration in drug design, formulation, and dosage regimen. For drugs that undergo high first-pass metabolism, small changes in the rate or extent of biotransformation can result in large changes in systemic blood levels. Changes in biotransformation can result from changes in liver function or from the effect of other drugs, nutrients, or food components on hepatic drug metabolizing enzymes.

2.2.3. BLOOD–BRAIN BARRIER

Many drugs, because of their physicochemical properties, have only limited ability to enter the brain. In general, the BBB restricts passage of macromolecules and substances that are either too hydrophilic (water soluble) or too lipophilic (fat soluble). Nutrients and other necessary substances can be actively transported across the BBB *(6)*. The morphologic basis for the BBB includes tight junctions between the epithelial cells lining the brain capillaries and transport mechanisms that pump substances out of the brain.

The permeability of the BBB depends on such factors as age, disease, and other influences, including nutritional state. Plasma-protein binding is also a factor, because drugs highly bound to plasma proteins are less able to traverse the BBB. Hence, drug interaction at the level of plasma-protein binding can affect BBB passage.

2.2.4. BIOLOGICAL MEMBRANES

Biological membranes are matrices containing phospholipid bilayers, cholesterol, proteins, and other constituents. Drugs can be transported around or through these membranes, depending on the composition of the particular membrane. Some mechanisms of drug transport are as follow *(7)*:

Passive diffusion. If a drug is sufficiently lipid soluble, it can diffuse down its concentration gradient (energy is not required, hence the diffusion is passive). For weak acids ($HA \Leftrightarrow H^+ + A^-$) and weak bases ($BH^+ \Leftrightarrow H^+ + B$), it is the un-ionized form (HA and B) that is more lipid soluble. Simple diffusion occurs according to Fick's law:

$$\frac{dQ}{dt} = -DA\frac{dC}{dx} \, ,$$

where the flux of drug across a membrane is dependent on a diffusion constant (*D*), the surface area (*A*), and the drug concentration (*C*). This type of diffusion favors molecules in the uncharged form, and hence is a function of the pH of the environment at the membrane and the pK_a of the drug according to relationships termed the Henderson-Hasselbach equations:

$$pK_a = pH + \log\left(\frac{HA}{A^-}\right)$$

for weak acids and

$$pK_a = pH + \log\left(\frac{BH^+}{B}\right)$$

for weak bases. As a consequence, absorption of weak acids (e.g., aspirin) is favored over weak bases in the low pH of the stomach. However, the total amount of absorption is usually greater in the intestines due to the greater surface area. Conversely, an absorption of weak bases is favored in the small intestine (higher pH), and the acidic environment of the kidney nephrons favors (in a pH-dependent manner) excretion of weak bases.

Filtration. Some vascular bed capillaries have pores or channels that allow the passage of low molecular weight substances, whether they are polar or nonpolar. Such capillaries serve as molecular sieves (filters) that exclude molecules larger than a certain size.

Carrier-mediated (facilitated) diffusion. Transport of some substances across membranes, although by diffusion down a concentration gradient, is facilitated by membrane-associated molecules (carriers). This type of diffusion does not require energy and is generally selective for molecules having specific structures or other recognized property. If the concentration of drug or nutrient exceeds the number of carriers, the process becomes saturated and further increase in drug or nutrient concentration will not increase the rate of their passage across the membrane.

Active transport. Some molecules are transported across biological membranes against their concentration gradient. Transport in this direction—up a concentration gradient—is not favored thermodynamically and, hence, does not occur spontaneously. It requires input of energy, which is commonly supplied by coupled biochemical reactions that, for example convert adenosine 5'-triphosphate (ATP) to adenosine 3',5'-cyclic monophosphate (catalyzed by Na^+/K^+-ATPase). Active transport is similar to carrier-mediated (facilitated) diffusion (discussed above) in that transport is mediated by a membrane-associated macromolecule (pump), it is saturable, and it is usually selective for certain drugs/nutrients (based on size, shape, or other characteristic). It differs in its requirement for energy and the ability to pump against a concentration gradient.

Endocytosis. Some drugs or nutrients can be transported across biological membranes by becoming entrapped (in "pits") and internalized (in "vesicles") in varying degrees of selectivity. Sucrose and insulin can be internalized in such a manner.

2.2.5. BIOAVAILABILITY

Because of the multiple barriers to absorption, the amount of drug that enters the systemic circulation is less than the amount administered (with the exception of intravenous administration). The proportion (fraction or percent) of an administered drug dose that reaches the systemic circulation is the drug's bioavailability. Other factors that affect a drug's bioavailability include the first-pass effect, solubility and stability, and the formulation of the drug (including the quality control of its manufacture). Additionally, a person's dietary patterns, nutritional status, and state of health can affect a drug's bioavailability.

2.2.6. FACTORS THAT AFFECT DISTRIBUTION

Multiple factors affect the distribution of substances in the body. Some are related to the substance itself, such as its physical characteristics (e.g., size, solubility) and its chemical characteristics (e.g., ability to form bonds with plasma proteins or other biochemical substances). Other factors are related to the state of the physiological system, such as concentration of plasma proteins, lipid content of barrier or target tissues, cardiac output, capillary permeability in target or other tissues, and many others. Many of these factors are a function of age, disease, or other influence.

2.3. Metabolism

Drug/nutrient substances are often biotransformed (metabolized) to other substances (metabolites) by a variety of biochemical reactions in a variety of locations throughout the body *(8)*. Almost all tissues can metabolize drugs, but the liver, GI tract, and lungs (for gaseous anesthetics) are the major sites of drug metabolism of most drugs in humans. The liver plays a predominant role in drug metabolism for two reasons: first, because of its strategic location relative to the portal circulation, and second, because it contains high levels of biochemical reactions that are capable of metabolizing foreign substances. In general, but not always, metabolites are less active and more water soluble (which favors excretion in the urine) than the parent substance. In some instances, active metabolites are formed from inactive parent drugs, in which case the parent is termed a prodrug. The most common chemical reactions that metabolize drugs or nutrients can conveniently

be categorized into two broad types: reactions that alter the basic chemical structure of the parent molecule—phase 1 reactions—and reactions that result in attachment of some endogenous substance to the parent molecule—phase 2 or conjugation reactions.

2.3.1. PHASE 1 REACTIONS

Phase 1 type reactions often occur in the cytosol, mitochondria, and microsomes (subcellular component containing membrane-associated enzymes on the smooth endoplasmic reticulum) of cells of the liver and other organs.

2.3.1.1. Oxidation. Oxidation (e.g., the addition of oxygen or removal of hydrogen from the parent molecule) is a common Phase 1 reaction. Microsomal oxidation is a major mechanism of metabolism of many drugs and nutrients because the substances typically have chemical structures that make them susceptible to oxidation reactions. There is an extensive system (family) of enzymes that are capable of catalyzing oxidation reactions. Primary components of this extensive system are cytochrome P450 (CYP) reductase and the many isozymes of CYP. Examples of microsomal oxidation reactions are *C*-oxidation or *C*-hydroxylation of aliphatic or aromatic groups, *N*- or *O*-dealkylation, *N*-oxidation or *N*-hydroxylation, sulfoxide formation, deamination, and desulfuration. Examples of nonmicrosomal enzymes having important roles in the metabolism of endogenous and exogenous substances include: alcohol- and aldehyde-dehydrogenase; xanthine oxidase; tyrosine hydroxylase; and monoamine oxidase.

The family of CYP enzymes is particularly important in studying metabolism because of the many drugs and nutrients that are metabolized by these enzymes and, in addition, the potential for drug/nutrient interactions *(9)*. For example, it is estimated that more than 90% of presently used drugs are metabolized by one or more of the CYP enzymes. Of the most commonly used drugs, about 50% are metabolized by the CYP3A subfamily; about 25% by the CYP2D6 isozyme; about 15% by the CYP2C9 isozyme; and about 5% by the CYP-1A2 isozyme. Because the enzymes are saturable, and can be induced or inhibited, the potential for DNIs exist.

2.3.1.2. Reduction. Reduction reactions (e.g., the addition of hydrogen or removal of oxygen from the parent molecule) occur both in microsomal and nonmicrosomal fractions of hepatic and other cells. Metabolism by reduction is less common than by oxidation for presently used drugs. Examples of such reactions include nitro-, azo-, aldehyde-ketone-, and quinone reduction.

2.3.1.3. Hydrolysis. Hydrolysis-type reactions can occur in multiple locations throughout the body, including the plasma. Examples of some nonmicrosomal hydrolases include esterases, peptidases, and amidases.

2.3.2. PHASE 2 (CONJUGATION) REACTIONS

The coupling (conjugation) of an endogenous substance to a drug or nutrient molecule typically alters its three-dimensional shape sufficiently to result in a decrease in biological activity. Conjugation also typically results in an increase in water solubility of the drug or nutrient, which decreases the amount that is reabsorbed through kidney tubules, thereby enhancing the fraction that is excreted in the urine. Conjugation with glucose (glucuronidation) is the most common conjugation reaction in humans. Other phase 2 reactions include glycine-, glutamate-, or glutathione-conjugation; *N*-acetylation (acetyl

coenzyme A as acetyl donor); *O*-, *S*-, or *N*-methylation (*S*-adenosylmethionine as methyl donor); and sulfate or sulfanilate formation (3'-phosphoadenosine 5'-phosphosulfate as the sulfate donor).

2.3.3. SEQUENCE OF METABOLISM

It is common for a drug or nutrient to be metabolized through several biotransformation reactions, resulting in the production and the elimination of several or many metabolites, each having its own pharmacokinetic and pharmacodynamic characteristics. It is also common for a substance to undergo a phase 2 type reaction following a phase 1 type reaction, but this sequence is not a requirement. It is possible for a phase 2 reaction to precede a phase 1 reaction.

2.3.4. INDUCTION OR INHIBITION

Many of the enzymes involved in the biotransformation of drugs and nutrients can be induced (increased in number or activity) or inhibited by a variety of chemical substances, including themselves and other drugs or nutrients *(10)*. Induction results in an enhanced metabolism of molecules that are biotransformed by affected pathways and results in a decrease in the levels of parent molecule and increase in levels of metabolites. Biological effect will be decreased if parent is more active than metabolites and increased if parent is a prodrug. The opposite occurs with enzyme inhibition.

2.3.5. FACTORS THAT AFFECT METABOLISM

Multiple factors can affect metabolism *(11)*, including genetics, typically manifested as polymorphisms; the chemical properties of the drug or nutrient, which determines the susceptibility to the various types of metabolic reactions; the route of administration, which affects the extent of the first-pass effect; dose, which can exceed the capacity of substrates for conjugation reactions; diet, which can also affect the capacity of substrates for conjugation reactions; age and disease, which can affect hepatic function; and still others.

2.4. Elimination

The biological effects of exogenous substances are terminated by the combined processes of redistribution, metabolism, and elimination *(12)*. The major site of drug elimination in humans is the kidney. Several factors affect the rate and extent of elimination, and accumulation occurs if the rate of absorption and distribution of a drug or nutrient exceeds the rate of elimination.

2.4.1. ROUTES OF ELIMINATION

In humans, the kidney is the most common route for elimination of many drugs, partly because the kidney receives about 20–25% of the cardiac output. Other sites include the lungs (particularly for the gaseous anesthetics), and through the feces, and (usually to a lesser, but no less important, extent) sweat, saliva, blood loss, vomit, breast milk, and so on.

Size exclusion prevents plasma proteins—and drug molecules that are bound to them— from passing through the glomerulus of a healthy kidney. The fate of molecules that pass into the nephron depends on its physicochemical properties. Lipophilic drugs (or the nonionized form of weak acids or bases) are more likely to be reabsorbed through the wall of the nephron back into the circulation. Hydrophilic drugs (or the ionized form of weak acids or bases) are more likely to be excreted in the urine. The pH dependence of ionization

is exploited clinically by adjusting the urine pH. Some substances are actively transported across the wall of the nephron either into or out of the lumen of the nephron. Such transport processes are generally saturable and are possible sites of DNIs.

2.4.2. RATE OF ELIMINATION

The rate of elimination of most drugs is described by first-order kinetics (i.e., exponential decay) according to $C_t = C_o e^{-kt}$ relating drug concentration (C_t) at time t to the original concentration (C_o). Other drugs are eliminated by zero-order (linear) kinetics. C_o is reduced by one-half in one *half-life* ($t_{1/2}$). In the case of zero-order elimination, equal amounts are eliminated each subsequent half-life. In the case of first-order elimination, equal fractions are eliminated in each subsequent half-life. In either case, the half-life is a function both of the drug and the conditions of the patient.

2.4.3. CLEARANCE

Rate of elimination (mass/time) is equal to the concentration of drug (mass/volume) times the clearance (volume/time). Clearance is the volume of a compartment (e.g., blood) per unit of time that is cleared of the drug due to elimination (e.g., metabolism and/ or excretion). The equation that relates renal plasma clearance (Cl), rate of excretion (R_e), drug concentration in plasma (C_p), and drug concentration in urine (C_u) is $ClC_p = C_uR_e$.

2.4.4. EFFECT OF MULTIPLE DOSING

When a drug or nutrient is administered according to a fixed-interval schedule, the rate of accumulation is predictable from the dose and half-life. For example, following the repeated intravenous dosing of a drug having first-order elimination kinetics, the mean drug concentration (C_m) can be estimated from the dose (D) and fraction of drug remaining (F) by $C_m = -D/\ln F$. The upper (C_{max}) and lower (C_{min}) bounds can be estimated by $D/(1 - F)$ and $FD/(1 - F)$, respectively. The actual clinical results depend on the patient's individual characteristics.

2.4.5. FACTORS THAT AFFECT ELIMINATION

In addition to the factors just cited, elimination can be accelerated by enzyme induction, increases in urine flow, or change in urine pH and can be slowed by renal impairment, change in pH, or other factors.

3. PHARMACODYNAMICS

The mechanism of a substance's action on biological tissue involves some modification of or interaction with ongoing physiological processes. In some cases, the target is foreign (e.g., bacteria or viruses) or aberrant (cancer cells). In other cases, the target is part of normal physiology (e.g., enzymes or receptors). Mechanisms of action that are shared or opposed by other drugs or nutrients can lead to interactions. Drug actions are quantified and evaluated by dose–response curves.

3.1. Mechanisms of Action

In the broadest sense, drug effects can be categorized into four major mechanisms *(13)*. They can kill invading organisms (e.g., most antibiotics or antivirals), they can kill aberrant cells (e.g., many cancer chemotherapies), they can neutralize acids (antacids), and they can modify physiological processes.

3.1.1. ANTIBIOTICS/ANTIVIRALS

Antibiotics and antivirals target biochemical processes of the invading organisms. For example, penicillins, cephalosporins, carbapenems, and monobactams, which have chemical structures that contain a β-lactam ring, disrupt cell walls or inhibit their synthesis. Sulfonamides and trimethoprim act on enzymatic pathways, resulting in the inhibition of folic acid synthesis. Aminoglycosides, tetracyclines, chloramphenicol, and erythromycin interfere with mechanisms involved in the synthesis of proteins. Quinolones inhibit bacterial DNA gyrase. Most antivirals work by inhibiting viral replication. In all cases, the clinical utility is significantly increased when the drug exhibits selectivity for biochemical processes of the target that are not shared by humans.

3.1.2. CANCER CHEMOTHERAPY

Much of current cancer chemotherapy (antineoplastic agents) involves the use of substances that are cytotoxic. In general, current antineoplastic drugs can be divided into four major classes: alkylating agents, antimetabolites, alkaloids, and antibiotics. Alkylating agents bind covalently to DNA, thereby impeding replication and transcription, leading to cell death. Antimetabolite drugs compete with critical precursors of RNA and DNA synthesis, thereby inhibiting cell proliferation. Alkaloids inhibit microtubular formation and topoisomerase function, thereby blocking cell division and DNA replication. Certain antibiotics inhibit RNA and DNA synthesis.

3.1.3. ANTACIDS

Excess gastric acidity is reduced by treatment with antacids, which are weak bases that convert gastric (hydrochloric) acid to water and a salt. Most antacids in current use contain aluminum hydroxide, magnesium hydroxide, sodium bicarbonate, or a calcium salt.

3.1.4 MODULATION

The mechanisms of action just discussed do not involve overt efforts to communicate with the normal ongoing physiological processes of the host. The chemical nature of cellular function and the communication within and between cells allows for modulation by endogenous chemical substances, drugs or nutrients. The targets of modulation include enzymes, DNA, and a variety of other molecules involved in the synthesis, storage, or metabolism of endogenous substances. Efforts to modulate processes that involve nervous system control directly or indirectly involve interaction with receptors.

3.2. Receptors

Many drugs interact with macromolecular components of cells that then initiate a chain of events which leads to the drug's effect. In a commonly used analogy, the receptor is like a light switch. A better analogy is that a receptor is like a dimmer switch because there is generally tonic activation. A receptor also serves to limit access to the switch to specific molecules (lock and key fit).

3.2.1. OCCUPATION THEORY

The most widely supported theory holds that receptors are activated when specific molecules bind (form weak intermolecular chemical bonds) to them and that the magnitude of such a drug's effect is related to the number (or the fraction of the total) receptors

that are occupied *(14)*. The formation of drug–receptor complexes is usually reversible, such that the reaction between drug molecule (*D*) and receptor molecule (*R*) is an equilibrium reaction that can be described and characterized—as any other equilibrium reaction—according to D + R ⇔ DR. The driving force for the reaction to proceed in the direction of drug–receptor complex depends on the Gibb's free energy difference (ΔG) according to $\Delta G = -RT \ln K_{eq}$, where *R* is the gas constant, *T* is temperature (Kelvin) and K_{eq} is the equilibrium constant *(15)*.

3.2.2. AGONISTS AND ANTAGONISTS

The vast majority of chemical substances cannot just fit a binding site on any receptor. Chemicals that bind to receptors are said to do so with a certain affinity, the magnitude of which is given by the reciprocal of the equilibrium constant, $1/K_{eq}$ (often designated as K_d). Only a subset of substances that bind to receptors are also capable of eliciting an effect through the receptor (i.e., have intrinsic activity or efficacy). Substances that have affinity and intrinsic activity are termed *agonists*, substances that have affinity, but not intrinsic activity are termed *antagonists*. Antagonists competitively or noncompetitively inhibit the access of agonists to their receptors. In the body, receptors mediate the effects of endogenous agonists such as neurotransmitters, hormones, peptides, and so on. Therefore, antagonist drugs—although lacking intrinsic activity—can produce biological effects by attenuating the signal of the endogenous agonist.

3.2.3. SIGNAL FIDELITY

One of the major functions of receptors is to provide the fidelity of the communication between neurons or other cells. The lock and key fit restricts access to molecules of specific three-dimensional shape. The fit is sufficiently flexible, however, that certain molecules (drugs) having three-dimensional shapes similar to the endogenous ligand can bind to their receptors (with greater or lesser affinity and intrinsic activity). In such cases, the fidelity of the normal signal is maintained by the chain of events that occurs post-receptor occupation (i.e., the signal transduction).

3.2.4. UP- AND DOWN-REGULATION

The number of receptors expressed at any given time is the difference between the number synthesized and the number destroyed or internalized and, thus, is a function of the age, health, and other characteristics of the individual. Additionally, repeated exposure to an agonist or antagonist can alter the number of expressed receptors. The change in receptor number is often interpreted as the body's attempt to counteract the action of the agonist or antagonist in an effort to reestablish homeostasis. More permanent change in receptor number can result from drug effects at the level of the gene.

3.3. Signal Transduction

Signal transduction refers to the post-receptor electrophysiological or biochemical sequence of events that lead to an agonist's effect. Broadly, transduction mechanisms can be divided into two types: ionotropic, in which activation of the receptor leads directly to influx of ions (such receptors can actually comprise the ion channel); and metabotropic, in which activation of the receptor actuates a series of biochemical second messengers that mediate the response *(16)*.

3.3.1. Ligand-Gated Ion Channels

Located on the membranes of excitable cells, ligand-gated ion channel receptors (LGICRs) are comprised of segments of transmembrane proteins that form pores of specific size and shape that allow the passage of certain ions. The LGICR usually displays selectivity for certain ions (e.g., Na^+, K^+, Ca^{2+}, or Cl^-). The magnitude or the rate of flow of the ions through the membrane is regulated by the binding of ligand to the LGICR. The receptor can be composed of subunits that can be expressed or coupled in different ways in different cells, thus mediating varied effects. Examples of LGICRs are the nicotinic cholinergic, $GABA_A$, glutamate, glycine receptors.

3.3.2. G Protein-Coupled Receptors

The G protein-coupled receptors (GPCRs) often include seven transmembrane (7-TM) regions, an N-terminal extracellular region, and a C-terminal intracellular region *(17)*. A group of guanosine triphosphate (GTP) protein subtypes are coupled to the receptor. Ligand activation of a GPCR induces guanosine 5'-diphosphate (GDP)-GTP exchange and modulation of associated second messengers such as adenylate cyclase, phosphoinositide pathways, and ion channels. Multiple G protein subtypes allow for selective responses *(18)*.

3.3.3. Tyrosine Kinase Receptors

These receptors span the cell membrane and their self-contained catalytic domain functions as an enzyme. Examples include receptors for certain growth factors and insulin.

3.3.4. Nuclear Receptors

These intracellular receptors modulate the activity of DNA or other regulatory molecules located within the nucleus and, consequently, the activation or inhibition of these receptors influences the synthesis and regulation of proteins (e.g., enzymes and receptors) and other cellular components.

3.4. Dose–Response Curves

The relationship between a dose and the corresponding response is a useful measure of drug–nutrient action from both a mechanistic and a practical standpoint. For example, the most commonly observed shape of a dose–response curve is consonant with the occupation theory. Given a reaction scheme of the form $D + R \Leftrightarrow DR$, it follows that the shape of the dose–response curve should be of the form that is actually observed experimentally (hyperbolic) *(19)*. Additionally, certain features of a dose–response curve—or a comparison between them—can yield valuable clinically useful information, such as a measure of relative potency or efficacy.

Several ways of displaying a dose–response curve are described in the following. The type of display can affect certain mathematical (statistical) analyses of the data, but this is beyond the present scope *(20)*.

3.4.1. Quantal

A quantal dose–response curve is one in which the dependent variable (usually plotted along an ordinate; the *y*-axis) is measured as an all-or-none outcome (e.g., the number of patients with systolic blood pressure greater than 140 mmHg). If plotted on rectangular
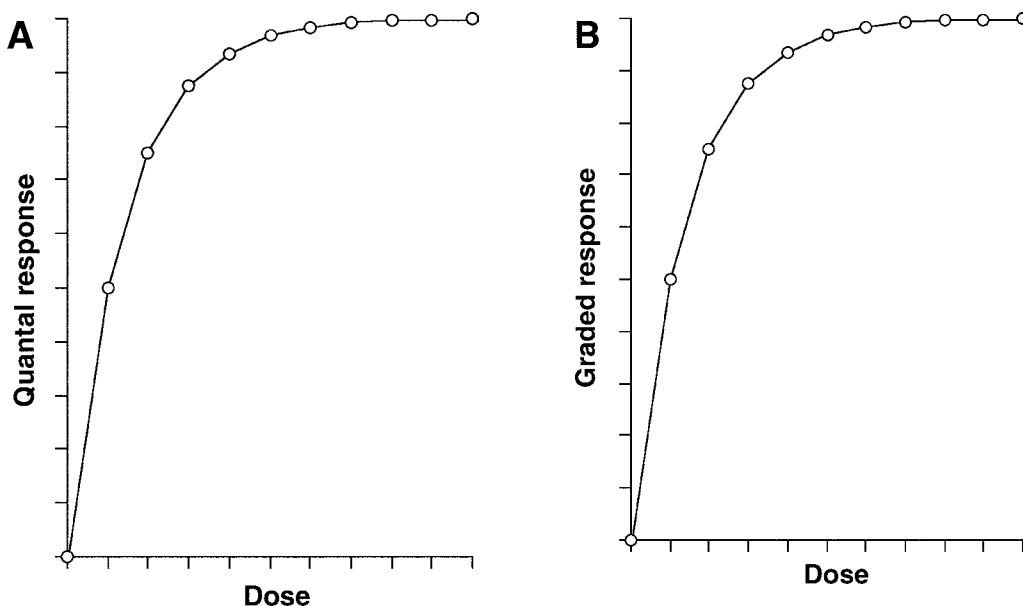
Fig. 2. (**A**) A quantal dose–response curve on rectangular coordinates. (**B**) A graded dose–response curve on rectangular coordinates.

coordinates, the set of points that are derived from plotting response against the administered dose (plotted along an abscissa; the *x*-axis) typically forms a pattern that approximates a rectangular hyperbola (Fig. 2A).

3.4.2. GRADED

A graded dose–response curve is one in which the dependent variable (usually plotted along an ordinate; the *y*-axis) is measured using a continuous scale (e.g., systolic blood pressure in mmHg). As with a quantal response, if plotted on rectangular coordinates, the set of points derived from plotting the measured response against the administered dose (plotted along an abscissa; the *x*-axis) typically forms a pattern that approximates a rectangular hyperbola (Fig. 2B).

3.4.3. LOG

For practical, and now partly unnecessary but historical reasons, dose–response curves are commonly constructed by plotting the response against the logarithm (base 10) of the dose. The shape of such curves becomes sigmoidal or S-shaped (Fig. 3). This has become so customary that such a plot is often what is meant by a dose–response curve.

3.4.4. POTENCY AND EFFICACY

From a dose–response curve it is possible to estimate the dose that would produce a specified level of effect. The choice of level is arbitrary, but the 50% effect level is convenient and commonly selected. The dose of drug estimated to produce 50% effect is termed the *ED50* (or equivalent) for a quantal dose–response curve and the D_{50} (or equivalent) for a graded dose–response curve. *Potency* is a comparative term that refers
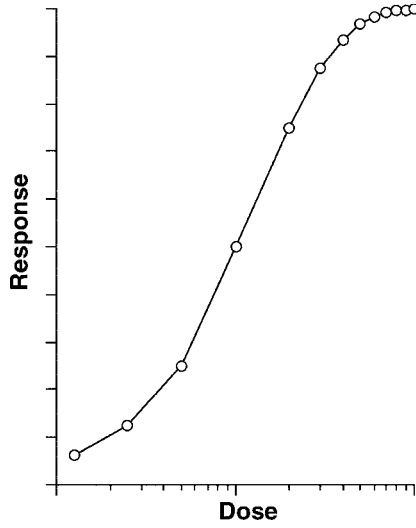
Fig. 3. Quantal or graded dose–response data plotted against $\log_{10}$(dose).
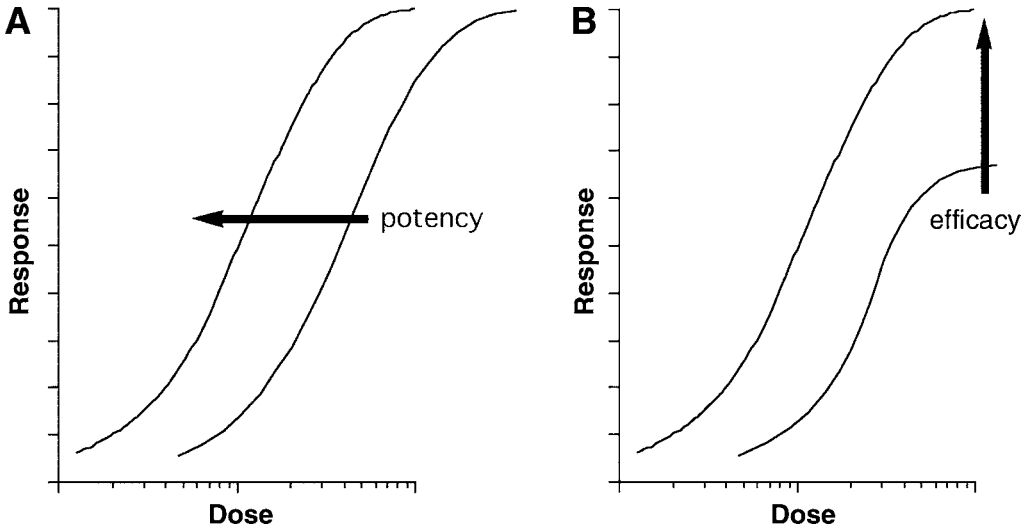
Fig. 4. (**A**) Potency is indicated by the location of a dose–response curve along the *x*-axis. (**B**) Efficacy is indicated by the maximal-attainable level of effect.

to the amount of substance required to produce a specified level of effect (Fig. 4A). Efficacy is a term that refers to a substance's maximal achievable level of effect (Fig. 4B). Potency and efficacy are independent characteristics.

3.4.5. ANTAGONISM

Antagonists, although lacking intrinsic activity, can produce effects when they attenuate the action of an endogenous agonist involved in a pathway that is tonically active and is in opposition to another pathway. For example, antagonists of the muscarinic cholinergic receptor attenuate the parasympathetic influence on heart rate, with consequent increase in heart rate owing to the less opposed influence of the sympathetic subdivision. Hence, such effects of an antagonist can be characterized by dose–response curves.

4. CONCLUSION

The principles of drug disposition and response outlined in this chapter form the basis for understanding DNIs discussed throughout this volume.

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3

Drug-Metabolizing Enzymes and P-Glycoprotein

Thomas K. H. Chang

1. INTRODUCTION

A drug interaction occurs when a drug or another substance modifies the pharmacokinetics or pharmacodynamics of a concurrently ingested drug. With respect to a pharmacokinetic drug interaction, the underlying mechanism may be the result of an alteration in drug absorption, distribution, biotransformation, or excretion. The most common pharmacokinetic drug interactions are those involving biotransformation, particularly the ones resulting from induction or inhibition of cytochrome P450(CYP) enzymes *(1)*. It is now recognized that drug-transport proteins, such as P-glycoprotein (P-gp), play a critical role in drug disposition *(2)* and are therefore targets for drug interaction *(3)*. Various types of drug interactions exist, including drug–drug interaction, nutrient–drug interaction, food–drug interaction, and herb–drug interaction *(4)*. In some cases, the consequences of a drug interaction are not clinically significant, but in other instances, it may lead to therapeutic failure *(5)*, severe adverse events *(6)*, or even fatality *(7)*. In fact, adverse effects due to drug interactions are one of the leading causes of deaths in hospitalized patients *(8)*. Drug interactions also have a high economic cost to the pharmaceutical industry because drugs have been withdrawn from the market as a result of adverse consequences. In some cases, the effect of a drug interaction may be beneficial because it reduces the need of a drug *(9)*.

The purpose of this chapter is to provide an overview of the human CYPs, uridine diphosphate glucuronosyltransferase (UGT), glutathione *S*-transferase (GST), and P-gp. The focus is on the function, induction, inhibition, tissue distribution, and pharmacogenetics of these proteins in humans.

2. CYTOCHROME P450

CYP enzymes are a superfamily of hemoproteins involved in the biotransformation of numerous drugs and other chemicals. Each CYP enzyme is denoted by an Arabic numeral designating the family (e.g., CYP1 family), a letter indicating the subfamily (e.g., CYP1A

subfamily), and an Arabic numeral representing the individual gene (e.g., CYP1A2 gene) *(10)*. CYP enzymes in the same family have greater than 40% amino acid identity and those in the same subfamily have greater than 55% identity *(10)*. Currently, there are 57 functional human CYP genes *(11)*. CYP enzymes that play a significant role in human drug metabolism are primarily in the CYP1, CYP2, and CYP3 families. This overview focuses on CYP3A, CYP2C9, CYP2C19, CYP2D6, CYP1A2, and CYP2E1, which are the major human CYP drug-metabolizing enzymes.

2.1. CYP3A

At least two CYP3A proteins are expressed in adult human liver. They are CYP3A4 and CYP3A5 *(12)*. CYP3A4 protein has been detected in all human liver samples and it represents, on average, approx 30% of the total CYP content in adult human liver *(13)*. In contrast, the CYP3A5 protein is detectable in only 20% of adult human liver samples *(14)*. Both CYP3A4 and CYP3A5 have been detected along the gastrointestinal (GI) tract *(15–18)*. In the case of the CYP3A5 protein, it is also present in the kidney *(19,20)*, lung *(21,22)*, and pancreas *(17)*.

More than 30 single nucleotide polymorphisms (SNPs) have been identified just in the CYP3A4 gene. Among the CYP3A4 allelic variants, CYP3A4*1B (A392→G) is the most common *(23)*. Its expression varies in different ethnic groups, ranging from 0% in Chinese and Japanese to 45% in African Americans *(24–26)*. However, this polymorphism does not appear to have any functional consequences with respect to drug clearance *(24,27,28)*. To date, 12 allelic variants of CYP3A5 have been identified. The most common is CYP3A5*3B (A6986→G), which is present in 95% of Caucasians and 27% of African Americans *(29)*. The homozygote CYP3A5*3B genotype is associated with very low or undetectable CYP3A5 protein expression *(29)*. The functional consequences of this genetic variant remain to be determined.

Numerous drugs with diverse chemical structures and pharmacological functions are substrates for the CYP3A4 and CYP3A5 enzymes (Table 1), which are usually referred to as CYP3A because most of the probes are unable to distinguish the function of CYP3A4 from that of CYP3A5. Both the expression and catalytic activity of these enzymes are subject to modulation (Table 1). CYP3A is inducible not only by drugs, such as rifampin *(30)*, phenobarbital *(31)*, phenytoin *(32)*, carbamazepine *(32)*, and efavirenz *(33)*, but also by a herb, St. John's wort *(34–37)*. It is now known that the mechanism of CYP3A induction involves transcriptional activation of the gene mediated by receptors, including the pregnane X receptor *(38)*, which is also known as the steroid and xenobiotic receptor *(39)* and the pregnane-activated receptor *(40)*, the constitutive androstane receptor *(41)*, and the glucocorticoid receptor *(42)*. For example, it has been reported that St. John's wort activates the pregnane X receptor and this was mediated by hyperforin, but not by hypericin *(43)*. In contrast to enzyme induction in which protein expression is enhanced, CYP3A protein levels can be reduced, as demonstrated by studies with grapefruit juice and Seville orange juice. In biopsy samples taken from human subjects, the ingestion of grapefruit juice *(44)* or Seville orange juice *(45)* was associated with a decrease in enterocyte CYP3A protein expression. These effects were attributed to 6',7'-dihydroxybergamottin *(45)*, which are present in grapefruit juice and Seville orange juice. However, grapefruit juice, but not Seville orange juice, enhances the bioavailability of cyclosporine *(45)*. Additionally, the activity of CYP3A enzymes can be altered by the co-administration of

Table 1
CYP3A Substrates, Inducers, and Inhibitors in Humans

Substrate (Reference)	Inducer (Reference)	Inhibitor (Reference)
Alfentanil (213)	Carbamazepine (32)	Amiodarone (214)
Alprazolam (215)	Efavirenz (33)	Clarithromycin (216)
Amprenavir (217)	Phenobarbital (31)	Delavirdine (218)
Amitriptyline (219)	Phenytoin (32)	Diltiazem (220)
Bosentan (221)	Rifampin (30)	Erythromycin (222)
Budesonide (223)	St. John's Wort (35)	Grapefruit Juice (224)
Buspirone (225)	Troglitazone (226)	Indinavir (227)
Cyclosporine (228)		Itraconazole (229)
Dextromethorphan (230)		Ketoconazole (47)
Dapsone (231)		Methadone (232)
Docetaxel (233)		Nelfinavir (227)
Ethinylestradiol (234)		Nefazodone (235)
Erythromycin (236)		Propofol (237)
Felodipine (238)		Ritonavir (239)
Indinavir (46)		Troleandomycin (240)
Ifosfamide (241)		
Imipramine (240)		
Irinotecan (242)		
Losartan (243)		
Lovastatin (220)		
Methylprednisolone (244)		
Midazolam (245)		
Nelfinavir (246)		
Nifedipine (247)		
Pimozide (248)		
Quinidine (249)		
Quinine (250)		
Ritonavir (251)		
Ropivacaine (109)		
Saquinavir (205)		
Sildenafil (252)		
Simvastatin (253)		
Tacrolimus (254)		
Triazolam (47)		
Verapamil (255)		
Vincristine (256)		

drugs or other substances (e.g., grapefruit juice) that are inhibitors of these enzymes (Table 1). Clinically significant CYP3A-mediated drug–drug interactions include the enhanced clearance of indinavir by carbamazepine that may lead to anti-HIV therapeutic failure (46) and the reduced clearance and excessive pharmacological effect of a benzodiazepine hynoptic, triazolam, by ketoconazole or itraconzaole (47).

2.2. CYP2C9

CYP2C9 is a major CYP enzyme expressed in liver and it can account for up to 30% of the hepatic total CYP content *(48)*. It is primarily a hepatic enzyme, but it has also been detected in human intestinal microsomes *(49)*. CYP2C9 is important in the in vivo metabolism of many drugs (Table 2), including tolbutamide *(50)*, *S*-warfarin *(51)*, phenytoin *(52)*, losartan *(53)*, celecoxib *(54)*, and glyburide *(55)*.

Allelic variants of CYP2C9 have been identified *(56,57)*. Compared to individuals with the CYP2C9*1 allele (i.e., the wild-type), patients with the CYP2C9*2 (Arg^{144}→Cys^{144}) or the CYP2C9*3 (Ile^{359}→Leu^{359}) allele have a decreased clearance of warfarin and a reduced daily dose requirement for the drug *(51,58,59)*. However, individuals with these alleles do not appear to be more likely to experience severe bleeding complications during long-term therapy *(60)*. The effect of CYP2C9 genetic polymorphism is drug-specific. For example, there is no relationship between CYP2C9 genotype (i.e., CYP2C9*1/*1, CYP2C9*1/*2, CYP2C9*1/*3, CYP2C9*2/*2, CYP2C9*2/*3, and CYP2C9*3/*3) and the metabolism of diclofenac in humans *(61)*. Ethnic differences exist in the frequency distribution of the CYP2C9 allele. The CYP2C9*2 allele is absent in Chinese subjects, but it is present in up to 10% of Caucasian Americans *(57)*. By comparison, the CYP2C9*3 allele is expressed in 2–5% of Chinese subjects and up to 20% of Caucasian Americans *(57)*.

The CYP2C9 enzyme is also subject to induction and inhibition. Rifampin is an inducer of this enzyme in humans (Table 2), and this drug increases the clearance of CYP2C9 drug substrates, such as tolbutamide *(62)*, phenytoin *(63)*, and *S*-warfarin *(64)*. Inhibitors of this enzyme include fluconazole *(65)*, miconazole *(66)*, fluvastatin *(67)*, amiodarone *(68)*, sulphamethoxazole *(69)*, and trimethoprim *(69)*. An example of a clinically significant drug–drug interaction involving CYP2C9 is the inhibition of warfarin clearance by fluconazole *(70)*.

2.3. CYP2C19

CYP2C19 is expressed primarily in human liver, although immunoreactive CYP2C19 protein has been detected in human intestinal microsomes *(49)*. CYP2C19 is subject to genetic polymorphism. To date, eight alleles of CYP2C19 have been identified *(71)*. The CYP2C19*2, CYP2C19*3, CYP2C19*4, and CYP2C19*6, and CYP2C19*7 alleles are associated with enzymes that have no functional activity, whereas CYP2C19*5 and CYP2C19*8 alleles result in enzymes that have reduced catalytic activity *(72)*. Ethnic differences exist in the frequencies of the CYP2C19 poor metabolizer phenotype, as assessed by the capacity to metabolize the *p*-hydroxylation of (*S*)-mephenytoin. For example, 12–20% of Asians are poor metabolizers, whereas the frequency is only 2–6% in Caucasians *(73)*.

CYP2C19 catalyzes the metabolism of many drugs in humans (Table 3). It is the major enzyme that metabolizes omeprazole *(74)*, lansoprazole *(75)*, and pantoprazole *(76)*. The enzyme can be induced by rifampin (Table 3), based on the finding that the administration of this drug to human subjects increases the urinary excretion of (*S*)-mephenytoin *(77,78)*. Another inducer of CYP2C19 is artemisinin. This antimalarial agent decreases the area under the concentration-time curve (AUC) of omeprazole in human subjects *(79)*. A number of drugs have been shown to inhibit CYP2C19 in vivo (Table 3), including omeprazole *(80)*, ticlopidine *(81)*, ketoconazole *(82)*, fluoxetine *(83)*, fluvoxamine *(83)*,

Table 2
CYP2C9 Substrates, Inducers, and Inhibitors in Humans

Substrate (Reference)	Inducer (Reference)	Inhibitor (Reference)
Celecoxib (54)	Rifampin (62)	Amiodarone (68)
Glyburide (55)		Fluconazole (65)
Phenytoin (52)		Fluvastatin (67)
Tolbutamide (50)		Miconazole (66)
S-Warfarin (51)		Sulphamethoxazole (69)
		Trimethoprim (69)

Table 3
CYP2C19 Substrates, Inducers, and Inhibitors in Humans

Substrate (Reference)	Inducer (Reference)	Inhibitor (Reference)
Amitriptyline (257)	Artemisinin (79)	Cimetidine (87)
Citalopram (258)	Rifampin (77)	Fluoxetine (83)
Clomipramine (259)		Fluvoxamine (83)
Diazepam (260)		Isoniazid (84)
Fluoxetine (261)		Ketoconazole (82)
Imipramine (262)		Moclobemide (85)
Lansoprazole (75)		Omeprazole (80)
Moclobemide (85)		Oral contraceptives (86)
Nelfinavir (263)		Ticlopidine (81)
Omeprazole (74)		
Pantoprazole (54)		
Phenytoin (264)		
Proguanil (265)		
Propranolol (266)		
Sertraline (267)		

isoniazid (84), moclobemide (85), and oral contraceptives (86). Inhibition of CYP2C19 occurs in a gene-dose dependent manner such that the extent of inhibition is the greatest in homozygous extensive metabolizers, intermediate in heterozygous extensive metabolizers, and little or no inhibition in homozygous poor metabolizers (72). Clinically relevant drug–drug interactions involving CYP2C19 include the inhibition of phenytoin metabolism by fluoxetine (87), cimetidine (87), isoniazid (84), and felbamate (87), resulting in increased phenytoin toxicity.

2.4. CYP2D6

CYP2D6 is expressed in human liver, but at a level (2–5% of total CYP content) less than that of CYP3A, CYP2C9, and CYP1A2. This protein is also present in various extrahepatic tissues, including the GI tract (88), brain (89,90), and lung (91), but at much lower levels when compared to the liver.

An important aspect of CYP2D6 is that many allelic variants (>50) of this enzyme have been identified, although most are quite rare. CYP2D6*1 is the wild-type, whereas CYP2D6*9, CYP2D6*10, and CYP2D6*17 have reduced activity (intermediate

metabolizer phenotype), and others such as CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6 have no functional activity (poor metabolizer phenotype) *(92)*. In some individuals, genetic duplication of the CYP2D6*2 allele results in enhanced functional capacity and this leads to the ultra-rapid metabolizer phenotype *(93)*. Ethnic differences also exist in the frequency in which the various CYP2D6 alleles are expressed. A striking example is with CYP2D6*10, which is expressed in up to 70% of Chinese subjects, but only in 5% of Caucasians *(94)*. In contrast, CYP2D6*4 is present in approx 20% of Caucasians *(95)*, but in less than 1% of Japanese subjects *(96)*. For drugs such as codeine, hydrocodone, and oxycodone, the consequences of a poor metabolizer phenotype is particularly significant because these drugs are bioactivated by CYP2D6. In fact, it has been suggested that codeine not be prescribed to patients with a CYP2D6 poor metabolizer phenotype *(97)*.

Numerous clinically useful drugs are substrates for CYP2D6 (Table 4), including many of the analgesics, antiarrhythmics, β-blockers, antidepressants, antipsychotics, and antiemetics. Various drugs can inhibit the functional activity of CYP2D6 (Table 4). Quinidine is a potent and enzyme-specific inhibitor of CYP2D6. There is no conclusive evidence that CYP2D6 is subject to enzyme induction by drugs. However, CYP2D6-mediated drug clearance appears to be enhanced during pregnancy *(98–100)*. An example of a CYP2D6-mediated drug–drug interaction is the inhibition of venlafaxine clearance by diphenhydramine *(101)*.

2.5. CYP1A2

CYP1A2 is expressed primarily in liver, with little or no known extrahepatic expression *(102)*. This enzyme is important in the bioactivation of aromatic amines and heterocyclic amines *(103)* and metabolism of clinically useful drugs (Table 5), including caffeine *(104)*, clozapine *(105,106)*, melatonin *(107)*, mexiletine *(108)*, ropivacaine *(109)*, tacrine *(110)*, theophylline *(111)*, and verapamil *(112)*. Large interindividual differences (up to 100-fold) in human hepatic CYP1A2 protein content have been reported *(113–115)*, which may be the result of genetic or environmental factors. Allelic variants of CYP1A2 have been identified in recent years. The G2964A and C734A polymorphisms are associated with high CYP1A2 inducibility *(116,117)*, whereas the A164C and T2464delT polymorphisms have no effect on CYP1A2 phenotype, as determined by the caffeine metabolic ratio *(118)*. This enzyme is subject to induction by various factors (Table 5), including exposure to environmental pollutants, such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin *(119)*, cigarette smoking *(120)*, consumption of charbroiled meats *(121)* and cruciferous vegetables *(122,123)*, and ingestion of drugs (i.e., carbamazepine *[124]*). The catalytic activity of CYP1A2 can be inhibited by drugs (Table 5), such as ciprofloxacin *(125)*, enoxacin *(126)*, fluvoxamine *(83)*, oltipraz *(127)*, and stiripentol *(128)*. CYP1A2-mediated drug–drug interactions have been reported; for example, the inductive effect of cigarette smoking *(120)* and the inhibitory effect of ciprofloxacin *(125)* on drugs metabolized extensively by CYP1A2.

2.6. CYP2E1

CYP2E1 is expressed in adult *(13,129)* and fetal liver *(130)*, in addition to lung *(131)*, placenta *(131)*, and brain *(132)*. Whereas a large number of small molecular weight organic solvents (e.g., ethanol) are substrates for CYP2E1, only a few drugs have been

Table 4
CYP2D6 Substrates and Inhibitors in Humans

Substrate (Reference)	Inhibitor (Reference)
Amitriptyline (257)	Amiodarone (268)
Carvedilol (269)	Cimetidine (270)
Chlorpheniramine (271)	Citalopram (83)
Cilostazol (272)	Diphenhydramine (273)
Citalopram (258)	Fluoxetine (83)
Clomipramine (259)	Fluvoxamine (83)
Codeine (274)	Methadone (275)
Desipramine (276)	Moclobemide (85)
Dextromethorphan (277)	Paroxetine (83)
Dihydrocodone (278)	Propafenone (279)
Encainide (280)	Quinidine (281)
Flecainide (282)	Sertraline (283)
Fluoxetine (284)	Terbinafine (285)
Fluvoxamine (286)	
Haloperidol (287)	
Hydrocodone (288)	
Imipramine (289)	
Methylphenidate (290)	
Metoprolol (291)	
Mexiletine (292)	
Nefazodone (293)	
Nicergoline (294)	
Nortriptyline (295)	
Ondansetron (296)	
Oxycodone (297)	
Perphenazine (298)	
Procainamide (299)	
Propafenone (300)	
Propranolol (266)	
Risperidone (301)	
Tramadol (302)	
Tropisetron (303)	
Venlafaxine (304)	
Zuclopenthixol (298)	

found to be metabolized by CYP2E1 (Table 6); that is, acetaminophen *(133)*, chlorzoxazone *(134)*, enflurane *(135)*, and sevoflurane *(136)*. Several SNPs of the human CYP2E1 gene have been identified, but they are not functionally relevant *(137)*. Various factors can influence the activity of this enzyme (Table 6). Chronic alcohol consumption is associated with an increase in hepatic CYP2E1-mediated enzyme activity *(138,139)* and this is accompanied by elevated protein and mRNA expression *(140)*. The levels of this enzyme are also elevated by fasting *(141)*, in individuals with obesity *(141,142)* or diabetes *(143,144)*, and in patients with nonalcoholic steatohepatitis *(145)*. This enzyme can also be induced by isoniazid *(138,146)* and all-*trans*-retinoic acid *(147)*. Inhibitors

Table 5
CYP1A2 Substrates, Inducers, and Inhibitors in Humans

Substrate (Reference)	Inducer (Reference)	Inhibitor (Reference)
Caffeine (104)	Charcoal-broiled meat (121)	Ciprofloxacin (125)
Clozapine (105)	Cigarette smoke (305)	Enoxacin (126)
Melatonin (107)	Cruciferous vegetables (123)	Fluvoxamine (83)
Mexiletine (108)	Carbamazepine (124)	Oltipraz (127)
Ropivacaine (109)		Stiripentol (128)
Tacrine (110)		
Theophylline (111)		
Verapamil (112)		

Table 6
CYP2E1 Substrates, Inducers, and Inhibitors in Humans

Substrate (Reference)	Inducer (Reference)	Inhibitor (Reference)
Acetaminophen (133)	Alcohol, multiple doses (138)	Alcohol, single dose (148)
Chlorzoxazone (134)	All-trans-retinoic acid (147)	Black tea (152)
Dapsone (306)	Diabetes (144)	Broccoli (152)
Enflurane (135)	Fasting (141)	Chlormethiazole (150)
Sevoflurane (136)	Isoniazid (multiple doses) (146)	Diallyl sulfide (148)
	Nonalcoholic steatohepatitis (145)	Disulfiram (149)
	Obesity (142)	Isoniazid (single dose) (146)
		Watercress (151)

of CYP2E1 are ethanol (acute ingestion) *(148)*, disulfiram *(149)*, chlormethiazole *(150)*, diallyl sulfide *(148)*, watercress *(151)*, broccoli *(152)*, and black tea *(152)*. A clinically significant CYP2E1-mediated drug interaction is the inhibition of acetaminophen bioactivation by acute intake of alcohol *(153)*. Interestingly, this metabolic reaction is enhanced by the consumption of multiple alcoholic drinks prior to ingestion of acetaminophen *(154)*.

3. URIDINE DIPHOSPHATE GLUCURONOSYLTRANSFERASE

In contrast to CYP, considerably less is known about the regulation and function of other drug-metabolizing enzymes, such as the UGT and the GST enzymes (*see* Subheading 4.). The UGTs are a superfamily of enzymes that catalyze the conjugation of drugs and other compounds, with UDP-glucuronic acid as a cosubstrate. In general, this type of metabolic reaction results in more polar and less toxic metabolites. Each UGT enzyme is denoted by an Arabic number designating the family (e.g., UGT1 family), a letter indicating the subfamily (e.g., UGT1A subfamily), and an Arabic number denoting the individual gene (e.g., UGT1A1 gene) *(155)*. UGT enzymes in the same family have greater than 45% amino acid identity and those in the same subfamily have greater than 60% identity *(155)*. In humans, two families of UGT enzymes have been identified to date, UGT1 and UGT2 *(156)*. The individual enzymes are UGT1A1, UG1A3, UGT1A4, UGT1A6, UGT1A7, UG1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10,

UGT2B11, UGT2B15, and UGT2B17 *(157,158)*. The mRNA of these enzymes is expressed in human liver, except for UGT1A7, UGT1A8, and UGT1A10 *(158)*. Extra-hepatic expression has been reported *(156,159,160)*, including small intestine (UGT1A1, UGT1A3, UGT1A4, UGT1A8, UGT1A10, UGT2B15), colon (UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A9, UGT1A10), stomach (UGT1A6, UGT1A7, and UGT1A10), kidney (UGT1A9 and UGT2B7), prostate (UGT2B15 and UGT2B17), and brain (UGT1A6 and UGT2B7).

Polymorphisms in the UGT1A1, UGT1A6, UGT2B4, UGT2B7, and UGT2B15 genes have been discovered *(161)*. Mutation in the UGT1A1 gene, as the consequence of having a thymine-adenine (TA)-repeat greater than six, leads ultimately to the absence of the UGT1A1 enzyme *(162)*. This results in hyperbilirubinemias, such as the Crigler-Najjar syndrome *(163)* and Gilbert's syndrome *(162)*. However, the clinical significance of UGT genetic polymorphisms on the pharmacokinetics and pharmacodynamics of thera-peutic agents remains to be established.

Information on the identity of the specific drug substrates catalyzed in humans by individual UGT enzymes is lacking. This is because of the absence of suitable UGT enzyme-selective probes (i.e., inhibitors and inducers) for use in vivo. However, pharma-cokinetic studies have shown that many clinically useful drugs undergo glucuronidation in humans. Drugs that are glucuronidated at substantial levels ($\geq$50% of the administered dose) include chloramphenicol *(164)*, ketoprofen *(165)*, lamotrigine *(166)*, lorazepam *(167)*, morphine *(168)*, *S*-naproxen *(165)*, oxazepam *(169)*, propofol *(170)*, temazepam *(171)*, zidovudine *(172)*, and zomepirac *(173)*.

UGT enzymes are subject to induction and inhibition in humans. Drugs, such as rifampin *(174)*, phenobarbital *(175)*, phenytoin *(175)*, carbamazepine *(176)*, and oral contraceptives *(177)*, have been reported to enhance the glucuronidation of various drugs. Interestingly, the consumption of watercress, which is a rich source of phenethyl-isothiocyanate, results in increased glucuronidation of cotinine in smokers *(178)*. Hepatic UGT enzymes are also induced in smokers *(179)*. Inhibitors of drug glucuronidation include valproic acid *(180)*, salicylic acid *(181)*, and probenecid *(182)*. With respect to the inhibition of lamotrigine elimination by valproic acid *(183)*, this drug interaction may lead to the development of Stevens-Johnson syndrome *(184)*.

4. GLUTATHIONE *S*-TRANSFERASE

GST enzymes catalyze the glutathione conjugation of electrophilic compounds of exogenous and endogenous origin. For many chemicals, including drugs, this represents an important detoxification pathway. In the human cytosolic GST superfamily, there are at least 16 genes and they are subdivided into eight subclasses (GSTA, GSTK, GSTM, GSTP, GSTS, GSTT, GSTZ, and GSTO) *(185)*. Additionally, microsomal GST enzymes have been isolated, but they are structurally distinct from the cytosolic forms. Human GST enzymes are expressed in a tissue-dependent manner *(186–189)*. For example, GSTA1 is present at high levels in liver, kidney, and testis, but absent in lung, heart, and spleen, whereas GSTP1 is expressed in lung, heart, small intestine, and prostate, but undetectable in liver. Most of the studies on the function of GST enzymes have focused on the role of these enzymes in the biotransformation of environmental carcinogens. Much less is known about the specific drugs that are metabolized by GST enzymes. However, drugs that are known to be in vivo substrates for human GST enzymes include

acetaminophen *(190)*, valproic acid *(191)*, and busulfan *(192)*. In humans, polymorphisms in the GST genes have been identified *(193)*, but very little is known about the clinical significance of the GST polymorphisms with respect to the pharmacokinetics and pharmacodynamics of therapeutic agents. A recent study indicated a lack of a relationship between the various GSTA1 alleles and the glutathione conjugation of busulfan *(194)*. Human studies on the induction of GST enzymes are limited. The oral administration of oltipraz, which has been evaluated as a cancer chemopreventive agent, has been shown to increase lymphocyte GST enzyme levels in human volunteers *(195)*. In other human studies, the consumption of Brussels sprouts for 1–3 wk has led to a modest increase in plasma GSTA levels *(196–198)*. Very little is known about the inhibition of GST enzymes in humans. In a recent study, the ingestion (daily for 4 mo) of Curcuma extract, which contains the dietary polyphenol curcumin, was reported to reduce GST activity in lymphocytes in human volunteers *(199)*. Similarly, eugenol, which is the main constituent of oil of cloves, has been shown to reduce human plasma GSTA enzyme activity *(200)*. Overall, much remains to be investigated about the effect of drugs and other factors on the expression and catalytic activity of individual GST enzymes in humans.

5. P-GLYCOPROTEIN

It has only been appreciated in the last several years that drug interactions occur not only as a result of induction or inhibition of drug-metabolizing enzymes, but also drug-transport proteins, such as P-gp *(3)*. This adenosine 5'-triphosphate-binding cassette transporter was originally discovered in tumor cells, whereby repeated exposure of the cells to cytotoxic agents led to overexpression of P-gp *(201)*. Because this membrane-bound protein functions as an efflux pump, the overexpression of P-gp leads to a reduction in intracellular drug accumulation, a decrease in cancer chemotherapeutic drug efficacy, and the development of drug resistance. P-gp is expressed not only in tumor cells, but also in normal cells, such as epithelial cells on the luminal surface of many organs, including the liver, intestines, and kidney *(202)*. The general function of P-gp in the small intestine, liver, and kidney is the secretion of drugs and other chemicals into the gut lumen, bile, and tubule lumen, respectively. It is also present in the blood–brain barrier, blood–testis barrier, and placenta to protect the central nervous system, testis, and fetus from xenobiotics.

In vitro studies have shown that numerous drugs with diverse chemical structures and pharmacological function have been reported to be substrates and modulators of P-gp. Table 7 lists substrates, inducers, and inhibitors of P-gp in humans. An interesting finding is that some of the substrates, inducers, and, inhibitors of P-gp (e.g., rifampin, St. John's wort, clarithromycin, cyclosporine, erythromycin, docetaxel, itraconazole, nelfinavir, quinidine, and verapamil) are also substrates, inducers, and inhibitors of CYP3A. A difficulty of this overlapping specificity is that it is difficult to predict the underlying mechanism of drug interaction. For example, the coadministration of garlic supplements and saquinavir has been reported to decrease the area under the plasma saquinavir AUC by 50% *(203)*. However, saquinavir is a substrate for both P-gp *(204)* and CYP3A *(205)*. Therefore, it is possible that constituent(s) in garlic is capable of inducing P-gp, CYP3A, or both of these proteins. In the case of talinolol, this drug is not metabolized by CYP3A, but is transported by P-gp. Thus, this drug could be utilized as an experimental probe to

Table 7
P-glycoprotein Substrates, Inducers, and Inhibitors in Humans

Substrate (Reference)	Inducer (Reference)	Inhibitor (Reference)
Cyclosporine *(307)*	Levothyroxine *(207)*	Clarithromycin *(308)*
Daunorubicin *(309)*	Rifampin *(206)*	Cyclosporine *(310)*
Digoxin *(311)*	St. John's wort *(35)*	Erythromycin *(312)*
Docetaxel *(313)*		Itraconazole *(238)*
Doxorubicin *(310)*		Nelfinavir *(314)*
Epirubicin *(315)*		Progesterone *(316)*
Etoposide *(317)*		Quinidine *(318)*
Loperamide *(319)*		Talinolol *(320)*
Paclitaxel *(321)*		Valspodar *(322)*
Quinidine *(229)*		R-Verapamil *(323)*
Saquinavir *(204)*		
Tacrolimus *(324)*		
Talinolol *(325)*		
Teniposide *(326)*		
Vinblastine *(327)*		

distinguish the effects of CYP3A from those of P-gp. Intestinal P-gp can be induced, as demonstrated by recent studies with human duodenal biopsy samples showing that repeated ingestion of rifampin *(206)*, levothyroxine *(207)*, and St. John's wort *(35)* increase duodenal expression of P-gp. Given that rifampin and St. John's wort induce both P-gp and CYP3A, drug interactions involving these drugs may be particularly significant. In fact, the reduction in blood levels of cyclosporine by St. John's wort *(5)* has led to transplant rejection *(208)*.

More than 20 SNPs in the *MDR1* (*ABCB1*) gene, which encodes P-gp, have been identified to date *(209)*. Studies have focused primarily on the C3435→T allelic variant, which occurs at a greater frequency in Caucasians and Asians (40–60%) than in Africans (<10%) *(209)*. However, the clinical significance of this polymorphism with respect to pharmacokinetics and pharmacodynamics is not known at the present time. For example, conflicting data exist on the effect of the C3435→T allelic variant on the disposition of digoxin *(210,211)*. Furthermore, it does not appear to have any effect on the pharmaco-kinetics of cyclosporine *(28)*. In a recent report, it was shown that in HIV patients with the homozygote TT genotype at position 3435 had reduced levels of MDR1 mRNA and P-gp in peripheral-blood mononuclear cells and a greater increase in CD4-cell count when determined 6 mo after antiretroviral drug therapy *(212)*. Further studies are required to confirm these initial findings.

6. CONCLUSION

This overview of enzymes and other proteins involved in human drug disposition provides a setting in which to appreciate the various drug–nutrient interactions.

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4   Nutrient Disposition and Response

Francis E. Rosato, Jr.

1. INTRODUCTION

Many factors are involved in the development of drug–nutrient interactions (DNIs). In order to better understand the potential for DNIs, an appreciation for control over food intake, as well as the digestion, absorption, and elimination of nutrients and their sites of storage and effect is necessary.

2. CONTROL OF FOOD INTAKE

A variety of factors, including gastrointestinal (GI) physiology, metabolic demands, external environment, appearance of food, psychological states, social traits, and disease states have been shown to play important roles in the ongoing cycle of initiating, maintaining, and terminating food intake *(1)*. However, our understanding of the exact mechanism of what controls food intake is continually evolving. For years, a specific anatomic region of the brain was thought to be the only area involved *(2)*. Experiments with rats were able to identify two regions of the hypothalamus that affected appetite. Stimulation of the lateral hypothalamus elicited a feeling of hunger while ventromedial stimulation elicited a feeling of satiety. Since these classic studies, the understanding of appetite regulation has evolved from an explanation based on anatomic distribution into one of a complex interaction between the central nervous system (CNS) and the periphery. This includes both short-term control over food intake and long-term control of energy balance *(3)*.

Hunger is the feeling that motivates people to seek food. This driving force appears to be generated by a variety of neuroregulators originating in and acting on specific sites of the brain. Some of these chemical messengers have been well studied (neuropeptide Y, opioids, galanin, norepinephrine, and benzodiazepines) *(1)*. These messengers appear to be under the influence of a multitude of controls that take into account the body's overall energy balance, timing of the last meal, taste, smell, appearance of food, emotions, stressors, gastric volume, exercise, and climate. The end result is food consumption.

As one continues to eat, hunger is replaced by the feeling of satiety. The stimulus required to generate this feeling also comes from multiple sources. These inputs are processed mainly by the brainstem in an area called the nucleus tractus solitarius. This area receives inhibitory stimuli from the mouth, stomach, and liver via the vagus nerve.

Also acting on the brain as appetite suppressants are neuroendocrine secretions from the periphery like cholecystokinin (CCK) from the small bowel and leptin from adipocytes *(2)*. Leptin has come to the forefront as a major factor in controlling food intake. This hormone is produced by adipocytes and has the effect of maintaining satiety. For this reason, it has been targeted as a possible drug treatment for obesity. Once achieved, the feeling of satiety leads to the cessation of a meal.

As time passes, the feeling of satiety waxes and is once again replaced by hunger. And once again the cycle starts over. Note as well that any number of medications may interfere at certain signaling points.

3. DIGESTION AND ABSORPTION

3.1. Overview

Digestion is the mechanical and chemical breakdown of foodstuff to a form that can be utilized by the body. This process occurs in the GI tract. The GI tract is a tubelike structure that consists of the mouth, esophagus, stomach, small intestine, large intestine, and anus. Although its main function is the digestion and absorption of nutrients (macronutrients—carbohydrates, protein, lipid, water; and micronutrients—vitamins, minerals), the GI tract also plays a role in the excretion of waste, and maintaining host immune defenses. There are a number of accessory organs that aid the GI tract in carrying out its primary task; these include the salivary glands, the liver, the gallbladder, and the pancreas. A variety of specialized digestive cells have evolved to meet the requirements of digestion and include chief cells of the stomach, pancreatic exocrine cells, and brush border cells of the small intestine. The GI tract orchestrates the use of these accessory organs and specialized cells in concert to convert carbohydrates, proteins, and fats from their complex molecular form into their more usable forms of monosaccharides, amino acids, and free fatty acids. The movement of the digested nutrients from the intestinal lumen into the blood or lymph fluid is called absorption. Absorption is a highly developed process that is very site specific and utilizes a variety of transport systems (i.e., passive, active, and simple diffusion or endocytosis).

3.2. Mouth and Esophagus

Digestion begins in the mouth where mastication decreases the size of the food bolus in preparation for its passage down the esophagus. The sight, smell, and taste of food all lead to the release of saliva and in particular α-amylase from the salivary gland. This enzyme begins the breakdown of dietary starch and remains active until neutralized by the acidic environment of the stomach. Saliva also serves as an antimicrobial and lubricant to aid in speech and swallowing. Swallowing is a highly coordinated action involving both voluntary and involuntary muscles. The process culminates in the relaxation of the lower esophageal sphincter allowing the deposition of a food bolus into the stomach. Altered physiology of the lower esophageal sphincter muscle leads to the clinical ailment known as acid reflux.

3.3. Stomach

The stomach's main function serves as a reservoir to ready food for absorption by the small intestine and thus plays a minimal role in the absorption of nutrients. Ethanol and

short-chain fatty acids (SCFAs) are the only products absorbed by the stomach during a meal. The lining of the stomach consists of three types of mucosal glands—cardiac, oxyntic, and antral. These glands contain highly specialized cells as well as simple mucosal cells. The gland with the most distinctive feature is the oxyntic. This gland contains both parietal and chief cells. Parietal cells secrete hydrochloric acid (HCl) and are responsible for maintaining the acid environment of the stomach as well as secreting intrinsic factor. This latter polypeptide plays an important role in the absorption of vitamin B_{12}. Chief cells release pepsinogen that is responsible for the digestion of proteins. The G-cells of the antrum secrete the hormone gastrin important for acid production. Mucosal cells throughout the stomach secrete mucus and bicarbonate. All of these gastric cells are under tight neurohormonal regulation. The combination of gastric distention and nutrients in the stomach leads to an increased release of acetylcholine, histamine, and gastrin that stimulate the release of HCl and pepsinogen. Pepsinogen is cleaved to its active form pepsin by HCl. The end result is the onset of chemical breakdown of nutrients into smaller molecules. To further maximize digestion, the stomach mixes food particles and gastric juices by continually contracting against the pylorus. This process of mixing and grinding is called trituration. The gastric phase of digestion is crucial in the overall absorption of nutrients as proven by a variety of malabsorption syndromes caused by alterations in gastric physiology or anatomy.

When a food bolus reaches the stomach, vagal stimulation and gastrin secretion promote gastric motility *(4)*. So as not to exceed the absorptive capacity of the duodenum, the body has developed some mechanisms based on food consistency and composition to regulate gastric emptying *(5)*. Normally, food must be broken down to less than 1–2 mm before it may pass through the pylorus. Thus, food that is poorly chewed or is high in fiber or fat will take longer to exit the stomach than proteins, which in turn will take longer to empty than liquids. Another mechanism is the inhibition of gastric motility by the hormone CCK. This hormone is released in response to high levels of fat and protein in the lumen of the duodenum. The last mechanism that slows gastric emptying is a phenomenon known as the "ileal brake." When incompletely digested carbohydrates are presented to the terminal ileum, a response to slow down gastric emptying occurs. The hormone peptide YY is suspected to play a role in this response *(4)*.

3.4. Small Intestine

The small intestine, which consists of the duodenum, jejunum, and ileum, has several unique features that allow it to play a significant role in digestion and absorption. First, the small bowel has the largest surface area of the entire GI tract thanks in part to its length (about 3 m) and unique anatomic configuration. The entire luminal surface consists of mucosal folds, each with fingerlike projections called villi. On the surface of each villi are more fingerlike projections called microvilli. The result is a surface area of approx 200 m^2 *(5)*. The small bowel also has a unique mechanism of motility. Contents are moved in a back and forth motion called segmentation. This ensures adequate mixing of luminal contents as well as a thorough interaction with the surface area. The cells that line the intestinal lumen, called enterocytes, are highly specialized. They play roles in digestion, absorption, storage, and electrolyte balance. Enterocytes are continually being renewed approximately every 3 d.

Digestion in the small bowel occurs in two phases—luminal and cellular. The luminal phase involves the help of the liver, gallbladder, and pancreas. As the acidic chyme is

expelled from the stomach the pancreas secretes a bicarbonate rich fluid that acts to raise the pH in the duodenum. The neutral environment optimizes the activity of pancreatic digestive enzymes. An enzyme/zymogen-rich cocktail containing amylase, lipase, phospholipase A2, nucleolytic enzymes, trypsinogen, chymotrypsinogen, proelastase, procarboxypeptidases, and procolipase are excreted by the pancreas in response to the variety of partially digested nutrients in the duodenum. The benefit of storing enzymes as inactive zymogens serves to protect the pancreas against autodigestion. Bile salts are also released from the liver and gallbladder in response to lipids. Bile is a detergent that acts to compartmentalize small lipid particles into easily absorbable units called micelles. Also playing roles in the luminal phase are a series of enzymes located on the brush border of the enterocytes. These enzymes, called ectoenzymes, serve to complete the digestive process. The end result of the luminal phase is the conversion of most carbohydrates to monosaccharides, proteins to amino acids and small peptide fragments, and lipids to free fatty acids and monoglycerides.

The cellular phase of digestion occurs after nutrients have entered the enterocyte's cytoplasm. Once inside the cell, peptidases breakdown di- and tripeptides into free amino acids. Also present in the enterocyte are enzymes that convert monoglycerides and free fatty acids back into triglycerides for incorporation into chylomicrons.

3.5. Large Intestine

The colon plays a limited role in the digestion of nutrients. Nonabsorbed carbohydrates that reach the ascending colon are either actively absorbed or converted to SCFAs by colonic bacteria. This process of fermentation helps to provide a fuel source for colonocytes. Dietary long-chain fatty acids are broken down but not absorbed. However, their presence affects water absorption and electrolyte balance. In cases where there is limited small bowel, the colon has been shown to adapt in order to carry out the absorption of nutrients.

3.6. Regulation

The process of digestion falls under the regulation of the CNS, GI hormones, neurotransmitters, and paracrine substances *(6)*. The neuronal axis responds to both external (smell, appearance) and internal (volume, nutrient content) cues from a meal. Input carried from cranial, vagal, and visceral afferent neurons stimulate the CNS via acetylcholine to increase glandular secretions, gastric motility, and pancreatic exocrine function.

G-cells of the gastric antrum release the hormone gastrin increasing acid production and gastric motility. Secretin is released in response to a pH less than 4.5 by S-cells of the duodenum and jejunum. It stimulates the secretion of bicarbonate by the exocrine pancreas to neutralize gastric chyme and promotes the release of bile from the liver. Cholecystokinin is released by I-cells of the duodenum and jejunum in response to fat or protein in the small bowel. Its action results in the contraction of the gallbladder and the release of pancreatic digestive enzymes. Somatostatin is a paracrine peptide released by D-cells of the GI tract and pancreas to reduce overall intestinal secretions, including HCl, pancreatic juice, and blood flow to the GI tract. A variety of other factors including, epidermal growth factor, motilin, gastric inhibitory peptide, peptide YY, glucagon-like peptides, bombesin, and pancreatic peptide play smaller roles in helping to regulate GI function *(7)*.

Absorption is the movement of nutrients, including water and electrolytes, from the intestinal lumen to the vascular or lymphatic systems. The body has developed several different types of transport mechanisms to facilitate absorption. These mechanisms can involve energy dependent or independent pathways, passive or active transport, simple diffusion, endocytosis, or even paracellular movement. Although the entire small bowel has the capacity for absorption, the vast majority of nutrients are absorbed by the jejunum. By the time gastric contents have reached the ileum, the process of nutrient absorption is near total completion. The best way to understand absorption is to follow the fate of the individual nutrients as they have been digested.

4. CARBOHYDRATES

The majority of dietary carbohydrates from a healthy diet are derived from plant starch. Glycogen from meats and disaccharides from refined sugars contribute a much smaller amount. The end result of digestion is the breakdown of complex (starch and fibers) and simple carbohydrates (sugars) into the monosaccharides glucose, fructose, and galactose. These three molecules, all hexoses, share a similar molecular formula. The major enzymes responsible for the digestion of carbohydrates are salivary amylase, pancreatic amylase, and brush border disaccharidases. These enzymes cleave the O-OH bonds between polysaccharides by a process called hydrolysis. After a meal, all carbohydrates are absorbed and only a small portion of resistant starch and dietary fiber remain undigested. These residual products are fermented to SCFAs by bacteria in the colon, which are later used as energy.

For the most part, the absorption of monosaccharides occurs in the small intestine exclusively through a group of hexose transporters. Glucose and galactose traverse the apical membrane of enterocytes through a sodium-dependent active transport system called SGLT-1. Fructose enters the epithelial cells, via facilitated diffusion, through a separate transport system called GLUT-5. Once inside the epithelial cell, all three monosaccharides are transported across the basolateral membrane by a passive diffusion transporter called GLUT-2. Once across the basolateral membrane the hexoses are transported by the portal system to the liver where their ultimate fate will be determined.

Glucose can be utilized in three different ways by the body. First, it can be taken up by the cells of the body with the help of insulin and used to meet immediate energy demands via glycolysis. The second possibility is that it can be converted to glycogen and stored for later use. The liver contains one-third of the body's total glycogen stores and muscle contains the remaining two-thirds. During periods of low blood glucose the liver converts glycogen back to glucose to be used to maintain the energy requirements of the body. Glycogen reserves in muscle are used solely to maintain their own energy requirements. The last option for glucose is its conversion to fatty acids for energy or storage as triglycerides in adipose tissue. This occurs only when the body's energy needs have been satisfied and glycogen stores filled.

A recent field of nutritional study focuses on the interaction of nutrients with genes and their protein products. Carbohydrates have been shown to effect the production of a variety of proteins. For example, the presence of glucose, galactose, and fructose in the GI tract have been shown to cause an increased expression of their respective hexose transporters *(7)*. Also, increased levels of glucose in blood have been shown to up-regulate the

production of a myriad of enzymes involved in glycolysis, fructose metabolism, and gluconeogenesis *(7)*. As we gain a better understanding of this field it is possible that nutrient–gene interactions could be used for the identification and treatment of a variety of diseases.

As one begins to understand the physiology of digestion and absorption it becomes apparent how malabsorption of carbohydrates can result from a variety of diseases. For example, pancreatic insufficiency brought on by chronic pancreatitis, surgical resection, or congenital defect like cystic fibrosis can lead to insufficient amounts of amylase. Alterations in the function of enterocytes via radiation injury or celiac disease can also effect carbohydrate absorption. And finally, a decrease in bowel surface area caused by congenital short gut, inflammatory bowel disease, or surgical resection can result in inadequate interaction between mucosal cells and nutrients.

5. PROTEINS

Digestion breaks down proteins into individual amino acids the body can use as it sees fit. In the stomach, hydrochloric acid denatures proteins exposing their peptide bonds to the proteolytic enzyme pepsin, breaking down proteins into amino acids and smaller peptide molecules. This digestive process is accelerated in the small intestine by a variety of pancreatic proteases. Enterocytes contain an enzyme on their apical border (enteropeptidase) that converts pancreatic trypsinogen to its active form trypsin. This enzyme cleaves peptide bonds and also activates other pancreatic digestive zymogens-chymotrypsinogens and procarboxypeptidases. This cascade-like action serves to protect the pancreas from autodigestion. These pancreatic proteases work in concert with intestinal peptidase, elastase, and collagenase to further break down proteins to peptide fragments, di- and tripeptides, and single amino acids. Individual amino acid uptake occurs along the brush border membrane through a variety of sodium-dependent transporters. These transporters have a specific affinity for each amino acid based in part on their electrochemical properties—neutral, dibasic, acidic, or imino. Di- and tripeptides are carried independently across the brush border membrane by a group of substrate selective carriers. Oligopeptides are also capable of being absorbed, however, once in the cytosol, aminopeptidases break them down to their respective amino acids. The advantage of having the capability to absorb multiple peptide configurations assures the maximal amount of amino acid absorption. These nutrients then exit the cells through membrane transporters and are carried directly to the liver for subsequent disposition.

It is important to note that the rate-limiting step in dietary protein metabolism is the intestinal absorption of amino acids. The body uses nutrient–gene interactions to regulate the number of mucosal cell transporters in response to the dietary load of protein *(7)*. During periods of excessive food intake or in disease states where protein is highly utilized, the number of mucosal cell amino acid transporters increases. The opposite effect is seen during periods of starvation.

Once amino acids reach the liver they can be utilized in one of three ways. The first use is to replenish the body's protein stores, which are continually being broken down. The second use of amino acids is for the production of energy. The carbon skeletons of amino acids can be converted into intermediates for the tricarboxylic acid (TCA) cycle as well as gluconeogenesis. The last use of amino acids is in the formation of nonprotein

compounds like nucleotides, neurotransmitters, catecholamines, hemoglobin, and albumin. All of these uses involve the production of ammonia by transamination or deamination reactions. This toxic byproduct is converted to urea by the liver and excreted via the kidneys.

6. LIPIDS

The average Western diet contains 60–100 g of fat daily, most of which consists of triglycerides; the remainder is a combination of sterols, phospholipids, and fat-soluble vitamins. The digestion of lipids begins with the secretion of pancreatic lipase. This enzyme cleaves the 1 and 3 positions along the glycerol backbone to form two free fatty acids and a monoglyceride. The mucosal cells of the duodenum release the hormone CCK in response to an increased concentration of lipids. This hormone is responsible for the release of pancreatic lipase and bile. Bile acts as an emulsifier to help with lipolysis. Once triglycerides are broken down to their constituent monoglycerides and fatty acids, they form bile micelles. These aggregations of bile salts and fatty acids act to orient the hydrophobic portions of the molecules inward and the hydrophilic portions outward toward the aqueous environment. This orientation allows for easy movement across the watery layer above the brush border and results in more efficient absorption. Once at the apical membrane, the contents of micelles enter the cell by simple diffusion and the micelle recycles back to the intestinal lumen. Short- and medium-chain fatty acids and glycerol are absorbed directly by mucosal cells and are transported to the portal circulation. Phospholipids are absorbed in a similar fashion to triglycerides. Sterols can be absorbed directly by mucosal cells.

Ninety percent of the bile secreted is reabsorbed by the distal small bowel and returned to the liver through portal blood flow. This recirculated bile can then be secreted again or stored in the gallbladder for further use. The route of recycling bile salts is known as the enterohepatic circulation.

Once absorbed into the enterocytes, free fatty acids are reassembled into triglycerides and packaged with cholesterol, phospholipids, and protein to form chylomicrons. Chylomicrons act as transport vehicles for the journey through the lymphatic system. Short- and medium-chain fatty acids are water soluble and are thus able to enter the blood by simple diffusion.

Those products of lipid digestion that are absorbed via the blood go directly to the liver and are used for the synthesis of more triglycerides, cholesterols, or other compounds. Those that are absorbed as chylomicrons reach the vascular system through the thoracic duct and have their lipids utilized by cells all over the body or store their fatty acids in adipose tissue. By the time a chylomicron reaches the liver all that remains are proteins and lipid remnants. This chylomicron remnant is then absorbed by the liver and converted into new lipoproteins.

7. VITAMINS

Vitamins are essential nutrients needed only in small amounts. They are distinguished from carbohydrates, proteins, lipids, and minerals by the fact they are absorbed in their natural state and by their organic nature. Historically, they have been grouped according to their solubility. The fat-soluble vitamins are A (retinol), D (calciferol), E (tocopherols

and tocotrienols), and K (phylloquinone). These vitamins are absorbed in a similar fashion to lipids with the help of chylomicrons and are stored in cells associated with fat. Many require transport proteins as carriers. These vitamins generally are less readily excreted and therefore are needed less frequently. The water-soluble vitamins are all of the B vitamins and vitamin C. They travel in the blood and are excreted by the kidneys. These vitamins are absorbed at various sites along the length of the small bowel by both energy dependent and independent transport systems. Vitamin B_{12} requires intrinsic factor (IF) for its absorption. IF is produced by parietal cells of the stomach. The IF-vitamin complex travels to the terminal ileum where it is absorbed by a specific receptor. Any compromise of IF production or the interaction between B_{12} and IF (i.e., gastrectomy, pancreatic insufficiency, ileal resection) will lead to poor bioavailability of dietary B_{12} and subsequent deficiency. It is important to note that deficiencies are extremely rare given the large hepatic stores of this vitamin but when present they affect multiple systems of the body. Fortunately, a balanced diet provides adequate amounts of all vitamins. The following is a list of vitamins, their actions, and physiologic effects of varying concentrations:

Thiamin (vitamin B_1): Part of coenzyme thiamin pyrophosphate used for energy metabolism. Plays a role in nerve signal transduction. Deficiency is common in the homeless and alcoholics. Symptoms manifest as beriberi or Wernicke-Korsakoff syndrome.

Riboflavin (vitamin B_2): Part of coenzyme flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) used for energy production. Found mainly in milk products, whole grains, and liver. Deficiency causes adenoflavinosis characterized by inflammation of membranes of the mouth, skin, eyes, and GI tract.

Niacin (vitamin B_3): Part of coenzyme nicotinamide adenine dinucleotide (NAD) and its phosphate form (NADP) used for energy metabolism. Precursor is dietary tryptophan. Deficiency leads to pellagra characterized by "the four Ds"—dementia, diarrhea, dermatitis, and death. Excess supplementation causes "niacin flush."

Biotin: Part of a coenzyme responsible for energy and amino acid metabolism as well as fat and glycogen synthesis. Avidin from egg whites decreases absorption. Present in variety of foods and also produced by bacteria in GI tract. Deficiency leads to CNS symptoms, hair loss, and rash.

Pantothenic acid: Part of coenzyme A used for energy metabolism. Present in a variety of foods. Deficiency includes fatigue, GI distress, and neurological symptoms.

Pyridoxine (vitamin B_6): Part of coenzymes pyridoxal phosphate (PLP) and pyridoxamine phosphate (PMP) used for amino acid and lipid metabolism. Also helps in the conversion of tryptophan to niacin and serotonin. Also responsible for the production of red blood cells. Alcohol acts as an antagonist. Deficiency leads to anemia, CNS symptoms, and dermatitis.

Folate: Part of coenzymes tetrahydrofolate (THF) and dihydrofolate (DHF) used in DNA synthesis. Deficiency leads to anemia, GI tract deterioration. It is important in the prevention of neural tube defects during gestation.

Cobalamin (vitamin B_{12}): Part of coenzyme responsible for new cell synthesis, maintaining nerve cells, and breaking down amino acids and some fatty acids. Found in animal products. Deficiency leads to anemia, progressive nerve degeneration, and sore tongue.

Ascorbic acid (vitamin C): Plays roles in collagen, thyroxin, and amino acid synthesis. It acts as an antioxidant and helps in the absorption of iron. Found abundantly in citrus fruits and vegetables. Deficiency leads to scurvy, poor wound healing, atherosclerosis, bone fragility, and loose teeth.

Retinol (vitamin A): Involved in vision, bone and tooth growth, maintenance of cornea, epithelial cells, mucosal membranes, and immunity. Found in milk and dairy products. Precursors are carotenoids found in leafy greens, fruits, and vegetables. Deficiency leads to visual problems, suppressed immune function, diarrhea, and kidney stones.

Calciferol (vitamin D): Involved in the mineralization of bones. Synthesized by the body. Found in milk and dairy products and fatty fish. Deficiency leads to rickets, osteomalacia, and decreased calcium and phosphorous levels.

Tocopherols/tocotrienols (vitamin E): Mainly functions as an antioxidant for lipid membrane and other components of cell. Found predominately in vegetable oils. Deficiency leads to erythrocyte hemolysis. Extremely high concentrations interfere with blood clotting.

Phylloquinone (vitamin K): Involved in synthesis of blood-clotting proteins. Found in green leafy vegetables and also synthesized by bacteria in gut. Deficiency leads to hemorrhage.

8. MINERALS

Minerals are inorganic compounds that are required in small amounts. They play a vital role assisting in processes of energy production, growth, hemoglobin synthesis, as well as the metabolism of carbohydrates, lipids, proteins, and vitamins. Minerals are absorbed and distributed throughout the body without alteration to their chemical structure. Excess amounts can be toxic, thus the body must be careful in their absorption. Minerals are usually divided into two groups, major and minor, depending on their required amounts. Calcium, phosphorous, potassium, sulfur, sodium, chloride, and magnesium are classified as major or macro minerals. Their requirements are often described in grams. Iron, zinc, copper, manganese, iodine, and selenium are considered minor or trace minerals and their requirements are measured in milligrams to micrograms. A normal balanced diet adequately supplies all required amounts of minerals. The following is a brief description of a few minerals.

Iron is absorbed from vegetables (non-heme iron) and meats (heme iron). The average dietary intake is 10–20 mg/d with men absorbing 1–2 mg/d, whereas menstruating women and iron-deficient people absorb 3–4 mg/d. Heme iron is the more readily absorbed of the two (10–20 vs 1–6%). Heme iron requires only the presence of gastric acid to expel the globin molecule. Non-heme iron requires gastric acid and other luminal agents like ascorbic acid to convert it from a ferric to ferrous configuration. Ferrous iron is readily soluble and more easily absorbed. Dietary factors such as phosphates, phytates, and phosphoproteins can render non-heme iron insoluble and impair its absorption.

Both dietary forms of iron are mainly absorbed by the duodenum. Some iron remains in enterocytes as ferritin while the remainder is transported through the blood bound to transferrin. Iron is lost on a daily basis through the exfoliation of mucosal cells. A deficiency in iron is manifested by anemia (microcytic), a decrease in serum ferritin, and increase in serum transferrin levels. Iron overload can be toxic. The genetic disorder hemosiderosis leads to iron deposits in the liver and eventual cirrohsis.

Zinc plays a variety of roles throughout the body including maintaining pancreatic function, wound healing, enzymatic reactions and blood clotting. Only about 15–40% of dietary zinc is absorbed. Various transporters have been identified for the absorption of zinc, but the exact mechanism still remains incomplete *(8)*. Certain animal proteins have been shown to modulate zinc absorption. Phytates have been shown to chelate zinc and prevent its absorption.

Phosphorous is the second most abundant mineral in the body. The vast majority is bound to calcium in teeth and bones. It is predominantly absorbed in the upper small intestine by a sodium cotransport system present on the apical surface of brush border cells. The transport system is highly dependent on vitamin D for its activity. There are no known dietary deficiencies of phosphorous because it is so ubiquitous in the food supply.

Calcium absorption is concentration dependent *(9)*. During periods of low calcium ingestion, active absorption occurs in the duodenum. Vitamin D plays an important role in transporting calcium out of enterocytes and into the vascular system. During periods of moderate to high calcium ingestion, the mineral is absorbed by passive diffusion in the jejunem and ileum. The regulation of calcium blood levels falls under the control of parathyroid hormone. An increase in this hormone leads to increased intestinal absorption, decreased renal excretion, and increased bone metabolism.

9. WATER ABSORPTION

The average person ingests 1–2 L of fluid a day plus an additional 6–7 L from GI secretions. Therefore, the body must be able to absorb large quantities of water. By the time ingesta reaches the large intestine, 80% of water has been absorbed *(10)*. Osmotic gradient is the principle by which water is absorbed. The absorption of water is dependent on the absorption of solutes, in particular sodium and glucose as part of the transporter SGLT-1. The absorption of nutrients results in a large accumulation of sodium and other molecules on the anti-luminal side of enterocytes. This causes a high osmotic gradient toward which water flows. The net result is movement of water between the tight junctions of enterocytes and into the blood. As water moves farther down the GI tract, the tight junction becomes less permeable. Water becomes more dependent on sodium absorption.

10. FACTORS INFLUENCING NUTRIENT ABSORPTION

10.1. Aging

The effects of aging can have a profound influence on the digestion and absorption of nutrients. Aging can impair memory, cognition, and vision, all of which make initiating food intake difficult. Tooth loss and decreased sensory input make the act of eating less enjoyable. The metabolic demands of the body change and metabolism declines. Older people have less muscle mass and increased fat, thus protein and carbohydrate consumption take precedence over fats in the diet. An older person has less total body water content and therefore is more easily subject to dehydration. Vitamin deficiencies are more prevalent in older people. B_{12} deficiency is common because of the increased incidence of atrophic gastritis. As it ages, the body is less able to synthesize the active form of vitamin D. Deficiencies in vitamin D are more common and are a result of decreased intake

coupled with the body's inability to synthesize the active form. Osteoporosis leads to calcium deficiencies. Iron-deficiency anemia is also a common problem found in older people secondary to decreased production of HCl by the stomach. These absorptive problems are often exacerbated by the presence of other comorbid diseases, the use of multiple medicines, or rigid learned dietary habits.

10.2. Disease

The effect of various diseases on absorption and digestion results in malnutrition and ultimately severe illness. Disease can be found along the entire GI tract and may result from genetic, infectious, or iatrogenic causes. These alterations can affect the luminal factors involved in digestion or impair the function of the brush border cells in absorption. Genetic diseases like cystic fibrosis and lactase deficiency are common throughout the world. Inflammatory conditions like pancreatitis, gastritis, and inflammatory bowel disease also lead to impaired nutrient absorption. Bacterial overgrowth and commonly acquired conditions like celiac disease, diabetes, and infectious gastritis also lead to impaired nutrient uptake. A variety of surgical procedures including gastric resection, short bowel syndrome, ileostomy, or colostomy lead to altered nutrient absorption. It is also important to note that diseases affecting other organs like the kidneys, the liver, and gallbladder can also have an effect on nutrient digestion and absorption.

11. CONCLUSION

The absorption and digestion of nutrients is a complex and highly coordinated process. Interactions between the CNS and peripheral nervous systems as well as the GI tract must act in concert to assure that metabolic demands are met. In an effort to better elucidate the effects of a multitude of diseases involving the GI tract as well as the interventions preformed upon it by the medical community, it is paramount that we understand the roles that chemical messengers, GI hormones, digestive enzymes, and mechanical stimuli play. We must always remember when caring for patients that age, disease processes, and altered physiologic states have profound effects on the milieu of nutrient assimilation. An understanding of the workings of each component, as an individual entity and in the overall picture, will allow for better care of patients. Future efforts in appreciating DNIs will require this level of knowledge.

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II Influence of Nutritional Status on Drug Disposition and Effect

5 The Impact of Protein-Calorie Malnutrition on Drugs

Charlene W. Compher

1. INTRODUCTION

Nutritional factors may influence the absorption, metabolism, distribution, and clearance of medications. This chapter focuses on malnutrition and its impact on the safe and effective management of medications. The scope of this chapter does not extend to a consideration of the effects of particular drugs on nutritional status.

1.1. Malnutrition

Malnutrition may be a chronic or acute problem, and primary or secondary to other processes *(1)*. Chronic starvation, resulting from inadequate food supply, results in protein and energy deficiency, a syndrome known as protein-energy malnutrition (PEM) or protein-calorie malnutrition (PCM). When the predominant deficiency is chronic undersupply of calories, the syndrome is called marasmus, as evidenced by extreme, unintentional weight loss or severe growth failure in children *(1)*. When the predominant deficiency is protein intake, the syndrome is called kwashiorkor, with attendant loss of muscle mass, often with ascites or edema. Some individuals may have combined deficiencies of protein and calories, termed marasmic–kwashiorkor *(1)*.

Malnutrition in children is defined by comparison to World Health Organization/ National Center for Health Statistics (WHO/NCHS) weight and height standards *(1,2)*. Underweight is defined as a child who is more than 2 standard deviations below the weight-for-age reference range. Wasting is defined as a child whose weight-for-height is more than 2 standard deviations below the reference. Finally, a height-for-age more than 2 standard deviations below the reference indicates stunting *(1,2)*.

Severe marasmus, kwashiorkor, and marasmus–kwashiorkor are seen in Western health care facilities, particularly in very ill, elderly patients. However, the more usual pattern in the general population occurs in normal, overweight or obese patients prior to hospital admission *(3)*. Weight loss during hospitalization is common, as is rapid development of severely depleted serum protein levels in response to injury, infection, surgical, or medical treatments, and prolonged limited intake of protein *(4)*.

Although protein and energy status have classically defined the syndrome, in the most typical presentation with starvation, the entire food supply is limited such that deficien-

cies of many other nutrients occur simultaneously *(1)*. A relatively recent observation in developing countries is increasing obesity concurrently with prevalent PEM. Obesity occurs when caloric supply is sufficient to promote chronic diseases (diabetes, hypertension, and cancer) but the nutrient content of the diet is poor *(5)*.

1.1.1. PRIMARY PEM

The prevalence of primary PEM is greatest in developing countries, particularly where famine occurs following natural or manmade disasters *(1)*. Worldwide, 800 million people from developing countries are undernourished, a figure that includes 193 million (36%) underweight, 230 million (43%) stunted in growth, and 50 million (9%) wasted children below the age of 5 *(1)*. The prevalence of underweight children is 36% in all developing countries, with a range from 11% in Latin America to 60% in South Asia *(2)*. The percentage of infants born small (<2500 g) is 19% in all developing countries, with a range of 11% in Latin America and East Asia to 34% in South Asia *(2)*. Although the overall percentage of malnourished children has been reduced in countries with economic and political stability, the actual total number is unchanged owing to burgeoning population growth. When natural disasters, such as droughts, floods, earthquakes, or famine occur, the prevalence of PEM in a developing country may be increased. Similarly, when manmade disasters such as wars, political upheavals, or economic crises occur, malnutrition prevalence in the population is exacerbated *(1)*.

The age groups at greatest risk of PEM are those with increased nutritional needs for growth, reproduction, or milk production—infants and pregnant or lactating women—*(1,2)*, and the elderly *(4)*. Maternal malnutrition peri-pregnancy is a key factor in the birth of an underweight newborn, and its development into a child with PEM *(1)*. Although marasmic malnutrition (wasting) is most common in children under 1 yr of age, weaning from breast milk later on is associated with kwashiorkor malnutrition when the available diet contains much lower protein content than milk. The elderly are particularly susceptible to PEM when their medical or socioeconomic status limits their ability to obtain and ingest nutritionally adequate diets *(4,6,7)*.

The prevalence of PEM is generally thought to be greater in rural than urban populations in developing countries, although urban prevalence is unacceptably high. In Turkey, stunting in children is 20.5% in rural vs 16.1% in urban children *(8)*. In Nigeria, 41.5% of rural children under 5 yr have PEM *(9)* vs 37.9% in an urban population *(5)*. The rapid increase in population growth in cities in developing nations often comes with limited planning and many health problems. The prevalence of malnutrition has not been substantially reduced in part due to extreme poverty, poor housing conditions, limited parental involvement in food preparation (parents working at low-paying jobs), and violence *(5)*.

The prevalence of vitamin and mineral deficiencies can outpace actual PEM prevalence. In Turkey, the prevalence of PEM in cities is 20%, however, iron-deficiency anemia is seen in 50% of preschool children, pregnant and lactating women, and in 33% of school-age children *(8)*. Deficiencies of iodine and vitamin A are also common.

Severe primary PEM is occasionally reported in developed countries in the setting of unusual dietary practices. Case reports of four children with PEM in the United States were associated with intake of a rice beverage as an alternative to milk, on the basis of suspected food allergies *(10)*. Another 12 cases of frank kwashiorkor in children 1–22 mo

old were referred to dermatologists over a 9-yr period in seven tertiary referral centers in the United States based on complaints of edema and flaky paint dermatitis, classic signs of kwashiorkor *(11)*. These cases were attributed to the substitution of low protein fluids for milk or formula, owing to a combination of perceived or true milk allergy, food faddism, or nutritional ignorance. Financial or social stresses were a factor in only 2 of the 12 cases *(11)*.

1.1.2. SECONDARY PEM

Severe PEM in developed countries is more commonly secondary to disease processes or their treatments, which limit adequate oral nutrient intake or increase nutritional requirements or losses *(12)*. This may be the result of a reduced ability to take adequate diet (such as cancers causing obstructions of the intestinal tract) or change in mental status (such as cerebrovascular accident, head injury, dementia, or severe dehydration). The ability to absorb nutrients may be compromised, as with malabsorption syndromes, cystic fibrosis, or intestinal infections. Other diseases or hospital treatments may increase nutrient requirements, typically significant infections, pulmonary diseases, acute injuries, surgery, and intensive chemotherapy or radiation therapy to treat malignancy. Nutrient losses may occur owing to changes in metabolism, cellular destruction in response to chemotherapy, or accelerated excretion.

Children with cancer have greater prevalence of PEM than healthy children in the population. In 65 children who presented to an outpatient setting for cancer therapy, 25% were at nutritional risk, with equal proportions of malnutrition and obesity *(12)*. By contrast, of those hospitalized for cancer treatment, 45% (41/91) were nutritionally at risk. Of these, 83% were malnourished and 17% were obese *(12)*. In an evaluation of all 1033 children diagnosed with acute lymphocytic leukemia in the United Kingdom between 1986 and 1991, wasting was prevalent at the time of diagnosis in 7.6% of boys and 6.7% of girls *(13)*.

Children with chronic diseases also have a remarkable prevalence of malnutrition. PEM has been described in 36–50% of two cohorts with juvenile rheumatoid arthritis in the United States *(14)*. In a group from Mexico, 14.7% of children in a cohort with rheumatoid arthritis or rheumatic fever were underweight by WHO/NCHS criteria, but albumin concentration was normal *(14)*.

For adult patients living independently at home, the prevalence of malnutrition is 1–8%, whereas the prevalence for institutionalized individuals rises to 25–60% *(4)*. This increased prevalence in institutionalized patients in part reflects health care decision making that supports keeping in institutions seriously ill individuals with complicated medical conditions. For hospitalized patients, the prevalence of malnutrition ranges from 35 to 65%, where higher acuity, critically ill patients also have more signs of malnutrition *(4,7)*.

In developed countries, milder forms of malnutrition and obesity may be associated with food insecurity. The term *food insecurity* describes the difficulty that relatively impoverished groups in the population have in obtaining optimal food intake throughout the entire month, and during irregular circumstances. Food insecurity is a chronic problem, particularly among the 2.5–3 million homeless Americans *(15)*. Food insecurity is generally associated with adequate caloric supply but poor food quality, leaving affected individuals susceptible to the development of low-grade vitamin and mineral deficiencies. Food insecurity fell by 11.3% and the prevalence of hunger fell by 15.6%, adjusted

for population growth, between 1998 and 2000 *(15)*. Federal food assistance programs were used by 50% of food-insecure households, whereas private food banks or churches provided food to 16.7% of the food insecure, a total of 2.4% of total US households *(15)*.

1.1.3. OUTCOMES OF MALNUTRITION

PEM is consistently associated with increased mortality, and often with infections. PEM is associated with 56% of all deaths of children aged 6 to 59 mo, where their death is attributed to the added impact of malnutrition on infectious disease *(1)*. Acute respiratory infections are associated with 30.3% of deaths in children, as well as a large proportion of deaths due to measles, pertussis, and HIV–AIDS *(2)*. In Malawi, 75% of admissions to nutrition rehabilitation centers are for kwashiorkor or marasmic–kwashiorkor, with a typical 20–30% mortality *(16)*. In 250 children admitted for care, 34% were HIV positive, with 62% having marasmus and another 35% marasmic–kwashiorkor. The mortality was increased 1.6-fold in HIV-positive relative to HIV-negative malnourished children (confidence interval [CI] = 1.14–2.24). The authors cited limited food supply and nursing resources in the rehabilitation centers as unfortunate factors in the mortality rates *(16)*.

In patients who are cared for in US medical facilities, malnutrition has been associated with poor clinical outcome and increased cost of medical care for 70 yr. Unintentional loss of more than 20% body weight predicted a threefold increase in mortality and morbidity in surgical patients with benign gastric ulcers *(17)*, whereas the frequency and severity of postoperative infection prior to antibiotics depended on the protein reserve of the patient *(18)*. In 87,078 consecutive surgical cases from 44 Veterans Affairs medical centers, of 54,215 patients who had a preoperative albumin concentration, albumin was negatively correlated with postoperative mortality regardless of risk associated with the particular surgical procedure *(19)*. Albumin concentration below the normal range was associated with a 1.5- to 9-fold risk of nosocomial infection and a 1.3- to 1.5-fold increase in length of hospital admission *(20)*. Hospitalized patients who are malnourished consistently have increased mortality and morbidity *(3,5,6,8–10,15–20)*.

Thus, at the current time, health care facilities are required by the Joint Commission for Accreditation of Healthcare Organizations (JCAHO) to develop and implement a plan for screening all patients for nutritional risk. Although the specific details of the nutritional screen vary among facilities, based on typical patient populations and laboratory assay methods, at least three factors are usually included. The first is unintentional weight loss or visible body wasting. The second factor includes difficulty with food ingestion or absorption, based on food availability and concurrent disease processes. The final factor is an assessment of serum protein concentrations, most commonly albumin.

2. REVIEW OF BASIC SCIENCE

2.1. Physiologic Changes With Varying Degrees of PEM

Because PEM develops gradually over weeks to months, a series of metabolic and behavioral adaptations occur, with the aim of preserving limited body tissue *(21)*. With prolonged severe limitations in nutrient intake, however, the process of adaptation is not successful and the patient succumbs, usually to death from an otherwise minor infection *(1)*.

Dramatic changes in body composition herald significant malnutrition. A loss of subcutaneous body fat stores occurs, leaving visible bony prominences.

Protein catabolism leads slowly to muscle wasting *(3,21)*, which can be detected in adults by squared off shoulders and limited biceps mass. With severe disease, visceral protein depletion (including reductions in serum albumin and total protein) results from reduced protein synthesis, leading to edema and ascites *(21)*.

With marasmic malnutrition, body fat stores are reduced and total body water increased, as measured by body composition. In a five-compartment model, fat mass is 22%, extracellular water 21%, intracellular water 39%, protein 15%, and minerals 2% during normal nutritional states. By the point of marasmic malnutrition, the fat mass has been reduced by two-thirds, and the extracellular water expanded 50% *(11)*.

When gradual starvation is not complicated by infection, the body reduces its production of less essential proteins, such as growth and sex hormones, insulin, and thyroid hormone *(21)*. The reduction in thyroid hormone causes a significant decline in metabolic rate and thus energy expenditure. Body cell mass, including red blood cells, T-lymphocytes, and complement are reduced, leading to anemia and fatigue. Reduced immune surveillance, in the setting of an overcrowded, unhygienic environment leaves malnourished individuals at far greater susceptibility to infection *(3,21)*. The production of enzymes, including those with a role in drug metabolism, is also reduced *(22–28)*.

The adaptive processes include reduced resting energy expenditure resulting from loss of metabolically active tissue, and reduced energy expenditure for activity as the malnourished individual is too weak for physical exertion, and reduced thermic effect of feeding as caloric supply is limited *(21)*. Thus, daily total energy expenditure is reduced.

Gradual loss in organ function occurs with prolonged, severe malnutrition *(21)*. Blood glucose concentration is initially maintained by the autocatabolism of body fats to glycerol (and free fatty acids) and of gluconeogenic amino acids. With severe or end-stage PEM or when severe infections limit hepatic function, blood glucose concentrations may drop. Total body potassium and zinc are lost with muscle catabolism. Cardiac output, heart rate, and blood pressure are decreased, with reduced venous return. Renal plasma flow and glomerular filtration rate are limited secondary to reduced cardiac output, but water and electrolyte clearance are unchanged. Diarrhea is common with PEM, for various reasons including limited intestinal secretions, bacterial overgrowth, nutrient deficiencies (particularly of vitamin A or zinc), and villous atrophy *(21)*. Hepatomegaly is associated with steatosis, as nutrient deficiencies prevent the export of fat from hepatocytes. Hepatic production of serum proteins (albumin, prealbumin, and transferrin) is reduced with continuing malnutrition, as are hemoglobin and hematocrit *(21)*.

2.1.1. REFEEDING SYNDROME

After the development of severe malnutrition, whether primary or secondary, patients are susceptible to refeeding syndrome during the early hours to days of their nutritional rehabilitation. This syndrome of acute declines in extracellular concentration of potassium, magnesium, and phosphorus occurs as these electrolyte and mineral elements shift intracellularly with glucose, in response to insulin secretion with feeding *(29)*. Two fatalities have been attributed to severe hypophosphatemia in the setting of overzealous parenteral refeeding, although hypokalemia may also have been a factor *(29)*. Thus, it is safest to restore nutritional deficits slowly, limiting glucose supply for several days, and carefully repleting electrolytes as indicated by serum concentrations. Because cardiac function may be impaired and fluid shifts can occur rapidly with refeeding, diuretics should be given when needed.

Nutrients supplied to the malnourished patient during refeeding can impact drug metabolism. High protein intake induces the microsomal or mixed function oxidase system (MFOS), which can alter the half-life of medications *(30)*. Carbohydrates have limited impact on drug metabolism, however aggressive carbohydrate intake may exacerbate refeeding syndrome, with attendant electrolyte shifts that can secondarily impact drug toxicity (see Subheading 2.3.3.). Deficiencies of essential fatty acids, which can occur with limited intake of linoleic or linolenic acid in as short a time as 2 wk, are associated with reduced activity of MFOS in the hepatic endoplasmic reticulum *(29)*. Thus, refeeding with fatty acids, intravenous lipid emulsion, or dietary corn oil, can stimulate the MFOS.

2.1.2. ALCOHOL

Alcoholics, particularly those admitted with acute intoxication or withdrawal, often have PEM, including weight loss, limited muscle mass, and fat mass *(31)*. Regardless of liver disease, continued alcohol consumption has been associated with weight loss, whereas abstinence produces weight gain. Some patients do not appear chronically malnourished, however, when daily alcohol intake is more than 30% of total kcal, nutrient intake of protein, fat, vitamins A, C, and thiamin, and calcium, iron and fiber are less than desirable *(31)*. Vitamin D deficiency is common and results in low calcium, phosphorus and magnesium levels. Vitamin K deficiency can arise with fat malabsorption (pancreatic insufficiency, biliary obstruction, or mucosal damage owing to folate deficiency). Folate deficiency is common (37.5%) in active drinkers, likely resulting from increased urinary and fecal losses and to limited hepatic vitamin retention *(31)*. Vitamin B_{12} deficiency may occur secondary to pancreatic insufficiency, limiting the release of the vitamin from its protein carrier in the intestinal lumen. Up to 50% of alcoholics may have subtle riboflavin deficiency. Magnesium and zinc status are generally reduced in alcoholics, in part due to increased urinary excretion magnesium and marginal intake of zinc. Iron deficiency may occur due to gastrointestinal bleeding, but excess hepatic iron, copper, and nickel stores are also seen with cirrhosis *(31)*.

Alcohol impairs digestion and absorption (diarrhea, motility changes, folate deficiency, alcoholic pancreatitis, bile salt deficiency), which may also limit drug absorption. Ethanol impairs hepatic amino acid uptake and synthesis of lipoproteins, albumin, and fibrinogen *(31)*, perhaps reducing protein carrier availability. In animal studies, the cytochrome P450 (CYP) system is induced by alcohol ingestion, a factor that speeds the clearance of other CYP-metabolized drugs and nutrients (e.g., vitamins A and C). Ethanol-induced vitamin A depletion is associated with reduced detoxification of xenobiotics *(32)*.

2.2. Animal Experiments

A series of animal experiments were designed to examine specific aspects of the impact of severe malnutrition on drug handling. Experiments conducted prior to 1972 verified consistently that oxidation rates of drugs were reduced with significant malnutrition *(23)*. More recent experimental findings are discussed in the following sections.

2.2.1. ANALGESICS

Salicylate ototoxicity was enhanced with magnesium and zinc deficiencies *(33)*. Zinc deficiency also enhanced a reversible salicylate-induced nephrotoxicity *(33)*.

2.2.2. CHLORAMPHENICOL

A limitation in protein carriers, which occurs commonly with PEM, reduced chloramphenicol distribution in rats. Hypoproteinemic rats, given a single dose of chloramphenicol, had higher drug concentration, with greater renal than hepatic drug distribution, and diminished plasma half-life *(34)*. The authors speculated that reduced protein binding of the drug allowed the higher drug levels and the shortened half-life.

During malnutrition, the metabolism of chloramphenicol is reduced. In guinea pigs fed a protein-depleted diet, total body and liver weight (but not hepatocyte number) were reduced *(35)*. Hepatic microsomes had reduced conjugation of chloramphenicol, due to a reduced uridine diphosphate (UDP)-glucuronidase activity per cell, and reduced response to induction by 3-methylcholanthrene *(35)*. These data suggest that the increased drug levels of chloramphenicol in malnourished patients may in part be owing to reduced drug clearance by the liver *(35)*. In malnourished rats treated with chloramphenicol, hepatic microsomal aniline hydroxylase and aminopyrine-*N*-demethylase activities were markedly reduced *(36)*. Mitochondrial oxidative phosphorylation, which was already inhibited by PEM, was further potentiated by chloramphenicol treatment.

2.2.3. GENTAMICIN

Gentamicin ototoxicity was enhanced with experimental magnesium and zinc deficiencies *(33)*. With magnesium deficiency, the hearing loss induced by gentamicin treatment was nearly complete and irreversible in 9 out of 25 (36%) rats. Magnesium deficiency can induce hearing loss independently of gentamicin, owing to low extracellular magnesium concentrations allowing influx and turnover of Na^+, K^+, and Ca^{++}, with a resulting reduction in cochlear blood flow *(33)*. Enhanced membrane permeability of the hair cells and thus increased ion pumping was the most likely mechanism behind increased ototoxicity with zinc deficiency *(33)*. Experimental dietary potassium depletion in the dog was associated with increased gentamicin nephrotoxicity, with the drug concentrated in the renal cortex of potassium-depleted animals *(37)*. Gentamicin administration also induced urinary potassium wasting *(37)*.

2.2.4. SULFADIAZENE

To examine the impact of malnutrition on sulfadiazine acetylation by the hepatic phase II conjugation pathway, a rhesus monkey model was employed *(38)*. States of normal nutrition, PEM, and nutritional rehabilitation were induced by change in quantities of diet. Total absorption of sulfadiazine was unchanged, although the peak was delayed in the group with PEM. The peripheral volume of distribution of the drug was reduced, as were the elimination rate constant and clearance rate. These latter two factors resulted in increased drug half-life and drug area under the concentration-time curve (AUC) in the group with PEM. Acetylation was only measured in hepatic tissue (representing 33% of total acetylation), and appeared unchanged by PEM. The authors suggested that the reduced volume of distribution of drug may be a key factor in reducing drug elimination *(38)*.

2.2.5. ANTITUBERCULARS

Isoniazid (INH) hepatotoxicity was examined in an experiment with caloric deprivation, PEM, and usual diet in rats *(39)*. After 2 wk of INH, all animals had transaminitis,

and proliferation of the rough endoplasmic reticulum in liver tissue. Glutathione activity was reduced in both liver and blood samples, suggesting reduced free radical defense. The INH-induced loss of glutathione activity was further exacerbated by concurrent malnutrition *(39)*. Similar findings were noted in a related experiment testing both INH and rifampicin *(40)*.

3. EFFECT OF MALNUTRITION ON DRUG DISPOSITION

Changes in drug disposition may vary with the degree of PEM. In severe PEM, drug absorption may be reduced, protein carriers limited, and metabolism slowed, resulting in higher drug concentrations and a potential for toxicity with drugs that have a narrow safety margin. In mild to moderate malnutrition, changes in metabolism may be minimal or of limited clinical significance, however, the clinical data to support this conclusion are very limited.

3.1. Absorption

The physical properties of medications, such as lipid-solubility, molecular weight, acidity, and biopharmaceutical properties impact their absorption *(22–28)*. During PEM, however, absorption may be reduced as a result of physiologic changes, particularly in children with severe PEM and in alcoholic adults *(31)*.

3.2. Distribution

In later stages of malnutrition, when hepatic protein synthesis is reduced, protein carriers for drugs may be limited, resulting in greater concentrations of free drug available for tissue use or elimination *(22–28)*. In established kwashiorkor, both extracellular fluid accumulation and low serum albumin concentrations prevail *(1,21)*, and may be exacerbated by the liver's inflammatory response to infection further reducing albumin synthesis. In addition to a reduction in carrier availability, the associated fluid shifts and edema may impact drug concentrations or tissue distribution.

3.3. Metabolism

Clinical reports to date have described a different pattern in the impact of malnutrition on drugs depending on the severity of malnutrition *(22–28)*. Reports in children have primarily reflected severe PEM (marasmus, kwashiorkor, or marasmic–kwashiorkor) with most children from India or Africa. In the few published adult studies, subjects have been mildly to moderately malnourished, likely of shorter duration, and in very small subject numbers. With the milder forms of malnutrition, oxidative metabolism of drugs is reported as unchanged or increased. By contrast, when the malnutrition has progressed to kwashiorkor, metabolism is consistently reduced.

Antipyrine is a compound exclusively metabolized by the liver, with very limited hepatic extraction, and is a suitable marker of MFOS activity *(41)*. The drug is protein-bound to a limited degree and its elimination and distribution are not impacted by hypoalbuminemia. In a group of 45 adult patients with inflammatory bowel disease, who had suffered more than 10% weight loss and/or reduction in albumin concentration (30 g/L, vs 40 g/L in 25 normal controls), CYP activity was evaluated by antipyrine metabolism *(41)*. Overall metabolic clearance was reduced, but weight-corrected clearance was unchanged. In 27 of these patients, who were restudied after 30 d of nutritional reple-

tion, clearances were normalized in those who had protein malnutrition but unchanged when the initial deficit was caloric *(41)*.

In 30 undernourished adults hospitalized with peptic ulcer disease or abdominal pain and only mild hypoalbuminemia, liver biopsy specimens were evaluated for aryl hydrocarbon hydroxylase (AHH) and CYP concentrations *(42)*. CYP was unchanged, but AHH increased in the undernourished men, a pattern suggesting increased ability to activate reactive metabolites concurrent with reduced ability to detoxify them.

3.4. Excretion

Renal clearance of drugs may be impacted by protein intake. Because renal tissue is spared until very severe stages of malnutrition, however, most reports to date do not report reduced renal drug clearance with PEM. The possibility that concurrent clinical comorbidities (e.g., hypertension, diabetes, renal disease) may play a role in altered renal drug clearance, particularly in elderly or metabolically stressed critical care patients, should be considered.

3.5. Drug Effects

The therapeutic effectiveness of a drug may be reduced or the prevalence of toxicity increased because of malnutrition. When absorption is reduced and/or excretion increased, adequate drug levels in serum or tissues may not be achieved. When the half-life of a drug is prolonged, owing to reduced hepatic metabolism or renal elimination or increased volume of distribution, toxic drug or drug metabolite levels can occur. In malnourished subjects, drugs with a narrow safety margin can produce toxicity at usual dosage levels if the drug's bioavailability is increased because of impaired hepatic function *(28)*. However, if the toxicity of a given drug results from its metabolite, then the slowing of CYP activity may actually reduce toxicity *(28)*.

3.6. Drug-Specific Clinical Evidence

The clinical evidence is rather limited in terms of number of drugs tested, the range of malnutrition described, and is composed almost entirely of pharmacokinetics data from very small numbers of subjects. Thus, negative findings may be based on sample sizes too small to state with any confidence that there is no difference.

3.6.1. ANALGESICS

Acetaminophen (paracetamol) is easily absorbed, rapidly distributed, has insignificant protein binding, and is metabolized to glucuronide and sulfate products eliminated renally *(28,43)*. In children with severe PEM, the biotransformation of acetaminophen was reduced, as evidenced by a prolonged half-life and reduced elimination. The authors suggested monitoring drug levels to avoid toxicity in patients with severe PEM *(43)*. By contrast, in adults with milder PEM, acetaminophen toxicity was not greater than in subjects with normal nutritional status, even with coadministration of vitamin C *(23)*. Acetaminophen pharmacokinetics were unchanged during a 5-d 500 kcal/d deficit diet in six obese subjects and during a 13-d 1000 kcal/d deficit diet in three obese patients, in a cross-over design study *(44)*. Both of these studies in adults *(43,44)*, however, were seriously underpowered to detect a significant difference, if one existed.

The impact of moderate malnutrition in children with rheumatoid arthritis or rheumatic fever on salicylate pharmacokinetics was examined *(14)*. The biotransformation of

salicylate and its AUC were reduced, relative to normally nourished controls. The authors suggest kinetic modeling of salicylates in patients with even moderate malnutrition *(14)*.

3.6.2. ANTIMICROBIALS

3.6.2.1. Chloramphenicol. For the treatment of community-acquired pneumonia in Gambian children under age 5 yr, oral chloramphenicol was prospectively compared to trimethoprim-sulfamethoxazole in a randomized clinical trial *(45)*. In 111 children with marasmic malnutrition, the two antibiotic regimens performed similarly to normally nourished controls, with 16 treatment failures in each group. The 32 treatment failures were slightly more malnourished (weight 59.3% standard vs 60.7%) than the 79 treatment responders and had a higher percentage of positive blood or lung aspirate cultures (31 vs 13%, $p < 0.05$). Serum proteins were not measured *(45)*. This study illustrates the difficulty in separating the impact of malnutrition alone from that of concurrent infection.

In 33 Ethiopian children aged 0.6 to 6 yr, nutritional status was determined to be normal in 8, marasmus in 8, kwashiorkor in 8, and marasmic–kwashiorkor malnutrition in 9 children *(46)*. Chloramphenicol absorption was erratic, with 30% absorption in patients with marasmic–kwashiorkor and 44% with kwashiorkor. With kwashiorkor, the clearance of chloramphenicol was reduced to approximately half normal, the half-life prolonged and effective drug concentration increased. The authors suggest individual drug monitoring owing to the great interindividual variation in pharmacokinetics *(46)*.

Chloramphenicol clearance was reduced after its incomplete metabolism in malnourished Ethiopian children *(47)*. The 34 children, ranging in age from 9 mo to 10 yr, were screened into three categories of malnutrition. Fourteen were underweight with normal serum protein, 10 were marasmic with slightly reduced serum protein, and 10 had kwashiorkor with marked reduction in serum protein concentration. Unbound chloramphenicol and chloramphenicol succinate were increased in serum, particularly in those with kwashiorkor, where the albumin concentration was significantly reduced. Chloramphenicol monosuccinate clearance was reduced owing to limited nonrenal clearance, and the fraction of prodrug excreted unchanged in the urine ranged from 0 to 51% (median 17%). The AUC of chloramphenicol was doubled in the children with marasmus and tripled in those with kwashiorkor, relative to those who were underweight. The authors suggest that if drug monitoring is not possible, measurement of serum total protein may assist in screening for patients who need dosage adjustment *(47)*.

By contrast to the data with malnourished children, chloramphenicol metabolism was not significantly changed from controls with normal nutritional status in six undernourished adults *(48)*, despite a significantly lower albumin concentration (29.7 g/L vs 42 g/L in normals). Replication of this study in a larger cohort would help to clarify whether there really is no difference or perhaps the study simply lacked statistical power.

3.6.2.2. Gentamicin. Gentamicin, an aminoglycoside antibiotic with a frequent renal injury profile, is commonly used for Gram-negative coverage in pediatric practice *(49)*. In 11 malnourished 3- to 10-mo-old infants, gentamicin was metabolized and eliminated normally, but its volume of distribution was increased, likely because of increased total body water, which had replaced muscle mass with starvation *(49)*. In a second group of six malnourished children aged 4–14 yr, gentamicin was reported as not different from normally nourished controls *(50)*. The half-life was almost doubled, the clearance nearly halved, and the maximal concentration increased 20%. The number of subjects was very

limited and the standard deviations very large, thus these differences were not statistically significant *(50)*. In a third group of six children with severe kwashiorkor, adequate gentamicin concentrations were achieved, although its half-life was prolonged *(51)*. Nutritional rehabilitation was associated with normalization of gentamicin half-life—a surrogate marker for clearance *(51)*.

In 86 critically ill adult patients, those who had malnutrition (defined as low albumin and >15% weight loss) were treated with parenteral nutrition *(52)*. These malnourished patients had increased volume of distribution with gentamicin, relative to patients without malnutrition, who received intravenous fluids *(52)*. The suspected mechanism was the expanded extracellular fluid space due to hypoalbuminemia, although total fluid intake or output was not controlled for in this study. The clearance of gentamicin, however, was not significantly changed. The authors advised to monitor gentamicin drug levels in critically ill patients to ensure adequate serum concentrations while avoiding nephrotoxicity.

3.6.2.3. Broad-Spectrum Antibiotics. Malnutrition has negative impact on wound healing and resistance to infection. In a prospective, randomized clinical trial of 302 adult surgical patients undergoing contaminated procedures, the benefit of prophylactic broad-spectrum antibiotics (clindamycin and gentamicin just prior to, 8 h after, and 16 h postprocedure) on wound infection was evaluated relative to nutritional status *(53)*. With a liberal definition of malnutrition (albumin <30 g/L, total iron-binding capacity <220 mg/dL, or weight loss >10% of usual weight), 51.7% of patients were malnourished. The malnourished patients experienced reduced wound infections in response to antibiotic prophylaxis (19.7% with wound infection if no antibiotic prophylaxis vs 6.2% with antibiotics, $p < 0.01$). This finding was associated with a significant reduction in length of hospital stay in malnourished patients (25.0 ±15.3 without vs 19.5 ±9 d with prophylactic antibiotics, $p < 0.05$). The patients who did not have malnutrition, however, received no significant benefit in terms of wound infection or length of stay *(53)*. This trial underscores the morbidity and health care costs associated with malnutrition.

3.6.2.4. Penicillin. Penicillin is easily absorbed, not metabolized, and renally eliminated *(43,54)*. In children with severe PEM, penicillin half-life was increased and renal filtration reduced, compared to normal controls. Both parameters normalized after nutritional rehabilitation *(43,54)*.

3.6.2.5. Sulfadiazine. Sulfadiazine is 50–55% protein bound and acetylated in the hepatic cytosol *(43,54)*. In six children with PEM, the rate of drug absorption was reduced, as evidenced by peak blood levels occurring 4–8 h later than in normally nourished controls. Free drug was eliminated at normal rates, but acetylated drug elimination was reduced, likely owing to limited biotransformation in the malnourished liver. In six undernourished adults *(55)*, sulfadiazine absorption and renal excretion were unchanged, although its metabolism was increased and protein binding reduced (40 vs 54% in normal controls). Therapeutic doses were achieved, however, so specific monitoring was not recommended *(55)*.

3.6.2.6. Tetracycline. Tetracycline is not biotransformed and is excreted as free drug in the urine *(56)*. Tetracycline pharmacokinetics in eight malnourished adults were compared to those of six well-nourished controls *(56)*. Oral drug absorption was reduced and the elimination rate increased *(56)*. The authors proposed reduced protein binding (albumin was significantly lower in the malnourished) as the most likely mechanism, and

suggested more frequent dosing interval in order to obtain therapeutic drug concentrations *(56)*.

3.6.3. ANTI-GOUT AGENTS

The impact of dietary protein and caloric intake on the clearance of allopurinol and its metabolite oxypurinol has been examined in a series of small cross-over studies of normally nourished men. Caloric intake had no significant impact on allopurinol or oxypurinol clearance, with observations ranging from 2600 kcal *(57)*, 1600 kcal *(59)*, to 400 kcal *(60)*. Allopurinol clearance also was not influenced by protein intake, but oxypurinol clearance was reduced during periods of limited protein intake *(57–60)*. Protein intake ranged from 3 g/kg/d to 0 g/kg/d. Clearances of inulin, creatinine, and oxypurinol were reduced on the low protein diet treatment (0.3 or 0 g/kg/d) vs higher protein intake (1.5–3 g/kg/d). No changes in allopurinol absorption, metabolism, or excretion were noted, but the clearance of oxypurinol was greatly reduced on the low protein arm *(58)*, and its half-life increased *(59)*. Although these four studies each involved a small number of subjects (five to seven each) and were conducted by the same group, the consistency of the data are reassuring, and suggest increased risk of toxicity with allopurinol use during periods of limited protein intake.

3.6.4. ANTIMALARIALS

Chloroquine pharmacokinetics were measured in eight malnourished adults with mean albumin concentrations of 30 g/L vs seven normal controls with albumin 37 g/L *(61)*. Drug half-life and distribution were unchanged, but clearance was significantly increased. Similar therapeutic concentrations were achieved, and no increased toxicity was observed, though this trial was subject to type II statistical error.

3.6.5. ANTITUBERCULARS

INH is acetylated by the liver. INH absorption was not impaired, but acetylation was slowed in 31 children with PEM *(62)*. The frequency of hepatotoxicity (as evidenced by transaminitis and jaundice), in a cohort of 130 children with PEM followed for 3.5 yr, was increased threefold relative to normally nourished controls *(28)*. Hepatic toxicity was not significantly impacted by acetylator status *(28)*. In 13 South African children with tuberculous meningitis, baseline PEM was generally improved after 6 mo treatment with nutritional supplementation and a four-drug regimen (20 mg/kg INH, 20 mg/kg rifampicin, 30 mg/kg pyrazinamide, and 20 mg/kg ethionamide) *(63)*. INH concentration and systemic elimination did not change after nutritional rehabilitation, although slow, intermediate, and fast acetylators were noted *(63)*. The differences in hepatotoxicity reported by these two studies may reflect the impact of treatment time (6 mo vs 3.5 yr) and statistical power derived from larger subject numbers.

In eight undernourished adults, who were free of tuberculosis, the peak plasma concentration, AUC, and protein binding of rifampicin were significantly reduced but the half-life was unchanged and renal clearance increased *(64)*. In 10 other undernourished adults who had tuberculosis, the AUC and protein binding were reduced further, and γ

glutamyl transferase levels elevated *(64)*, suggesting that toxicity risk may increase with the combination of malnutrition and disease.

3.6.6. DYSPEPSICS

The impact of a 7-d, 1000-kcal deficit, 0.3 g protein/kg diet on pharmacokinetics of a single intravenous dose of cimetidine was measured in a cross-over design with a group of five normal volunteers *(65)*. Although cimetidine renal clearance was unchanged, fractional excretion of the drug was significantly increased, suggesting net tubular secretion of the drug during the protein- and calorie-restricted diet.

4. LIMITATIONS OF CURRENT DATA

The greatest limitation in currently available data is the dearth of trials comparing the impact of malnutrition on drug action, which leaves health care providers with limited evidence on which to base practice decisions. Many available studies have examined antibiotics, such as chloramphenicol and tetracycline, that are less commonly used today—whereas a broad spectrum of newer drugs are in current use with no data on the impact of malnutrition on their action.

The quality of clinical trials is somewhat limited. For ethical reasons, prospective randomized controlled trials of a drug vs placebo in a malnourished cohort with an indication for the drug in question cannot be undertaken. Thus, available data are largely from case-control or open-label observations, study designs that are prone to bias. Because both malnutrition and infection can independently impact hepatic protein synthesis and fluid shifts, a further confounder is the difficulty in independently evaluating the impact of infection from that of malnutrition. A further difficulty is finding large enough cohorts of patients with similar degrees of malnutrition to power a comparison of one drug to another.

In the realities of clinical practice, malnutrition proceeds along a continuum that begins with mild, short-term deficits and can progress to severe, protracted losses of fat, muscle, and organ function, ending in death. The preponderance of data regarding malnutrition and drugs is from these more extreme degrees of PEM. The few studies with underweight but not wasted children and with critically ill adult patients in conditions of severe metabolic stress, suggest that drug distribution and metabolism may be impacted by lesser degrees of malnutrition. Thus, we have limited data on which to make decisions about the risk and effectiveness of drug therapy, based on malnutrition.

For clinical purposes, it would be most helpful to see future evaluation of medications using malnutrition (and obesity) stratifications by universally accepted standards, such as the WHO/NCHS *(1)* standards for children and National Heart, Lung, and Blood Institute body mass index categories for adults *(66)*. Clinical trials and bedside practice will continue to use height and body weight as surrogates for the much more difficult to obtain body composition measures of metabolically active tissue.

Simple, inexpensive, and rapid feedback methods for monitoring drug concentrations in the field or primary provider's office would be very helpful in high-risk patients. Noted

discrepancies with findings should be reported in order to encourage continued discussion of the topic.

5. FUTURE RESEARCH NEEDS

Clinical trials with pharmacokinetic modeling of representative members of drug classes are needed in large patient groups with varying degrees of protein and calorie malnutrition. Trials are also needed in cases with single nutrient deficiencies, particularly those that impact on major metabolic pathways.

Animal experiments should be undertaken with measurement of total body water, fat and protein compartments during PEM and various levels of obesity—to clarify some of the difficult questions regarding drug distribution, sequestration into body compartments, and protein binding. Animal models also could provide a clean experimental evidence base for drug handling during single nutrient deficiencies.

Because critically ill patients in current hospital practice have considerable rates of nutritional risk at admission, and nutritional status can worsen during prolonged hospital care, pharmacokinetics studies are indicated in patients with varied levels of metabolic stress so that the concurrent impact of nutritional status on drug effectiveness can be evaluated. Data on the impact of concurrent feeding with enteral or parenteral nutritional support in patients with various levels of malnutrition and clinical stressors are sorely lacking, and have the potential to radically change medical practice.

6. CONCLUSION AND CLINICAL RECOMMENDATIONS

First and foremost, all patients who are ill enough to require medications should be screened for malnutrition, using standard parameters. The components of this evaluation, as a minimum should include evaluation of body weight relative to standards, of serum protein status, and the likelihood of nutrient deficiencies due to dietary practices. Because all health care facilities in the United States are required to have a process in place for nutritional screening, it may be possible to obtain a report from the facility's systematic evaluation of patients who are at nutritional risk.

Second, the available research is fairly consistent at recommending the advisability of monitoring for drugs with a narrow safety profile in high-risk patients owing to their malnutrition. With the huge prevalence of malnutrition in various clinical states (e.g., cancer, HIV, geriatrics, etc.) and clinical settings (intensive care units, skilled nursing facilities, nursing homes, chemotherapy centers), this could be an impossible task. To be successful in this effort, inexpensive, and widely available drug-monitoring systems for field, clinic, and even home use will need to be developed.

Clearly, because malnutrition alone can lead to death, efforts should be maximized to minimize time delay in using medications effectively in patients with concurrent malnutrition.

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6 Influence of Obesity on Drug Disposition and Effect

Joseph I. Boullata

1. INTRODUCTION

Differences in drug responses between patients are a result of many potential sources of variability. These may include age, gender, genetics, and disease states—both acute and chronic. Included in the latter are states of altered nutritional status. Providing appropriate therapeutic drug monitoring requires an understanding of the influence of these factors on drug disposition and effect *(1)*. In order to make better use of invaluable medications, altered drug effect needs to be explained or, better yet, predicted prior to use. A better understanding of the influence of obesity on drug disposition and drug effect may lead to more measured use of medications in this group of individuals.

1.1. Definitions and Prevalence of Obesity

Obesity is a chronic disorder with a complex pathophysiology involving genetic and environmental factors, which ultimately impact the balance between energy intake and expenditure, and manifests as excess body fat. It is associated with significant risk of morbidity and mortality, as well as increased health care costs, and reduced quality of life. Morbidity includes diabetes, which has seen a 61% increase in prevalence since the early 1990s and is expected to accelerate as the obesity epidemic continues *(2)*. Obesity is considered a major risk factor for coronary heart disease and the second leading cause of preventable death in the United States after tobacco use *(3,4)*. The risk of comorbid disease (e.g., diabetes, heart disease, hypertension, dyslipidemia) is tied to the degree of obesity.

Excessive body weight is best described by the body mass index (BMI)—an expression of an individual's weight relative to height, in kilograms per meter squared (kg/m^2). Obesity, as a disorder of excess body fat (including that stored in the midsection), is best defined in terms of the BMI and waist circumference for adults (Table 1) *(5)*. The BMI and waist circumference are closely linked to health risks associated with overweight (BMI ≥ 25) and obesity (BMI ≥ 30) *(6,7)*. Morbidity increases at a BMI of 25 or greater, although this may vary with specific populations. The BMI has been adequately com-

Table 1
NIH Classification of Overweight and Obesity in Adults

| | | *Relative Disease Risk* | |
| | *BMI* | *Men—WC ≤ 40"* | *> 40" (102 cm)* |
Class	*(kg/m²)*	*Women—WC ≤ 35"*	*> 35" (88 cm)*
Normal	18.5–24.9	—	—
Overweight (pre-obese)	25–29.9	Increased	High
Obesity I (moderate)	30–34.9	High	Very high
Obesity II (severe)	35–39.9	Very high	Very high
Obesity III (morbid)	≥ 40	Extremely high	Extremely high

From ref. *5*. BMI, body mass index; WC, waist circumference.

pared to direct measurements of body composition *(8)*. Definitions of obesity used in drug investigations often rely on an arbitrary weight cutoff relative to an idealized weight (e.g., actual weight ≥ 120% of "ideal" weight). This can be problematic without a standard definition, or a substantiated reference weight that could provide a more rational basis for classifying individuals in these studies. An evaluation of various reference weights is discussed in the next section.

Definitions of obesity in children have been less well defined, but age and gender cutoff values for BMI linked to adult definitions have been proposed *(9)*. The issue in children revolves around how much adiposity is necessary for, and at what point is it excessive during, growth. The recent linking of percent body fat data with BMI can allow for study of relationships between body composition and morbidity in children *(10)*. Up to this point, obesity has been defined somewhat arbitrarily by the percentile ranking of BMI within the population distribution, such that a BMI between the 85th and 95th percentiles indicates overweight, and above the 95th percentile indicates obesity *(11)*.

Using these definitions, the prevalence of obesity continues to climb across all age groups. Current estimates are that 65% of American adults are overweight (34%) or obese (31%) *(12)*. This translates to more than 100 million adults in the United States making it the most prevalent chronic disease. Morbid obesity (BMI ≥40), associated with the most severe adverse health consequences, has nearly tripled since the 1990s *(13)*. Both overweight and obesity are also highly prevalent in children and adolescents with rates continuing to rise *(14)*. The rates of obesity are reported to be 10.4 to 15.3% in children and 15.5% in adolescents in the United States *(15)*. The National Health and Nutrition Examination Survey (NHANES) data suggest that childhood obesity has doubled, while the rates have tripled for adolescents in a span of 20 years *(15)*. This trend of increasing prevalence of obesity in adults and children is present outside the United States as well *(16–18)*.

Given the higher risk of morbidity in obese individuals, higher health care needs, including the use of medications is expected. The difficulty in addressing appropriateness of medication regimens in obese patients is in part based on limited drug-specific data and on varying clinical approaches to describing or even recognizing obesity.

1.2. Assessing Body Weight for Drug Dosing

Although not perfect, the most valid and practical indicator of obesity is the BMI. This tool gained universal approval and was recommended for use in determining body habi-

tus and risk for morbidity and mortality a number of years ago *(19,20)*. BMI is the best predictor of the effect of body weight on health risks, but is not easily adapted, and therefore has been considered of little practical use, for the dosing of medications. Although weight-based dosing of a drug is less likely to be problematic at a BMI of less than 30, in obesity, the use of a patient's actual (i.e., total) body weight may be inappropriate and can increase the risk of adverse effects. But something as basic as which weight should then be used for drug dosing in obese individuals has been fraught with controversy. Numerous dosing terms and predictive equations have been used (Table 2). The term *dosing weight* is universally acceptable whether referring to an actual total body weight, or an alternative body weight—as one would consider in volume overloaded or obese patients. The derivation of the best dosing weight for use in obesity is unclear. Adjusting a body weight for dosing in obesity will depend on the substance (e.g., creatinine, nutrient, drug) being evaluated or dosed and how it is handled differently, if at all different, in obesity. Dosing may be based on the total body weight (TBW) or on the lean body weight (LBW) or on some adjusted weight in between the other two depending on the drug. The terms used to describe body weight in this chapter refer to their original descriptions as summarized in Table 2 *(21–25)*. The reader is encouraged to appreciate the differences between the equations by calculating each body weight term using their own data.

The life insurance tables, from the earliest versions to those of 1983, are the source of the terms "ideal" and "desirable" body weight. They were derived from data on low-risk, otherwise healthy, young persons able to afford life insurance as collected beginning in the 1930s *(26–29)*. These data from a limited population sample describing an "ideal" or "desirable" weight for a given height are also reflected in a simple-to-use regression equation derived from those tables *(21)*. The weight-for-height provided in the insurance tables, or by the equation based on those tables, is not an "ideal" to be aimed for, is not representative of the general population, and is not necessarily of any value to drug dosing in obese patients. Additional predictive equations for "optimum" body weight and for LBW have been described and continue to be widely used *(22,23)*.

The "optimum" weight equation was described for diabetic persons with a medium-sized frame for use in determining an approximate caloric requirement *(22)*. The suggestion was made to increase by 10% for patients of "heavy" frame, and decrease by 10% for those of a "light" frame. As can best be determined, this equation is empirically derived but considered adequate for its intended purpose in clinical practice. In a case report discussing gentamicin toxicity, the size of the daily dose as a function of body weight was described *(23)*. The weight used to estimate creatinine production was critical in determining creatinine clearance and hence drug dosing. The suggestion was made to use LBW, with obese patients requiring an adjustment in TBW to derive their lean weight, based on an empiric equation. This equation is one of the most frequently cited for determining a patient's LBW despite not being based on any actual subject measurements *(21,23)*. The optimum and LBW values derived through these two equations have even been improperly referred to quite often as "ideal" body weight. However, the very concept of "ideal" body weight was questioned years ago in well-supported and valid critiques *(20,30,31)*.

Even though ideal body weight may correlate with BMI in overweight and possibly in level I obese individuals, this has not been shown true at all levels of obesity *(32)*. But

Table 2
Equations for Estimating Body Weights

Body Weight Term	Equation for Men	Equation for Women
Ideal weight	52 kg + 1.9 kg/in > 5 ft	49 kg + 1.7 kg/in > 5 ft
Optimum weight	106 lbs + 6 lbs/in > 5 ft	100 lbs + 5 lbs/in > 5 ft
	[48.2 kg + 2.7 kg/in > 5 ft]	[45.5 + 2.3 kg/in > 5 ft]
Lean weight	50 kg + 2.3 kg/in > 5 ft	45.5 kg + 2.3 kg/in > 5 ft
Body cell mass	$\dfrac{(kg)[79.5 - (0.24)(kg) - (0.15)(y)]}{73.2}$	$\dfrac{(kg)[69.8 - (0.26)(kg) - (0.12)(y)]}{73.2}$
Lean Mass	(1.1013)(kg) − (0.01281)(BMI)(kg)	(1.07)(kg) − (0.0148)(BMI)(kg)

From refs. *21–25*.

kg, kilogram of body weight; in, inches; ft, feet; lbs, pounds; y, years of age; BMI, body mass index in kg/m^2.

more to the point, if the purpose is to (a) define a reference "normal" weight with which to compare obese individuals, and to (b) derive proposed dosing adjustments for obese subjects, then several factors beyond height and weight need to be considered. To be of most value, a reference weight should be based on actual height/weight data from a representative sample of the entire population, or better yet, should be based on the body composition of a reference sample. External measures of obesity (i.e., BMI) remain more practical than obtaining body composition data, however, the latter should be used to better define parameters in studies of drug disposition. Body composition is likely much more important for this purpose than height and weight alone. Age and gender influence body composition and should be taken into account in determining "normal" expected body weights. Age and gender influence lean tissue, which in turn influences metabolic rate *(24)*. Having dispensed with "ideal" weight as a reference point for patients, a focus on lean body mass is needed.

Equations for lean body mass and body cell mass have been described. The equations take into account age and the greater absolute lean body mass found in obese patients *(24,25)*. A proportion of the sample populations used to derive these equations were in fact obese, although the numbers of morbidly obese patients were small *(33)*. It has been suggested that the lean body mass equation *(25)* may under predict true lean body mass of the morbidly obese subject *(33)*. This may require revisiting the data in order to readjust the constants *(33)*. Regardless, this remains the only equation that takes BMI into account. It is proposed that this equation best reflects lean body mass—until further body composition analysis yields a more accurate predictive equation or population-specific equations *(34)*. The lean body mass from this equation should be used as the reference standard, for the true LBW, on which to compare TBW between obese and nonobese individuals for the purposes of understanding drug disposition. Either in its original format or the more condensed form below *(35)*, where TBW is the total body weight in kg and Ht is the height in cm:

$$\text{Men: } (1.10)(TBW) - (120)(TBW/Ht)^2$$

$$\text{Women: } (1.07)(TBW) - (148)(TBW/Ht)^2$$

It is hoped that improved equations will be developed based on more recent data from a more diverse population coincident with body composition. This data may be available from a broad national sample *(36)*. Such body composition data may be helpful in addressing the dosing issues of obese individuals. Depending on body composition, the distribution of a drug under study can be identified and corrections to body weight can be inferred. In this way, a dosing weight is based on the drug rather than relative to a standard weight for height. Dosing weight correction factors have been used to adjust body weight to a value between the TBW and LBW for dosing, although most have not been systematically studied. The general equation often used to adjust body weight is:

$$DW_{OB} = LBW + (CF)(TBW - LBW)$$

where DW_{OB} is dosing weight for obesity, LBW is the lean body weight, CF is a correction factor, and TBW is the total body weight. The LBW will vary depending on the method used to determine it—but again the lean body mass equation is suggested *(35)*. After all, the distribution of body fluid is related to the lean body mass, and overall metabolic activity is also associated with the lean body mass. If a single dosing weight correction factor is used for all obese patients, instead of being individualized to the drug being administered, some drugs may be significantly underdosed, whereas others may be given in overdose. The correction factor is a fraction of the "fat" weight (i.e., beyond LBW) that normalizes the volume of distribution in an obese patient to that in a nonobese patient. Data is based on the excess weight beyond the predicted LBW with which a drug's pharmacokinetic characteristics are best correlated. This relationship is rarely, if ever, correlated to a patient's actual lean body mass. What was not recognized early on, and has carried forward virtually unaddressed by continual use of ideal body weight, is that not only is it not necessarily physiological, but excess weight is more than just adipose tissue and the composition varies between obese subjects. Unfortunately, there is not an abundance of body composition data. In general, nonobese, middle-aged adults have a fat mass of about 20 kg that corresponds to about 25% of TBW in men and about 33% of TBW in women. Obese individuals have, on average, a larger lean body mass than their nonobese peers, accounting for 20–40% (mean 29%) of the excess weight in obesity *(37)*. In other words, as much as 60–80% of the excess weight in obesity may be adipose tissue.

Unfortunately, most pharmacokinetic studies in obesity make use of predictive equations without the benefit of actual body composition data. In dosing medications, most clinicians make general assumptions for the dosing weight in obese patients focusing on the excess fat. But it is the lean body mass that correlates well with total body water—including the central compartment, metabolic activity, and can be correlated with drug clearance. Clinicians need to keep in mind that obesity can influence the tissue distribution of a drug, its clearance, and its clinical effect. However, this occurs not simply because of excess fat mass, but because of other physiological changes. This translates into modified dosing strategies for initial and maintenance doses. This is especially important for medications for which minimal effective concentrations or narrow therapeutic indices exist.

Although from a practical standpoint medications that follow weight-based dosing in adults warrant important consideration in obesity, understanding the broader impact of obesity on drug disposition and effect to explain or predict drug effects in obesity is stressed.

2. BASIC SCIENCE

A review of how obesity impacts drug absorption, distribution, metabolism, excretion, and action should be based on the available scientific data. It is interesting to note the discrepancy that exists across the study of obesity. Despite major improvements in the understanding of the societal, economic, pathological, and clinical outcomes of obesity, there remains only limited study of pharmacokinetics and pharmacodynamics in this disorder at the current time *(35)*. One should understand that it is not a simple task in any human study to clinically assess pharmacokinetics and pharmacodynamics. In hepatic drug metabolism, for example, blood flow, protein binding, and tissue binding are each important factors that need to be taken into account and are also each difficult to assess. Many of the assumptions made may not always be accurate for obese individuals. In fact, persons with obesity can be considered quite a heterogeneous group. Subjects with a BMI of 30–35 may be quite different than those with a BMI of 45 and greater. A given BMI cannot differentiate the degree of fatness between individuals *(38)*. Indeed, within a group of individuals at the same BMI, there may be differences in body composition that ultimately influence drug distribution and clearance.

Variability in fat mass may occur with a number of factors. Fat mass increases as individuals age. Gender is also a factor, with women having higher body fat mass than men in general. Inactive individuals are likely to have higher fat mass than those who are more active. Ethnicity can also be a factor with individuals of Native American, Hispanic American, and Asian heritage more likely to have higher percent body fat than Caucasians, who in turn may have higher percent body fat than Africans or Polynesians *(39–42)*. Percent body fat may differ between individuals of the same BMI *(39,42)*. Even the anatomic distribution of that fat, including the blood flow to those depot sites, may vary by gender and ethnicity *(43)*. Each of these variables will need to be accounted for in future study of the influence of obesity on drug disposition and effect. Anatomic and physiological changes that occur with obesity may impact on a drug's absorption, distribution, and elimination through metabolism or excretion.

2.1. Absorption

Altered gastrointestinal (GI) transit time and a higher splanchnic blood flow may modify drug absorption including a reduction in the bioavailability of drugs with high extraction ratios. However, the limited data suggest that oral drug absorption including drugs with higher extraction ratios may be no different in obese individuals (e.g., cyclosporine, dexfenfluramine, midazolam, penicillin, propranolol) *(44–47)*. Absorption from transdermal or subcutaneous administration is not well characterized in obesity. Intramuscular injection in many cases may be better characterized as intralipomatous, which has not been well studied either.

2.2. Distribution

The distribution of a drug throughout the body following absorption is determined by several factors—some related to the drug (e.g., lipophilicity, degree of ionization), others related to the body (e.g., blood flow, tissue-binding sites). Plasma-protein binding, body composition, tissue size, tissue permeability, and drug affinity for various tissues each determine a drug's distribution. Knowledge of body composition, regional blood flow, and plasma-protein binding is necessary.

2.2.1. BODY COMPOSITION

Obese subjects have a larger fat mass and a larger lean body mass in absolute terms compared to nonobese individuals of the same age, height, and gender. In relative terms, lean tissue as a percent of TBW is reduced, whereas percent adipose tissue mass is increased. In other words, not all the excess weight in obesity is made up of fat relative to the nonobese individual. The extra lean tissue makes up about 20–40% of the excess weight, about 29% on average across a BMI range of 29–47 *(37)*. This increase in lean body mass does not hold for patients with obesity associated with Prader-Willi syndrome or Cushing's syndrome *(37)*. Weight-based drug dosing would need to take into account the relative distribution into various tissue compartments. Total body water in obesity was estimated to include approx 30% water content in excess tissue *(48)*. Although lean body mass may be determined through bioelectrical impedance analysis or whole body densitometry, neither of these is yet clinically practical across all settings. An equation that at least takes gender, weight/height, and BMI into account allows an estimate of lean body mass (see Subheading 1.2.).

2.2.2. BLOOD FLOW

There are increases in blood volume, cardiac output, and organ mass in obesity that also can influence drug distribution. The proportion of cardiac output that reaches the adipose tissue is relatively small (~5%) compared with the blood flow to lean tissue and viscera, and might be reduced further with increasing degrees of obesity *(49,50)*. Adipose blood flow may actually be less in morbidly obese individuals compared to the moderately obese or thin *(51)*.

2.2.3. PROTEIN BINDING

Drugs can bind to several circulating proteins—albumin, α_1-acid glycoprotein, and the lipoproteins. Albumin concentrations do not appear to be altered as a result of "moderate" obesity, whereas α_1-acid glycoprotein levels are increased *(52)*. This suggests an inconsistent alteration in drug affinity in obese individuals. The effect that obesity has is more likely on α_1-acid glycoprotein than on albumin, thereby decreasing the unbound fraction of basic drugs in some but not all instances *(52–54)*. Drugs bound to α_1-acid glycoprotein may exhibit lower free drug concentrations (e.g., propranolol), or no change in free drug levels (e.g., triazolam, verapamil), whereas the free level of drugs bound to albumin do not appear to change (e.g., phenytoin, thiopental). Despite little difference in serum albumin concentrations in obese individuals, there may be increased binding of fatty acids to the albumin molecule, thereby potentially altering drug-binding sites. The clinical significance of any changes is unclear. The associated tissue binding that may determine the clinical relevance of alterations in unbound plasma drug concentration is not known. There are a balance of drug affinities between tissue components and plasma proteins that ultimately determine clinical significance. Alterations in the concentration of, or affinity for, plasma proteins may influence drug availability to the tissues where it may be active or may instead be cleared. It may come down to the competition between a drug's binding characteristics in vivo between lean tissue, transport proteins, and adipose tissue. Lipoprotein levels can also be elevated in obese individuals potentially impacting on pharmacokinetics and effect (e.g., cyclosporine) *(55,56)*. The potentially altered tissue perfusion and tissue binding has not been well studied in obesity.

2.2.4. Summing Up Distribution

It may be expected based on body composition that lipophilic drugs have a larger volume of distribution in obese patients. Although this is sometimes the case (e.g., bisoprolol, diazepam, thiopental), it is not always so (e.g., cyclosporine, digoxin, procainamide). Hydrophilic drugs may actually have a larger volume of distribution (e.g., aminoglycosides, ampicillin, cefamandole, cefotaxime, ciprofloxacin, nafcillin) or a similar volume of distribution (e.g., cimetidine, ranitidine) in obese patients. A point to remember is that a drug's lipophilicity, based on its oil-to-water partition coefficient, is only one of several characteristics of a drug and unlikely to be the driving factor to overcome other factors (e.g., blood flow, in vivo binding competition) in determining drug distribution on its own *(57,58)*. Lipophilic agents do not necessarily have larger distribution volumes in obese individuals and some may not even be stored in adipose tissue *(59)*. Distribution of a hydrophilic drug into adipose tissue or into the excess lean tissue that supports the excess fat mass may need to be taken into account for dosing. Most hydrophilic drugs distribute to a limited degree into excess adipose tissue, but may distribute into excess lean tissue. Besides increases in fat and lean body mass, obesity is associated with increases in organ mass, cardiac size and output, blood volume, and regional flow. Even polar compounds may not behave similarly with regard to volume of distribution and body weight *(58)*. Antipyrine distributes into body water and exhibits a slightly higher absolute volume of distribution in obese subjects (predicted by a higher *absolute* body water in obese subjects), but significantly reduced volume of distribution when corrected for TBW (predicted by a lower *relative* body water) *(32)*. This important point suggests that comparisons of drug distribution between obese and nonobese individuals should be done on the basis of TBW. That is, the volume normalized to TBW rather than the absolute volume of distribution. A decreased volume of distribution when normalized to TBW indicates a drug that distributes less into the excess adipose tissue. This indicates that antipyrine distributes into the excess body weight above the estimated LBW by a factor of 30%, which incidentally correlates with estimates of excess lean tissue.

2.3. Elimination

The elements that determine elimination of a drug, whether through metabolism or excretion, may be altered in obese individuals. Increased cardiac output, fatty infiltration of the liver, portal inflammation and fibrosis, increased renal plasma and creatinine clearance are all known to occur in obesity *(60–62)*.

2.3.1. Hepatic

The fatty infiltration of the liver could affect hepatic metabolic activity. Fatty infiltration of the liver is more severe with increasing BMI, and may impact on the organ's metabolic activity. Using antipyrine as a marker of hepatic oxidative enzyme function, drug half-life was increased in obese individuals compared to lean volunteers *(63)*. However, this was because of an increased apparent volume of distribution, although no change in drug clearance was observed *(63)*. The volume of distribution for antipyrine corrected for TBW is significantly reduced in obese patients given distribution limited to lean tissue (described in Subheading 2.2.4.) *(63)*. Given the multiple pathways by which antipyrine can be metabolized, it is not clear whether there is actually no change

in activity of any specific pathway, or whether the measured effect is the resultant net effect across pathways—some increased, others decreased. Drugs that undergo significant first-pass hepatic extraction appear to have similar rates of clearance in obese compared to nonobese individuals indicating that hepatic extraction is not dependent on body weight. Some, but not all, drugs that undergo hepatic oxidation and conjugation may have increased clearance in obesity.

Hepatic drug clearance through phase I reactions may be increased (e.g., prednisolone), decreased (e.g., methylprednisolone, triazolam), or unchanged in obesity. This variability may be explained by specific enzyme activity. For example, the activity of CYP2E1 may be increased (e.g., chlorzoxazone), whereas CYP3A activity may be reduced or unchanged (e.g., erythromycin, cortisol) as body mass increases in obesity *(64–67)*. Markers for specific CYP3A isoenzymes will be necessary to differentiate the impact of obesity on each of them. Based on caffeine as a marker of CYP1A2, there appears to be no difference in activity of this isoenzyme between obese and nonobese individuals *(63)*. All told, there remains very little isoenzyme-specific data. Some phase II reactions may be altered. The activity of both glucuronide and sulfate conjugation appear to increase in obese individuals and may impact on drug clearance (e.g., lorazepam, oxazepam) *(69,70)*. On the other hand, activity of glycine conjugation or of acetylation does not appear to be altered by obesity *(71,72)*. Adipose tissue itself possesses metabolic capacity that may be increased based on the larger fat mass. Although the findings of altered metabolic enzymes from animal models of obesity are many, the extrapolation of each unique model (e.g., overfeeding versus genetic defect) to the human condition is considered poor *(73,74)*.

2.3.2. RENAL

Although using actual body weight may overestimate creatinine clearance predictions, and the empirically derived LBW underestimates it, a 30% adjustment appears to be the best predictor, although requiring prospective confirmation *(75)*. This reflects the more metabolically active lean tissue, the source of creatinine, rather than renal capacity. Generally, renal drug clearance can be increased in obesity (e.g., aminoglycosides, cefamandole, cefotaxime, cimetidine, ciprofloxacin, lithium, procainamide). This is partly a result of increased glomerular filtration, whereas indirect evidence suggests that tubular secretion is also increased thereby further affecting renal drug clearance in obesity *(72,76–78)*. Increased drug clearance is the result of increased tubular secretion (e.g., cimetidine, ciprofloxain, procainamide) and reduced tubular reabsorption (e.g., lithium). Increases in glomerular filtration as measured by creatinine clearance can be increased in obese individuals *(62,79,80)* but have also been reported to be unchanged in some obese patients *(76,81)*. The reasons for this discrepancy are not clear but may relate to variability in body composition (i.e., actual lean body mass) and in renal dysfunction among the various obese subjects and patients.

2.4. Drug Effect

Even if, after taking any pharmacokinetic changes into account, a normal drug concentration is achieved and delivered to the site of action in an obese patient, the clinical effect of the drug may still be other than expected. This may occur with alterations in target-tissue sensitivity, whether at the level of the drug target or a downstream effect. There

may be increased sensitivity to some drugs (e.g., glipizide, glyburide, prednisolone, triazolam) *(54)* and decreased sensitivity to others (e.g., atracurium, verapamil) *(82)*. Receptor expression or affinity may be altered. The drug effect may be more pronounced, including toxic effect, as an extension of pharmackokinetic variables or pharmacodynamics, but is poorly predictable *(83)*. Given the wide number of genes and loci implicated in obesity *(84)*, whether owing to mutations, phenotypic associations or linkages, the possibility exists for associations or overlap with genetic markers of drug metabolism or drug response.

2.5. Integrating the Data/Approach

Loading doses of a drug will be based on information about a drug's volume of distribution as it relates to TBW (L/kg) (or body composition when possible). On the other hand, maintenance doses will be based on the total clearance of the drug from the body (L/h) as documented in obese subjects or patients. When volume of distribution is normalized to TBW the extent of drug distribution into the excess weight, which is of mixed composition, beyond the LBW, has given rise to the figures (correction factors) used to adjust the body weight. This, however, assumes that the subject's LBW is correctly estimated, and that excess tissue is adipose alone. This being the case, there should be no significant difference in values between men and women. However, the degree of distribution into the excess weight above the predicted ideal or lean weight, is reported to differ for the hydrophilic analgesic acetaminophen with men having an apparently higher distribution into the excess tissue *(85)*. This would be accounted for by the higher proportion of lean tissue in men, including more lean tissue in the excess weight above the predicted lean weight.

Therefore, the ratio of TBW-normalized volume of distribution in obese subjects to that in nonobese subjects can help guide which body weight should be used for weight-based loading doses:

V_D/kg TBW_{OB} : V_D/kg TBW_{Non-OB}	Dosing Weight
≥ 1	Actual TBW
0.7 up to 1	An adjusted body weight
<0.7	LBW

For example, the volume of distribution for vecuronium is about 0.5 L/kg TBW in obese patients and about 1 L/kg TBW in nonobese individuals. The ratio of the value in obesity to the value in controls is 0.5 ($0.5 \div 1$), suggesting the use of LBW for the loading dose of this drug. And a similar approach using total body clearance may be possible in guiding which body weight should be used for weight-based maintenance doses in drugs whose activity throughout the dosing interval is concentration dependent:

$Cl_{T\,OB}$: $Cl_{T\,Non-OB}$	Dosing Weight
≥ 1	Actual TBW
< 1	Adjusted or LBW

For example, the clearance for vecuronium is about 16 L/h in obese patients and about 20 L/h in nonobese individuals. The ratio of the value in obesity to the value in controls is about 0.8 ($16 \div 20$), suggesting the use of adjusted or LBW for the maintenance dose

of this drug. Of course, data from well-designed studies examining drug-specific volume of distribution and clearance, as well as drug effect between obese and nonobese individuals will provide the best guidance compared to the empiric advice presented here.

3. CLINICAL EVIDENCE

This section provides an overview of some of the drug-specific data available in the literature to help guide decision making in the pharmacotherapy of patients with obesity.

3.1. Anticonvulsants

The dosing of phenytoin can be complex enough in patients with a healthy BMI given the many factors that can impact on its disposition. In obesity, the volume of phenytoin's distribution is increased both in absolute terms and when normalized to TBW *(86)*. This indicates that the drug distributes especially into the excess adipose tissue of obese individuals. The significant distribution of phenytoin into adipose tissue sets the stage for potential redistribution from this site *(87)*. The data suggest that a loading dose for phenytoin should be based on an adjusted body weight using a correction factor of greater than 1, in other words dosing based on at least TBW. At the same time, the metabolic clearance of phenytoin appears to be increased in obesity *(86)*. This does have the potential to decrease following successful weight loss *(88)*. Conversely, obese individuals have a slightly reduced clearance of carbamazepine, which increases following reduction in body weight associated with increased physical activity *(89)*. Whether the increased clearance results from weight loss itself, a decrease in hepatic fat, or the effect of dietary changes on drug clearance is unclear. Along with a lower clearance, the volume of distribution of carbamazepine is lower in obese individuals when normalized to actual body weight, despite a higher absolute volume of distribution *(89,90)*. This suggests that an adjusted body weight may be used for initial dosing of carbamazepine in an obese patient, but that maintenance doses could be administered at longer intervals. Doses of phenobarbital should be based on TBW in order to achieve therapeutic concentrations in obesity *(91)*.

3.2. Antimicrobials

Dosing adjustments of antimicrobials as a class are rarely made based on body weight or degree of obesity, but are based instead on drug-specific data. This drug-specific information will determine whether adjustments should be made, or whether dosing should take actual, lean, or an adjusted body weight into account. A number of findings on the dosing of antimicrobials in obesity have been recently reviewed *(35,92)*. Much is based on the degree of drug distribution into lean and fat mass, and on the influence of obesity on drug clearance. Some studies have sought to optimize doses of moderately lipophilic antimicrobials in obese patients *(35)*. Based on a summary of the literature, recommendations for dosing have been provided. These recommendations include drug-specific correction factors for antimicrobials requiring dose adjustment in obesity *(35,92)*.

For β-lactam drugs, a correction factor of 0.3 is suggested for use in the dosing weight equation—although no clinical study data exist to support this. Using patients as their own control before and after intestinal bypass-associated weight loss, the volume of distribution for ampicillin decreased from 0.6 L/kg to 0.41 L/kg, indicating some distri-

bution into adipose tissue for this hydrophilic compound *(93)*. Although the absolute volume of distribution is increased for nafcillin, no significant difference is seen in the TBW-normalized volume of distribution or in total clearance in a morbidly obese patient *(94)*. This would imply the potential to dose nafcillin based on actual body weight, and the authors suggest dosing modification upward to 3 g q6h in obesity *(94)*. An area of concern is the preoperative dosing of antimicrobials to prevent postoperative infection in obese patients undergoing surgical procedures. A 1 g dose of cefazolin as antibiotic prophylaxis for surgery in patients with BMI greater than 40 resulted in serum concentrations below the minimal inhibitory concentration for several organisms *(95)*. An adjustment to 2 g cefazolin reduced surgical site infection rates from 16.5 to 5.6%, $p < 0.03$ *(95)*. Cephalosporin clearance may also be increased in obesity, requiring repeated dosing during an operation that lasts longer than 2–3 h *(96)*.

The aminoglycosides are quite similar to each other from a physicochemical standpoint, exhibiting comparable pharmacokinetic properties. This includes volumes of distribution that approximate the extracellular fluid volume. Obese individuals would be expected to exhibit increased absolute volumes of distribution given the increase in total body water, but lower values when adjusted for TBW. The typical weight-based dosing of aminoglycosides takes renal function into account in determining a dosing interval. Dosing aminoglycosides in obese patients using actual body weight can result in higher than expected serum concentrations, whereas LBW may result in subtherapeutic levels. A suitable correction factor for establishing a dosing weight that lies between lean and actual weights varies with the study and may differ with degree of obesity, and presence of infection. A well-recognized method for predicting gentamicin parameters is to use an adjusted dosing weight that incorporates only 40% of the excess weight—that is, a correction factor of 0.4 in the dosing-weight equation *(81)*. This would provide the basis for an initial dose of aminoglycoside. Given the variability in correction factors determined for aminoglycoside dosing in obesity *(97)*, it has been suggested that serum concentrations still be used to monitor the patients *(92)*. Aminoglycoside clearance is increased in obesity *(98–100)*. Renal clearance of aminoglycosides may be increased in obesity, but this may be balanced out with the increased volume of distribution, so that if an adequate dose is administered, no change in dosing interval is necessary. Larger doses of isepamicin are required in obese, as compared to lean, intensive care unit patients to achieve similar serum concentrations *(101)*. This is despite a slightly lower volume of distribution normalized to TBW, indicating some distribution into the excess adipose tissue.

Following single dose administration of vancomycin, volume of distribution was higher in morbidly obese patients compared to nonobese individuals *(102)*. The TBW-adjusted volume of distribution was lower in obese patients compared to control subjects. Clearance of vancomycin may be increased in obesity, but may be less pronounced at higher BMI *(79,80,102)*. However, the difference in clearance disappeared when normalized to TBW, suggesting that the actual TBW should be used for dosing vancomycin in obese individuals *(102–104)*. A recent case report of a patient with a BMI greater than 100 suggests that the TBW-adjusted volume of distribution was only slightly lower, and the clearance was only modestly elevated compared to values in nonobese patients *(105)*. This again confirms that TBW can be used for dosing vancomycin. Monitoring of serum trough concentrations may help reduce the fear of using such large doses in the face of

the variable effect on clearance, and could identify patients who may require more frequent dosing.

The increased absolute volume for distribution for ciprofloxacin in obese individuals becomes slightly below that of controls, proportional to BMI, when normalized to actual body weight *(76)*. This indicates that ciprofloxacin distributes less into the excess adipose tissue than into the fat-free tissue. It has been estimated to distribute into about 45% of the excess body weight (i.e., a correction factor of 0.45) *(76)*. Drug clearance, including renal clearance, is also increased in obese individuals *(76)*. Given both the reduced weight-adjusted volume of distribution and the increased drug clearance for ciprofloxacin in obesity, dosing can be based on an adjusted weight using a correction factor of 0.45, which can provide serum levels within the recommended range *(106)*. Trovafloxacin pharmacokinetics following a single dose in morbidly obese patients appear similar to nonobese individuals with similar subcutaneous and deep adipose tissue drug concentrations *(107)*.

Pharmacokinetic parameters for antifungal agents in obese patients have not been evaluated. Amphotericin has been dosed based on TBW given the much greater volume of distribution for this drug in obesity *(108)*. No clear data exist for dosing of the azoles in obese patients, although it has been suggested that volume of distribution and clearance of fluconazole is greater in obesity *(109)*. A higher dose of fluconazole is recommended for obese patients based on the higher drug clearance observed in an obese patient compared to data in nonobese patients *(110)*. Flucytosine dosing has been based on an estimated LBW in an obese patient that yielded acceptable serum drug concentration *(108)*. This seems rational given the lower volume of distribution normalized to TBW and the reduced clearance identified. In that patient case, amphotericin was also used, with maintenance doses based on actual body weight.

The limited data available for sulfonamides and macrolides does not establish which weight can be used for dosing in obesity, or whether dosing should be different in obese patients. It has been suggested that antimycobacterial agents be dosed according to LBW, based on a single case report *(111)*.

3.3. Chemotherapy

Given that many chemotherapeutic agents are hydrophilic and expected to distribute poorly into adipose tissue, dosing recommendations in obese patients could be based on an adjusted or an estimated LBW. To limit the interpatient variability associated with the often narrow therapeutic indices of many chemotherapeutic agents, body surface area is often used instead to guide dosing. However, in obese patients use of the body surface area that incorporates TBW, or the Calvert equation that incorporates the Cockroft-Gault equation, to dose chemotherapy may result in increased drug exposure with the subsequent risk of treatment toxicity *(112)*. Unfortunately, not much data exist to guide dosing. Ifosfamide may distribute into adipose tissue more than expected, as described by a larger volume of distribution and longer elimination half-life, which may impact on potential for toxicity *(113)*. Exposure of doxorubicin may also be greater in obese patients compared to nonobese patients, in this case based on decreased drug clearance without a change in volume of distribution *(114)*. Another drug with reduced clearance described for obese patients is cyclophosphamide *(115)*. The apparent clearance of busulfan was

higher in obese patients than nonobese, but an adjusted body weight using a correction factor of 0.25 eliminates any difference, and is therefore suggested for dosing this agent *(116)*. For the renally eliminated drug carboplatin, using an adjusted body weight based on a correction factor of about 0.5 provided the best prediction of drug clearance in obese patients *(117)*. A typical dosing approach resulted in excessive exposures (based on area under the concentration-time curves) to 4-hydroxy-cyclophosphamide, tepa, and carboplatin in a morbidly obese patient *(112)*. It is suggested that an adjusted body weight be used for dosing cyclophosphamide, thiotepa, and carboplatin, with consideration to obtaining drug concentrations. There was a reduced weight-adjusted volume of distribution for all three agents, a slight increase in clearance for cyclophosphamide and thiotepa, but a slightly reduced clearance of carboplatin *(112)*.

3.4. Immunosuppressants

Volume of distribution corrected to TBW is lower in obese individuals for both prednisolone and methylprednisolone without apparent changes in plasma-protein binding to albumin or transcortin *(118,119)*. However, the clearance of prednisolone is increased in obesity and correlates with TBW *(118)*. Although there may be increased clearance of prednisolone in obese patients, the increase in sensitivity to the drug means no dose change is warranted. TBW is used to dose this drug. Conversely, there is a significant reduction in clearance of methylprednisolone with obesity, such that reduced dosing frequency may be needed, and LBW is used *(119)*. Infusion of cortisol in obese patients who had undergone study of fat area allowed recognition that drug clearance (absolute and body weight-corrected) was much higher in those with larger intra-abdominal fat areas *(120)*. Cyclosporine may accumulate in adipose tissue, but its pharmacokinetic parameters do not change significantly in obese patients other than a reduced volume of distribution per kilogram of TBW *(46,121)*. This suggests that cyclosporine dosing should be based on LBW in obese individuals *(46,122)*.

3.5. Neuromuscular Blockers

Vecuronium distributes into lean tissue even in obese patients as indicated by the reduced volume of distribution per kilogram of TBW *(123)*. As a result, dosing of this neuromuscular blocking agent should be based on LBW, particularly because prolongation of drug effect has been reported in obese patients *(123)*. Recommendations have been made to dose rocuronium on LBW also, based on findings of a lower volume of distribution and clearance in patients with a higher BMI *(124,125)*. Although time to onset of rocuronium was slightly shorter in obese women, duration of effect and spontaneous recovery time were no different between obese and normal weight groups *(126)*. Neither the volume of distribution per kilogram TBW nor total drug clearance differed between groups, although patients were not morbidly obese, indicating that 0.6 mg/kg TBW could be used. Although the absolute volume of distribution for atracurium is unchanged in obesity, it is decreased significantly when normalized to total weight *(82)*. This indicates that dosing should be based on LBW. A possible alteration in protein binding and/or desensitization of acetylcholine receptors may account for the reduced sensitivity of obese patients to atracurium *(82)*. Doses may need to be adjusted upward based on hyposensitivity in these patients.

3.6. Sedatives, Anesthetics, and Analgesics

Although benzodiazepines as a class are considered highly lipophilic, the impact of obesity on the apparent volume of distribution varies with the specific agent. This does not appear to be an effect of plasma-protein binding, which remains no different between obese and control subjects. It was often considered that a correlation existed between the coefficient of distribution into octanol:water and distribution into adipose tissue. Diazepam, with the highest octanol:water partition coefficient, as well as midazolam with one of the lowest coefficients each have a significantly higher TBW-adjusted volume of distribution in obese individuals compared to controls, indicating distribution into excess adipose tissue. On the other hand, lorazepam and oxazepam with intermediate partition coefficients exhibit no difference in volumes of distribution adjusted to TBW between obese and control subjects *(32)*. The clearance of benzodiazepines appears to be increased in obese individuals *(32)*. The clearance of lorazepam and oxazepam increase in obese individuals and appear to be correlated with TBW *(70)*. This is documented for diazepam, nitrazepam, and lorazepam, which undergo oxidation, nitroreduction, and glucuronidation, respectively. Furthermore, obese subjects are more sensitive to the same dose of triazolam than are nonobese individuals *(54)*.

The very lipophilic agent propofol would be expected to distribute predominantly into adipose tissue. However, both the absolute and corrected volume of distribution are not significantly different between obese and nonobese individuals *(127)*. This may be accounted for in part by the high hepatic clearance, which appears to be related to TBW. This, in turn, suggests that propofol maintenance dosing in obese individuals should be based on actual body weight. Thiopental, despite being highly lipophilic, may need to be dosed lower in obese patients undergoing anesthesia, not because of volume of distribution, which is clearly larger in these patients even when adjusted to TBW, but because of increased drug sensitivity *(128,129)*. The volatile anesthetics halothane and enflurane are metabolized through the liver to a greater extent in obese patients as determined by levels of toxic metabolites, while having prolonged release of metabolites from adipose tissue *(130,131)*.

The synthetic opioid analgesics are also lipophilic compounds. Sufentanil has an elevated volume of distribution per kilogram of actual body weight but a clearance not much different in the obese compared to nonobese individual *(132)*. This suggests that TBW could be used for dosing sufentanil in obesity, with a reduced maintenance dose based on clinical effect relative to drug redistribution. However, remifentanil has a significantly lower normalized volume of distribution and clearance in obese patients suggesting that LBW would be more appropriate for dosing, and that TBW-based dosing would result in excessively high drug concentrations *(133,134)*.

The over-the-counter analgesic acetaminophen is a hydrophilic molecule with an expected lower volume of distribution, adjusted to TBW, in obese subjects *(69)*. Clearance of acetaminophen is increased in obesity, which may necessitate more frequent dosing. So, initial dosing of this drug would not have to be increased in obese patients, but could be adjusted. The volume of distribution for ibuprofen, once corrected to TBW, is reduced in obese subjects relative to controls and not accounted for by plasma-protein binding, which remains unchanged *(135)*. Ibuprofen clearance is increased significantly in the obese subjects and correlates with TBW.

3.7. Other

Limited data exist for most other drugs, including those used in cardiovascular, pulmonary, and GI illness. Verapamil tends to have a larger volume of distribution in obese patients, but not different than normal weight patients when adjusted to TBW, and clearance is not altered *(136,137)*. Additionally, obese patients may require higher drug concentrations to achieve similar cardiac effects as that in control patients *(137)*. The distribution volume and the clearance of digoxin appear unaffected by obesity based on single dose studies *(138,139)*. This follows from the limited distribution of the drug into adipose tissue, and allows for the continued recommendation to administer digoxin based on LBW. Lidocaine distribution normalized to TBW reveals similar values for obese and control subjects, and should therefore be dosed based on TBW *(140)*.

Low molecular weight heparin (LMWH) dose and volume of distribution determine the peak drug level, which in turn has been associated with the bleeding risk. Because the volume of distribution for LMWHs is expected to be similar to plasma volume, dosing per kilogram is not expected to differ between obese and nonobese individuals. Only limited study exists thus far in obese patients. Based on a preliminary report, dalteparin doses should make use of TBW *(141)*. No apparent difference exists between obese and nonobese individuals in volume of distribution normalized to TBW or in drug clearance. Unfortunately, the effects of obesity on the absorption characteristics have not been examined. Tinzaparin pharmacodynamics are not influenced across body weights of up to 165 kg (BMI ≤ 61) when dosed at 75 and 175 units/kg of TBW *(142)*. The pharmacodynamic effect of enoxaparin does not seem to differ between obese and nonobese subjects *(143)*.

Theophylline, although considered a polar compound, is more lipophilic than caffeine but does not correlate perfectly well with either LBW or TBW. Theophylline salts distribute predominantly into lean tissue even in obese individuals, indicating that loading doses should be based on a LBW *(144,145)*. As clearance may be increased in obesity, a close monitoring program should be in place to adjust dosing, particularly if weight loss occurs. Histamine-2 receptor antagonists, as expected by their hydrophilic nature, have a much smaller volume of distribution normalized to TBW, but may have an increased clearance *(77,146)*. Clearance may be increased in obesity, in part because of active tubular secretion of the drugs.

A mood-stabilizing drug such as lithium, with a narrow therapeutic index, would be important to evaluate in obesity. Lithium's volume of distribution normalized to actual body weight is considerably smaller in obese individuals, which is in line with the fact that it distributes to lean tissue *(78)*. The clearance of lithium is, however, increased in obesity *(78)*. From these findings, it would follow that initial dosing should be based on LBW, and that maintenance doses should be larger to maintain therapeutic levels. Trazodone is another mood-stabilizing agent but with considerable distribution into adipose tissue based on an increased volume of distribution even when corrected to TBW *(147)*.

3.8. Obesity Treatments

3.8.1. MEDICATIONS

Drugs used to manage obesity have been studied as well. Presumably, appetite suppressants would only be used when indicated and the issue of alterations relative to control individuals would not be relevant. Although no longer on the U.S. market,

dexfenfluramine was found to distribute proportionally into both the excess fat and lean tissue, despite being considered lipophilic *(47)*. It appears from limited data that sibutramine pharmacokinetics are unchanged in obese individuals compared to nonobese subjects *(148)*. In an open-label study, adolescents receiving orlistat therapy to manage obesity also received a multivitamin supplement that included lipid-soluble vitamins *(149)*. Nevertheless, serum concentrations of vitamin K and vitamin D were reduced, the latter significantly enough to warrant a recommendation for regular monitoring despite prophylactic supplementation. Given the reduction in fat absorption induced by orlistat, several lipophilic drugs have been evaluated in single dose studies during the course of an orlistat regimen in nonobese subjects *(150)*. Absorption of amiodarone was reduced by 27%, however, orlistat had no significant effect on the pharmacokinetics of fluoxetine or simvastatin.

Given the anticipated surge in the incidence of type 2 diabetes among obese individuals in the coming years, it would be wise to study the use of hypoglycemic agents in this population. The oral clearance and distribution volume of glyburide and glipizide do not appear to be significantly different between obese and nonobese diabetic patients, although some interindividual variability was noted and volume of distribution normalized to TBW was lower for glyburide in obese patients *(151,152)*. Obese patients also appear to be more sensitive to the effects of glyburide requiring lower daily doses to maintain therapeutic effect *(152)*.

Obese patients may also have cardiovascular disorders requiring drug therapy. β-Adrenergic receptor antagonists, β-blockers, have been studied in obesity with particular attention given to the degree of lipophilicity amongst agents in this class. Although propranolol is more lipophilic than bisoprolol, the corrected volume of distribution of each drug is reduced in obese subjects consistent with distribution into excess lean tissue rather than excess adipose tissue *(53,153,154)*. There are also no apparent differences between obese and nonobese in volume of distribution or clearance for sotalol, a much less lipophilic β-blocker than propranolol or bisoprolol *(155)*. Generally, these agents have a slightly reduced volume of distribution per kilogram of body weight in obese subjects than in controls regardless of degree of lipophilicity not explained by hemodynamic effects or protein binding but likely correlated with the distribution coefficient of each at physiologic pH *(35)*.

3.8.2. SURGICAL INTERVENTION

Turning briefly to bariatric surgery, which has helped certain morbidly obese patients who are willing to commit to the necessary restrictions, reduce their body mass and, potentially, some comorbid risks as well. The most common surgical approaches include gastric restriction, gastric bypass, or intestinal bypass *(156)*. Aside from the very real perioperative risks and the GI complications associated with this disfiguring of the GI tract, comes the alteration of nutrient and drug disposition. The malabsorption of nutrients is expected and has been documented for calcium, magnesium, iron, group B vitamins including cobalamin, vitamin D, and other fat-soluble vitamins. Based on the alteration in those portions of the GI tract normally responsible for preparing orally administered drugs for absorption, these procedures would be expected to alter drug absorption either by reducing time for disintegration and dissolution, or reducing the surface area and sites for absorption *(157)*. The data is extremely limited at the present

Table 3
Values in Obesity for Volume of Distribution and Clearance of Select Drugs

| Medication | V_D | | Cl | Reference |
	(L)	(L/kg TBW)	(L/h)	
Acetaminophen	109	0.81	29	69
Amikacin	26.5	0.18	9.5	99
Atracurium	8.6	0.07	26.6	82
Bisoprolol	182	2	14.8	153
Carbamazepine	98.4	0.87	1.19	89
Ciprofloxacin	269	2.46	53.8	76
Cyclosporine	230	2.5	42	46
Diazepam	292	2.81	2.3	85
Digoxin	981	10.7	19.7	139
Doxorubicin	1119	14	53.5	160
Gentamicin	23.5	0.17	8.5	99
Glyburide	47	0.44	3.2	151
Glipizide	19.5	0.2	2.3	152
Labetalol	368	3.8	90	153
Lorazepam	131	1.25	6.1	85
Methylprednisolone	104	0.9	21.3	119
Midazolam	311	2.66	28.3	44
Oxazepam	97	0.84	9.4	70
Phenytoin	82.2	0.68	3.5	86
Prednisolone	44.1	0.3	11.1	118
Propofol	17.9	1.8	1.46	127
Propranolol	230.5	2.7	44.3	155
Ranitidine	86	0.8	34.5	146
Sotalol	80	0.9	9.4	155
Sufentanil	547	5.8	1.25	132
Theophylline	40.5	0.4	3.3	144
Tobramycin	19.2	0.23	7.5	161
Trazodone	162	1.4	8.7	147
Vancomycin	43	0.26	11.3	102
	52	0.32	11.8	80
Vecuronium	44.7	0.47	15.6	123
Verapamil	858	7	59.6	136

V_D, volume of distribution; L, liters; L/kg TBW, liters per kilogram of total body weight; Cl, clearance; L/h, liters per hour.

time—for example, based on serum drug concentrations, the absorption of oral penicillin is apparently not altered following gastroplasty for morbid obesity *(158)*.

4. LIMITATIONS OF THE DATA AND FUTURE RESEARCH

Although reference to altered drug disposition in obese individuals can be found in the literature across a number of years, there has been little concerted effort to study this and to provide clinical recommendations. There is clearly a paucity of data when it comes to

Table 4
Suggested Dosing Weight for Use in Obesity

Medication Example	Dosing Weight in Obesity	
	Loading Dose	Maintenance Dose
Aminoglycosides	Adjusted body weight[a]	Adjusted body weight,[a] or by therapeutic response
Amphotericin	Total body weight	Total body weight
Atracurium	Lean body weight	Total body weight
Carbamazepine	Total or adjusted	Lean body weight
Ciprofloxacin	Adjusted body weight[a]	Adjusted body weight[a]
Cyclosporine	Lean body weight	Lean body weight
Flucytosine	Lean body weight	Lean body weight
Lithium	Lean body weight	Larger than nonobese
Phenytoin	Adjusted body weight[a]	Adjusted body weight[a]
Propofol	Total body weight	Total body weight
Theophylline	Lean body weight	Adjusted body weight[a]
Vancomycin	Total body weight	Total body weight
Vecuronium	Lean body weight	Lean body weight
Verapamil	Total body weight	Lean body weight

[a]Correction factor varies with the drug and study findings.

evaluating the effect of obesity in general—let alone specific degrees of obesity or body composition, or bariatric surgery, or the influence of severe weight loss or extreme weight cycling—on the disposition and effect of medications. Much of the data is generated following single dose, rather than multiple chronic doses as used in clinical practice, or from single case reports or case series often involving heterogeneous groups. It remains difficult to predict the influence of obesity on drug disposition and effect based solely on simplistic factors (e.g., drug lipophilicity). Dosing guidelines based on single case reports or small case series, as described in the previous sections, cannot be made with as much confidence as those based on more rigorous evaluation in a pharmacokinetic or pharmacodynamic study.

One significant area that requires more effort is a method to clinically evaluate body composition of obese patients, or at least to better evaluate population estimates of body composition in subgroups of the obese—by gender, ethnicity, degree of obesity. Whole body densitometry, bioelectric impedance, dual-energy x-ray absorptiometry, and other methods can be used to determine lean body mass as long as limitations in technique are accounted for. Estimates may vary depending on data source and patient group *(159)*. This potential interindividual variability needs to be addressed.

Another area requiring focus is the determination of individual drug characteristics in obese individuals—pharmacokinetic and pharmacodynamic. Determine, drug by drug, the volume of distribution, clearance, and therapeutic effect in each. It may become important to evaluate drug disposition in patients of similar BMI, body composition, and even ethnic background. Differing body composition should be examined not just between degrees of obesity, but also within a group of individuals of the same BMI. The activity of specific CYP isoforms in pre-obese, obese, and morbidly obese subjects should be docu-

mented. In this way drug regimens may be better suited to an individual patient to maximize the effectiveness of a drug regimen and limit potential toxicity. Early phase drug studies for new compounds should account for pharmacokinetic differences by body composition.

Suggestions made in this chapter regarding the lean body mass equation, use of the volume of distribution normalized to TBW, and total body clearance between obese and nonobese individuals needs to be evaluated prospectively.

5. CONCLUSION AND RECOMMENDATIONS

The practice of using dosing regimens in the obese patient based on data obtained in nonobese individuals may increase the risk of drug toxicity or therapeutic failure. Similarly, generalizations cannot necessarily be made about agents from a related class when data is only available for one of them in obesity. A therapeutic dosing strategy can be developed for obese patients. Specific volume of distribution and clearance data on a drug can be used to determine a therapeutic dosing strategy for the drug in an obese patient. This requires use of drug-specific data in obese individuals (Table 3). Loading doses can be based on volume of distribution data, instead of simply on degree of lipophilicity, and maintenance doses can be based on drug clearance data. Weight-based approach to loading doses will depend on the distribution of the drug in obese individuals as determined by the volume of distribution per kilogram compared to that in the nonobese (Table 4). For drugs with a clearance that appears to be correlated with increasing weight, use TBW for dosing, and of course consider the need to modify dosing intervals based on pharmacodynamics. On this last point, any available pharmacodynamic data should supplement recommendations based on pharmacokinetic parameters. Close patient monitoring is always required.

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III Influence of Food or Nutrients on Drug Disposition and Effect

7 Drug Absorption With Food

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1. INTRODUCTION

Oral input is the most convenient route for drug administration so the large majority of drug products are oral dosage forms. This dictates consideration of the timing of drug administration with respect to the time of meal ingestion. There are several reasons for taking a drug with a meal or nutrient beverage. It may be expedient for clinical staff in hospitals and assisted living centers to administer a drug at a time when meals are provided for inpatients. Outpatient compliance with the prescribed drug dosage regimen may be aided with administration at regular mealtimes. Some drugs are irritating in the gastrointestinal (GI) tract and their administration with food or a nutrient beverage can diminish this effect as compared to administration with water.

For some drugs, meal administration can alter oral drug absorption and, possibly, therapeutic effect compared to fasted-state drug administration with water. In this regard, oral drug–meal interactions can be described as pharmacokinetic and pharmacodynamic interactions.

One of the more dramatic pharmacodynamic drug–nutrient interactions (DNIs) with significant clinical repercussions may occur subsequent to administration of a monoamine oxidase inhibitor drug with meal components containing tryptamine or tyramine. A depressed patient on oral tranylcypromine therapy who ingests cheese as a meal component *(1)* illustrates a classic example for such an interaction requiring emergency care for the resultant hypertensive crisis. This extreme example illustrates a direct pharmacological interaction in which a meal component alters clinical response to oral drug administration dictating marketed product insert warnings and special prescription labeling. Another interaction in this class occurs when oral anticoagulant therapy is impacted by the ingestion of sushi, which has a high vitamin K content *(2)*. Such pharmacodynamic interactions are the topic of another chapter in this text.

Pharmacokinetic interactions are reflected by meal influences on drug plasma levels and are the focus of this chapter. Clinically significant changes correspond to maximum drug plasma levels varying above or below the therapeutic range with meal administration. These changes are often mediated by a meal effect on the extent of drug absorption and are most serious for drugs with a narrow therapeutic window for which effective

under- or overdose critically impacts patient health. Such changes dictate prescription labeling to take the drug with or without food and health care professional counseling on the timing of oral drug administration with respect to meal intake. A more common pharmacokinetic effect is represented by a delay in therapeutic drug concentrations from meal-induced increases in gastric emptying time without a change in systemic availability and extent of absorption. Although this interaction is not of concern for many drugs, a meal-induced delay in absorption may be a significant clinical event to a patient on an oral analgesic drug hoping to achieve rapid pain relief.

Following initial review of this topic *(3)*, a number of recent review articles on drug–food interactions are available in the literature *(4–10)*. Because this text is intended for health care professionals as opposed to drug development scientists in the pharmaceutical industry, this review is geared toward a patient-care perspective. A listing of drug administration timing with respect to meal effects on the pharmacokinetics of the most commonly prescribed drugs is provided (Tables 1 and 2). Additionally, guidelines for clinical meal-effect studies are outlined based on regulatory considerations.

2. REVIEW OF BASIC SCIENCE

The potential for a meal to influence drug absorption depends on drug and dosage form physical–chemical properties as well as meal effects on GI physiology. Drug properties and the rate of dosage form release of drug into solution in the GI tract define rate-limiting steps in the drug absorption process. Drug dissolution, intestinal permeability, and gastric emptying determine the rate of absorption. However, both intestinal and hepatic first-pass metabolism can couple with these absorption rate limits to effect systemic drug availability. Each of these rate limits can be influenced by meal input.

The extent of drug absorption is determined by drug residence time at sites of absorption and sites of chemical degradation and enzymatic metabolism in the GI tract. Some drugs are unstable in stomach acid so gastric residence time is a critical physiological variable *(11)*. Because GI pH is region-dependent and ionizable drug solubility is a function of pH, drug dissolution and precipitation can impact drug availability in solution for absorption. Furthermore, GI pH can affect intestinal permeability of ionizable drugs. Both drug intestinal permeability and metabolism may be saturable as well as region-dependent so at a given dosage, administered fluid volume, gastric emptying, and intestinal transit combine to play a role in rate and extent of drug absorption. Each of these variables can be influenced by meal input.

2.1. Drug Absorption Dependence on Drug Properties

Drug aqueous vs lipid solubility are key properties in determining rate limits to intestinal absorption of drugs. Many drugs owe some of their potency to their ability to permeate cells membranes and gain access to sites of pharmacological action. Good membrane permeability is generally a function of good lipid solubility (lipophilicity). This is accompanied by poor hydrophilicity (referring to aqueous solubility) so the absorption rate of these drugs is limited by poor dissolution into the aqueous media of the GI tract. Dosage formulation can sometimes reduce this problem because drug dissolution rate also depends on the powder drug surface area exposed to water. Drug powder surface area can be increased by micronization and for a low-dose (0.25 mg) drug like digoxin; this

Table 1
Medications to be Administered on an Empty Stomach

Generic Name	Brand Name	Clinical Effect/Reason
Bisphosphonates		
Alendronate	Fosamax	Dairy products/food can impair
Etidronate	Didronel	absorption; administer 2 h prior to meal
Risedronate	Actonel	
Captopril	Capoten	Food decreases absorption; administer 1h before or 2 h after a meal
Cefaclor	Ceclor	Food delays absorption; take 1 h before or 2 h after a meal
Dextroamphetamine	Adderall	Acidic foods/juices will impair absorption
Digoxin	Lanoxin	Food delays absorption; take consistently with respect to meals
Diltiazem	Tiazac, Cardizem	Increased absorption in the fasting state; administer before meals
Furosemide	Lasix	Increased absorption in the fasting state
Glipizide	Glucotrol XL	Increased absorption and improved clinical effect when administered 30 min prior to meal
Levothyroxine	Levoxyl, Synthroid	Increased absorption in fasting state; take at same time daily and consistently with respect to meals
Phenytoin	Dilantin	Food alters absorption; take consistently with respect to meals
Proton pump inhibitors		
Esomeprazole	Nexium	To improve absorption and maximize
Lansoprazole	Prevacid	clinical effect, administer before
Omeprazole	Prilosec	meals
Pantoprazole	Protonix	
Rabeprazole	Aciphex	
Quinolones		
Ciprofloxacin	Cipro	Cations (Ca, Fe, Zn, etc.), antacids, and
Norfloxacin	Noroxin	dairy products will decrease
Tetracyclines		absorption
Minocycline	Minocin	Absorption significantly impaired by
Tetracycline	Sumycin	iron/milk/food
Theophylline	TheoDur, TheoBid, SloBid	Food may decrease absorption; take consistently with respect to meals
Warfarin	Coumadin	Food alters absorption; take consistently with respect to meals
Zafirlukast	Accolate	Food decreases absorption

Note: List is based on 2001 top 200 brand/generic prescribing by prescription volume. Note that drug–food interactions may exist for other medications not included on this list (e.g., anti-HIV medications). Many medications also have interactions with grapefruit juice.

Ca, calcium; Fe, iron; Zn, zinc.

Table 2
Medications to be Administered With Food

Generic Name	Brand Name	Clinical Effect
Carbamazepine	Tegretol	Food increases absorption
Divalproex	Depakote	Decreased GI upset
Fenofibrate	Tricor	Increased bioavailability
Glyburide/metformin	Glucovance	Decreased GI upset from metformin
Labetalol	Normodyne	Food increases absorption; take consistently with respect to meals
Metformin	Glucophage (reg and XR)	Decreased GI upset
Metoprolol	Toprol, Toprol XL	Food increases absorption; take consistently with respect to meals
Nitrofurantoin	MacroBid	Improved tolerance and increased bioavailability
Potassium chloride	K-Dur, Klor-Con	Decreased GI upset
Tamsulosin	Flomax	Food alters bioavailability; take consistently 30 min after same meal daily
Venlafaxine	Effexor	Decreased GI upset

Note: List is based on 2001 top 200 brand–generic prescribing by prescription volume. Note that drug/food interactions may exist for other medications not included on this list (e.g., anti-HIV medications). Many medications also have interactions with grapefruit juice.

GI, gastrointestinal.

greatly improves drug absorption into the systemic circulation. Some increase in absorption via micronization is observed for a high-dose (500 mg) drug like griseofulvin, but the improvement is only modest. Enhancing drug absorption through increased dissolution surface area depends on the amount of drug that can be dissolved within the small intestinal transit time. This is, of course, more difficult to achieve at higher doses.

As would be expected, many lipophilic drugs are better absorbed when administered with a meal that has fatty components. Absorption may increase as a direct function of meal fat content. A good example of this is the first-marketed HIV-protease inhibitor, saquinavir. This drug was approved quickly despite the fact that an oral dose administered with water resulted in only 5–10% of this high-dose drug reaching the systemic circulation. It was observed that when patients took this medication with a high-fat meal, systemic availability increased 5- to 10-fold. Newer dosage forms take advantage of this by putting the drug in a lipid vehicle inside a soft-gel capsule *(12)*.

Hydrophilic drugs possess good aqueous solubility and dissolve quickly but do not permeate lipid membranes very readily. The absorption of these drugs is therefore rate-limited by membrane permeability rather than dissolution. Coadministration with meals does not typically affect the absorption of hydrophilic drugs. Some hydrophilic drugs are exceptional and have high membrane permeability due to membrane transport by nutrient carriers. Several amino acid and small peptide drugs fall into this category. Although it might be anticipated that protein meals would inhibit the absorption of these drugs, this has not been observed in clinical practice *(13)*.

Another class of hydrophilic drugs with good membrane permeability includes compounds of sufficiently small molecular size (< 200 Daltons) that they permeate membrane paracellular pathways. Because neither dissolution rate nor membrane permeation is rate-limiting to absorption, gastric emptying controls the rate of absorption of these smaller drugs. The effect of meal intake on gastric-emptying rate is a point discussed in a later section of this chapter. The analgesic drug, acetaminophen, falls into this class of compounds *(14)*.

Drugs may also have both poor dissolution rates and poor membrane permeability. Such drugs are not poorly water soluble because they are lipophilic but rather because they have a high capacity to form intermolecular hydrogen bonds. Such compounds tend to have high melting points and form poorly dissolving crystals. Although food can negatively affect the absorption of such compounds, they rarely make it to the market as oral drug products because their properties dictate poor oral absorption even in the fasted state *(15)*.

2.2. Drug Absorption Dependence on Dosage Form Properties

The most clinically significant food effects on oral drug delivery have been in association with the administration of extended or modified release-dosage formulations of narrow therapeutic window drugs *(16–18)*. Because these formulations typically contain very high doses of high permeability drugs, meal-component interactions with formulation components that alter the intended release rate can produce an effective under- or overdose. In the extreme, meal-induced "dose dumping" as a bolus drug-release process of the entire dose of a modified-release formulation can result in toxicity in individual patients *(19)*.

Less dramatic meal effects on modified-release dosage forms are seen as meal-controlled delays in oral drug delivery to the systemic circulation. Because non-disintegrating particles greater than 2 mm in diameter do not empty from the stomach with the gastric liquid contents *(20)*, oral drug delivery from dosage forms with these properties may be influenced by meal intake. Such dosage forms are subject to emptying with the timing of the interdigestive migrating motility complex (IMMC) under the control of the circulating gut peptide, motilin *(21)*. Following administration of a meal, this complex is disrupted and gastric emptying is influenced by other gut peptides *(22)* as regulated by caloric density and intestinal feedback control *(23)*. Gastric emptying control by IMMC is not re-established until most of the meal calories have been emptied. As a result, with high-caloric density input, gastric emptying of nondisintegrating dosage forms greater than 2 mm in diameter may experience substantial time lags before emptying into the intestine and absorption delays may be reflected in delayed drug plasma levels *(24)*.

2.3. Meal Effects on GI Transit and Drug Absorption

Although mean small intestinal transit time (between 3 and 4 h) is remarkably independent of fasted vs fed-state conditions *(25)* several drugs *(26,27)*, drug excipients *(28)*, and over-the-counter products *(29)* have been shown to influence the extent of drug absorption via influences on intestinal transit. Careful studies have shown that a drug's small intestinal residence time in human subjects is in the range of 200 min whether it is administered with or without a meal *(25)*. However, gastric emptying rate is a function of both volume and caloric density.

2.3.1. ADMINISTERED VOLUME

In many studies of meal effects on drug absorption, a comparison of fasted vs fed conditions is not controlled for administered volume *(9)*. This is certainly consistent with the variability in patient fluid intake with oral drug administration of prescription drugs and may therefore represent a legitimate statistical comparison. Although such studies may verify whether or not there is a significant food effect on oral drug bioavailability, fasted-state pharmacokinetics may depend on administered volume for several reasons. When a drug is administered with a noncaloric aqueous liquid, the rate of human gastric emptying of liquid containing dissolved drug and small drug particles is first-order and dependent on volume load after an initial lag period. When a drug is administered with small volumes of fluid in the range of 2 fluid ounces (60 mL), emptying of the gastric contents is more dependent on the IMMC than is the case when larger volumes in the range of 8 fluid ounces (240 mL) are administered *(30)*. Thus, emptying of a drug contained in the gastric fluid contents will be more erratic with respect to the time of drug administration for smaller than larger coadministered fluid volumes. Additionally, the first-order gastric emptying of larger volumes is more rapid than for smaller volumes for all phases of the IMMC.

Meal administration is typically high volume, but intestinal feedback control dictates that gastric emptying rate and resultant drug delivery to absorption sites in the small intestine is a function of caloric load or density (calories per volume administered). Furthermore, if fasted-state drug administration is conducted under low-volume conditions compared to the typical high volumes consumed with meal administration, initial intestinal drug concentrations will be much higher in the fasted-state condition as compared to meal coadministration. Additionally, certain meals may dictate significant gastric, intestinal, biliary, and pancreatic secretions that can further dilute fed-state drug concentrations as compared to the fasted state. For those drugs that show nonlinear characteristics as a function of local concentrations, such differences in the volume of administration can complicate the interpretation of food-effect studies. It would be advisable to administer the same volume of noncaloric fluid in fasted-state studies as the volume of meal administered in fed-state studies. Although this only controls initial conditions, because meals will influence GI fluid absorption and secretions, a more mechanistic comparison is offered when meal effect studies control for volume.

2.3.2. CALORIC LOAD

Caloric feedback signals from the intestine that control gastric emptying have been studied for simple carbohydrate, fat, and protein meals. Triggers for these signals include sodium-monosaccharide cotransport *(31)*, peptide digestion *(32)*, and chylomicron formation *(33)*. The magnitude of the signal and the extent of gastric-emptying inhibition are a function of the extent of nutrient and intestinal sensor contact down the length of intestine *(34,35)* and therefore depend on both digestion and initial caloric load. The pattern of calorie-regulated gastric emptying is different than for volume-controlled gastric emptying *(30)* and has been studied in most detail for simple glucose meals *(36)*. With respect to oral drug delivery, calorie intake will result in a different volumetric input rate of gastric-liquid-containing drug into the intestine than for noncaloric liquid intake. This will, in turn, influence differences in rates of coadministered drug delivery to sites of absorption and first-pass elimination in the upper intestine with nutrient vs noncaloric

input. Caloric control of intestinal drug delivery rates from gastric emptying can result in less variability in oral drug pharmacokinetic profiles compared to drug administration with small volumes of noncaloric fluid. This is the case because the timing of gastric emptying with an IMMC will be highly variable with respect to the time of oral drug administration.

2.3.3. MEAL TYPE

Although different meal types provide a similar rate of fluid delivery from the stomach to small intestine based on caloric density *(37)*, intestinal fluid volumes and resultant drug concentrations depend strongly on meal type. Simple carbohydrate meals may result in substantial water absorption in the small intestine *(38)* that may, in theory, result in more concentrated drug solutions in the intestinal lumen. Protein meals promote higher intestinal fluid volumes as the result of significant pancreatic secretions *(32)* that may, in theory, result in more dilute drug solutions. Even greater intestinal volumes should result from intake of high-fat meals because pancreatic and biliary secretions will be stimulated to a greater extent than with other meal types *(39)*. The fed-state balance between intestinal fluid secretion and intestinal water absorption is very much a function of the rate at which complex meals are converted to simple nutrients. Simple carbohydrates tend to be rapidly broken down in the upper GI tract, whereas protein and fat digestion are slower processes (39). The greater extent of upper intestinal water absorption observed with simple carbohydrate meals as compared to protein meals is the result of both differences in the rate of digestion and differences in the absorption pathways of the resultant elementary nutrients. Most monosaccharides are absorbed by sodium-dependent cotransporters that promote intestinal water absorption *(40)*. Although a number of sodium-dependent transporters support amino acid transport, many intestinal amino acid transporters utilize sodium-independent mechanisms for mucosal absorption *(41)*.

2.4. Physical Chemical Interactions in the GI Tract

Absorption of drugs that are coadministered with meals may be altered both by meal-component influences on GI physiology as well as meal-component influences on drug and dosage form properties.

2.4.1. MEAL VISCOSITY

Although this factor is certainly related to meal type based on digestibility, the fact that meal viscosity can be studied independent of caloric input dictates consideration as an additional meal-effect factor. A clinical example is provided later in the chapter. As opposed to the effect of high fluid volume intake resulting in local gastric pressure distention, which speeds gastric emptying, high viscosity intake slows gastric emptying *(42)*. If insufficient digestion occurs in the gastric contents to substantially reduce the solution viscosity entering the small intestine, several factors may effect drug absorption following oral administration. First, higher viscosity may increase upper intestinal residence time. Additionally, based on the inverse dependence of solute diffusivity on medium viscosity, diffusion of dissolved drug from the intestinal lumen to sites of absorption at the intestinal membrane will be slowed. Finally, high viscosity can slow drug dissolution rate by decreasing solute diffusion away from the solid drug surface *(43)*.

2.4.2. MEAL EFFECTS ON GI pH

Medium pH can impact both the solubility and membrane permeability of ionizable drugs. Because meal intake may alter gastric and upper intestinal pH, the ionization state of weak acid and weak base drugs with pKa in the range of GI pH variation will be affected. Because nonionized drug has greater membrane permeability than an ionized drug, nutrient effects on mucosal microclimate pH might be expected to influence the absorption of drugs in this class. Enterocyte metabolism of glucose lowers microclimate pH via sodium–proton exchange *(44)*. However, little overall effect on drug absorption is observed.

Food effects on weak acid drugs are not common *(4)*, because ionized drugs promote high solution concentrations in the intestine and permeability of the nonionized compound is frequently high enough to shift ionization equilibrium toward favorable absorption. The previously marketed nonsteroidal anti-inflammatory drug (NSAID), bromfenac, may be exceptional in this regard *(45)*. This drug showed a reduced analgesic effect when administered with a meal. This unusual meal effect for a weak acid drug with a pK_a within GI pH variation may be a function of bromfenac's exceptionally low dose as compared to other NSAIDs.

The potential for meal effects on weak base drugs, with pK_a in the range of GI pH variation, is greater than for weak acids. This is a function of their potential to precipitate at intestinal pH or high gastric pH as promoted by some types of meals *(46)*. A clinical example is provided later in the chapter.

2.4.3. MEAL CALCIUM CONTENT

There is experimental evidence that the stomach controls the rate of soluble calcium delivery to the small intestine. This element of intestinal feedback control has been verified indirectly by observations on the rate of gastric emptying of calcium chelators. The observation of feedback control appears to be an indirect effect of the capacity of calcium chelators to remove ionic calcium from the tight junctions *(31)*. In isolated intestinal tissue and cell culture, removal of calcium from the tight junctions may result in an increase in paracellular solute transport *(47)*. A defense mechanism to slow the delivery of calcium chelators from the stomach would thus serve a protective feedback-control function. Because a number of elementary nutrients resulting from fat digestion sequester calcium *(31)*, this may provide a parallel feedback control mechanism to that of caloric content in controlling the rate of gastric emptying. Additionally, to the influence of this factor on the rate of gastric delivery to the small intestine and the availability of the paracellular pathway for absorption, calcium is known to bind a number of drugs, like tetracycline, reducing their availability for absorption in the intestine *(48)*.

2.4.4. DRUG BINDING TO MEAL AND BILIARY COMPONENTS

Drug binding, complexation, and micellar sequestration, including bile acid interactions, can reduce effective drug concentration in the intestinal lumen and can reduce absorption. Over-the-counter product effects including antacid effects on drug binding, oil emulsion product effects on drug sequestration, and fiber effects on viscosity may mediate a number of these interactions.

Drug binding to nutrient components has been most often cited with drug coadministration with enteral nutrient products. These interactions may include both reversible

and irreversible binding components when drug–nutrient coadministration is through nasogastric tubes *(49)*. Drug binding to the protein component of common enteral nutrient feeding products has also been reported *(50)*.

2.4.5. MEAL EFFECTS ON FIRST-PASS ELIMINATION

The significant clinical impact of grapefruit juice on the oral bioavailability of several drugs *(51)* brought meal-component effects on first-pass drug elimination to the forefront of food-effect studies. This is an example of a meal component directly inhibiting the activity of first-pass elimination factors dictating an increase in oral bioavailability. Such inhibitory effects can lead to dramatic increases in oral drug delivery *(52)*. Meal input can influence drug first-pass elimination elements through saturation as well as inhibition. It has been stressed that oral drug dosage form administration factors, including coadministered meals, influence drug concentration gradients that are the driving forces for drug absorption. For example, meal lipid solubilization of an orally administered drug may serve to increase lipophilic drug concentration in the GI lumen. Oral bioavailability is further determined by intestinal and hepatic biological components with activities that may or may not be saturated as a function of local drug concentration gradients. By impacting local drug concentration gradients around first-order to zero-order transition points for saturable absorption and first-pass elimination components, meals can exert an effect on oral bioavailability independent of inhibition on first-pass elimination.

2.4.5.1. First-Pass Metabolism. Meals can affect both intestinal and hepatic first-pass metabolism. With regard to nutrient component inhibitory effects, phase I pathways have been observed to be impacted to a greater extent than phase II pathways *(53)*. Because grapefruit juice inhibits cytochrome P450-3A4 (CYP3A4), which has been shown to be responsible for the intestinal metabolism of the greatest number of drugs and drug candidates, this elimination element has been the focus of DNI studies. Drug candidate screening now includes human hepatocyte, microsomal, or recombinant enzyme metabolism data. Because CYP3A4 is a component of this screening, a measure of the potential for intestinal metabolism is also available. Caco-2 monolayers enhanced in CYP3A4 have been developed to screen drug candidate intestinal metabolism coupled to membrane transport control factors *(54)*. Basic studies to isolate the grapefruit juice component responsible for CYP3A4 inhibition has generated broader investigations of elementary nutrient factors that might impact this important drug-metabolizing enzyme *(55)*.

Other drug-oxidizing enzymes in the intestine *(56)* and liver *(57)* may be influenced by nutrient intake. In animal studies, it was reported that methionine and cysteine inhibited flavin monooxygenase (FMO)-mediated cimetidine sulfoxidation *(58)*. This interaction is less important in humans and cimetidine's safety further reduces clinical significance. The absorption of a narrow therapeutic index drug that undergoes FMO-mediated sulfoxidation, has been shown to not be influenced by meal intake *(59)*. However, for a new drug entity, the screening of a battery of metabolizing enzymes and further basic investigations on elementary nutrient effects on metabolism may yet uncover meal effects on drug metabolizing enzymes other than CYP3A4 (*see* Chapter 2).

2.4.5.2. Intestinal Export Permeability Limitations. Current research has implicated P-glycoprotein (P-gp)-mediated drug export as a factor limiting intestinal permeability of some compounds *(60)* and has led to further investigations on the effect of nutrients on this elimination pathway *(61)*. Inhibition of P-gp by dietary flavanoid com-

ponents has been reported *(62)*. Because P-gp substrates are typically hydrophobic and poorly water soluble, saturation of P-gp is difficult to achieve. However, elevated drug concentrations through meal-lipid solubilization could lead to a nonlinear concentration dependence of P-gp-mediated drug export *(63)*. For lipophilic compounds that are P-gp substrates, the combined effects of increased permeability via P-gp inhibition with an increase in drug concentration through solubilization by a high-fat meal might be projected to substantially increase absorptive flux. Most P-gp substrates are neutral or weak-base hydrophobic compounds *(64)*. Some weak acid drugs are substrates for intestinal multidrug-resistance proteins and/or multispecific organic anion transporters such as cMOAT *(65)*. There may be additional intestinal membrane proteins mediating drug and/or drug metabolite export yet to be identified that could interact with the nutrient components of a meal *(66)*.

There is evidence that drug metabolites are substrates for intestinal exporters and it is proposed that intestinal metabolism and mediated mucosal export are coupled processes in intestinal drug elimination *(67)*. The function of such coupling, with respect to CYP3A4 and P-gp, is suggested to promote efficient intestinal elimination *(68)*. Because most metabolites are less hydrophobic than their parent drug, they might be weaker substrates for P-gp. Efficient intracellular metabolite production would set up a favorable metabolite-to-drug ratio, minimizing potential competition for P-gp export *(69)*. Some inhibitors of P-gp are also inhibitors of CYP3A4, and these include some compounds that are meal components *(70,71)*. Given the possibilities of inhibition and saturation of coupled intestinal drug-elimination components, the impact of meal intake on first-pass metabolism may be mechanistically complex.

2.4.6. MEAL EFFECTS AND REGIONAL-DEPENDENT ABSORPTION

Many drugs possess sufficient lipophilicity to promote high permeability throughout the small and large intestine *(72,73)*. However, for some compounds, intestinal absorption and elimination may not be homogeneous or even continuous processes throughout the entire small intestine. This is the case for some drugs that are absorbed by a carrier-mediated process *(74)* and is generally true for drugs of moderate lipophilicity as a function of a reduction in absorbing surface area in the lower small intestine *(75)*. For small hydrophilic compounds predominantly absorbed through paracellular pathways, it would be anticipated that permeability would decrease with distance down the intestine because paracellular pathways become more restricted by the tight junctions *(76)*. However, this has not been confirmed with the paracellular marker compound mannitol *(77)* and regulation of this pathway may be variable as a function of intestinal region *(78)*. What may prove to be a significant factor in regionally dependent drug absorption are differences in drug elimination as a function of intestinal region *(69)*. Furthermore, resultant differences in the rate of absorption and elimination in different regions of the intestine can dictate variability in the rate of drug presentation to the liver.

Recent studies indicate that region-dependence in the absorption of some drugs may underlie a significant meal effect on systemic drug availability following oral administration *(69,79)*. When drug absorption is better in the upper small intestine than in the middle and lower regions, meal factors that serve to reduce drug availability to the absorbing membrane may produce negative effects on systemic availability. These factors may include drug-binding interactions with meal components or any physical hin-

drance to drug transport provided by meal intake in the upper intestine that reduces drug availability to sites of absorption. Reduced drug absorption in the upper intestine can result in delivery of lower drug concentrations to sites of first-pass elimination. It is possible that drug administration without meals may provide intestinal concentrations sufficient to saturate first-pass metabolism, whereas administration with a meal results in drug concentrations below first-pass saturation levels. Based on a limited set of studies, the potential for a negative meal effect is more likely if there is region-dependent absorption.

2.4.7. MEAL EFFECTS ON SPLANCHNIC BLOOD FLOW

Just as nutrient effects on region-dependent drug absorption should alter rate of drug delivery to sites of first-pass elimination, meal effects on splanchnic blood flow would be anticipated to alter the rate, and possibly extent, of first-pass drug elimination. This may be the case with meal effects on alcohol elimination and possibly underlie varying meal effects on high first-pass drugs like propranolol.

3. CLINICAL EVIDENCE

The first HIV-protease inhibitor on the market was saquinavir. The need for treatment with this drug class dictated approval despite a low 5% oral bioavailability. This was because of the low intrinsic solubility and high first-pass metabolism of this drug. Although orally administered as a mesylate salt at 600–800 mg three times a day, this low pK_a weak-base drug may dissolve in the acid pH of the stomach but would enter the upper small intestine at concentrations three orders of magnitude above its intrinsic solubility. Such a high level of supersaturation would promote the potential for intestinal precipitation. Observations that saquinavir administration with a high-fat meal increased oral bioavailability 5- to 10-fold *(80)* led to the development of a lipid-melt soft-gel capsule formulation that similarly increased oral bioavailability *(12)*. This tremendous increase in bioavailability, as a function of dosage formulation, is likely owing to a combination of solubilization of the drug in the intestine by lipid meal components and the resultant saturation of some elements of first-pass elimination, particularly in the intestine. Saturation of intestinal CYP3A4 and P-gp should result in a faster rate of absorption and a higher rate of drug presentation in the portal vein to the liver.

The third drug marketed in this class of compounds was indinavir, which showed a decrease in bioavailability when administered with meals *(81)*. Goals in the molecular design of this drug included the addition of a weak-base moiety with higher pK_a to increase its solubility. It is administered as a sulfate salt at a dosing regimen similar to that of saquinavir. As was the goal of this molecular design ploy, it is likely that indinavir achieves higher concentrations in the GI tract and a higher driving force for absorption as compared to saquinavir when administered without meals. The higher intestinal indinavir concentrations compared to saquinavir saturate elements of first-pass elimination resulting in oral indinavir bioavailability 10-fold higher than the initial saquinavir product. However, when the drug is administered with a high-caloric meal, a 60% reduction in indinavir bioavailability is observed. When the drug is administered with a light meal of low caloric density, the meal effect can be minimized *(81)*.

Possible contributions to a negative meal effect on indinavir were investigated in HIV-infected patients as a function of meal type *(46)*. Indinavir plasma levels and gastric pH were simultaneously measured as a function of time after oral indinavir administration.

In this clinical study, protein meals produced the greatest and most statistically consistent reduction in oral indinavir bioavailability as compared to administration with an equal volume of water. Gastric pH, as measured by radiotelemetry in these patients, showed that the protein meal caused a lengthy (4 h) pH elevation (around pH = 6.0 over this time period) as compared to other meal types or drug administration with water. Only slight pH elevations of short duration were observed with the other meals because they offer little buffer capacity to gastric acid secretion. It is suggested that the protein meal will provide the greatest potential for poor dissolution and/or precipitation of indinavir in the stomach as a function of elevated pH.

However, all meal types produced a significant negative meal effect on indinavir oral bioavailability, although not to as great an extent or as consistently from patient to patient as the protein meal. Meal types studied in addition to the high-caloric protein meal included high-caloric carbohydrate and high-caloric lipid meals as well as a noncaloric viscous meal. It is likely that high-caloric density meals, as well as high-viscosity meals slow gastric emptying and the rate of drug transport in the intestinal lumen to sites of first-pass elimination to an extent that they are no longer saturated.

Other contributions to the negative meal effect have been investigated in isolated animal and tissue experiments to include influences of intestinal regional differences (69). In the case of indinavir, rat intestinal perfusion studies show high permeability in the upper intestine and dramatically reduced permeability in the lower small intestine. The drug is metabolized by CYP3A4 in both the upper intestine and liver and the predominant intestinal metabolite is excreted into the intestinal lumen. Interestingly, no metabolism is observed in lower small intestine and metabolism is greatly reduced in the mid-jejunum as compared to the upper jejunum. Indinavir is also a substrate for intestinal P-gp and this may account for its poor permeability in the lower intestine where P-gp exports drug that is absorbed into the enterocyte back to the intestinal lumen. The fact that CYP3A4 metabolism dominates indinavir elimination in the upper small intestine while P-gp secretion controls its elimination in the lower small intestine permits some mechanistic studies in the rat. Reaction-coupled transport in the form of cellular metabolism subsequent to cell entry increases the rate of indinavir absorption into the enterocyte by increasing the concentration-gradient driving force for cellular entry. If metabolite export competes with drug export by P-gp, this could promote drug absorption across enterocytes in the upper small intestine while there would be no such competition in the lower small intestine (69).

Continued elimination as the drug moves down the intestine will depend on regional CYP3A4 and exporter activity as well as on changes in drug concentration down the intestinal tract. Meal effects on the rate of drug delivery to these sites of first-pass elimination might be anticipated to produce alterations in bioavailability. The potential for a positive meal effect from lipid-enhanced solubility compared to negative meal effects via slowing delivery to saturable sites of first-pass elimination may also be determined by variation in these elimination factors as a function of intestinal region. Some evidence for this might be gleaned by a comparison of indinavir with nelfinavir, the fourth HIV-protease inhibitor to reach the prescription marketplace. Nelfinavir shows a positive meal effect similar to saquinavir (82). In rat intestinal perfusion of upper jejunum compared to lower ileum, nelfinavir showed no region-dependent permeability as compared to the dramatic regional permeability differences just cited for indinavir (69).

4. PRACTICAL ISSUES AND REGULATORY CONSIDERATIONS

Food and drug intakes often coincide, because meals habitually serve as temporal reminders to patients of timely drug administration. Drugs may also be intentionally coadministered with meals to minimize GI side effects, a common practice for certain drug classes (e.g., NSAIDS). Administration of drugs concomitantly with or in close proximity to meals could result in a significant increase or decrease in the overall rate and extent of drug absorption and, as a consequence, may occasionally compromise efficacy or lead to adverse effects. These situations justify drug administration under a fasted state. Theo-24, which is a specific once-daily theophylline product, and alendronate, which is a bisphosphonate for improving bone mineral density are examples in this category *(83)*. On the other hand, when changes in the rate and extent of absorption lead to lower side effects or improved efficacy, concomitant administration with meals is desirable and is generally recommended (e.g., atovaquone) *(83)*. Often, changes in rate and extent of drug absorption resulting from food–drug interactions are unlikely to be clinically significant. In such cases, Food and Drug Administration (FDA)-approved labels are either silent with respect to how the drug should be administered, or may state that the drug could be taken without regard to meals (e.g., loratadine) *(83)*. Regulatory agencies generally make these assessments and recommendations after reviewing food-effect bioavailability studies for new drug applications (NDAs), factoring in their exposure-response relationships and clinical safety and efficacy database submitted with the sponsors' registration dossier.

Food intake may influence drug exposure owing to the effect that meal components have on the physiological system, which, in turn, may influence absorption (e.g., grape-fruit juice inhibits CYP3A4-mediated drug metabolism, high-fat, high-calorie meals prolong gastric emptying time and may also affect drug solubility). Drugs may also physically or chemically bind to specific food items (e.g., digoxin bioavailability may be lower with a high-fiber meal) and as a result may affect drug exposure. In the following sections, guidelines for meal-effect studies are provided from a regulatory perspective.

4.1. Drug Classification and Food Effects

4.1.1. BIOAVAILABILITY

Various physicochemical and physiological bases for food–drug interactions have been alluded to in this chapter (i.e., including delayed gastric emptying, secretions affecting GI pH and solubilization, changes in splanchnic blood flow, meal components affecting metabolism or transport systems, and chelation or complexation processes). Prediction of changes in drug exposure due to GI perturbations have been attempted using the Biopharmaceutics Classification System (BCS) of drugs (Table 3) *(84)*. It has been postulated that important food effects on bioavailability are least likely to occur with many rapidly dissolving, immediate-release drug products containing highly soluble and highly permeable drug substances (BCS class I). This is thought to be a consequence of pH- and site-independent absorption of Class I drug substances, their insensitivity to differences in dissolution and their extensive absorption *(85)*. Because the proximal intestinal region is the primary site of drug absorption, a Class I drug may undergo delayed absorption owing to meal-related prolonged gastric emptying time (resulting in longer T_{max} and lower C_{max}) with an overall unchanged extent of absorption (area under the concentration-time curve [AUC]), (e.g., immediate release theophylline) *(86)*. This

Table 3
Biopharmaceutics Classification System

Class	Solubility	Permeability	Examples
I	High	High	Acetaminophen
II	Low	High	Phenytoin
III	High	Low	Cimetidine
IV	Low	Low	Amphotericin B

From ref. *84*.

concept seems to hold true unless the drug undergoes high first-pass elimination, is highly adsorbed, complexed or unstable in the gastric milieu. Immediate-release propranolol and metoprolol are BCS Class I drugs that undergo high first-pass elimination. A large increase in the extent of absorption is observed when these drugs are administered with food *(87)*. The latter is partly attributable to the splanchnic blood flow changes caused by meal intake. Because dissolution of low solubility drugs may be enhanced with food, bioavailability may be superior, if taken with meals (e.g., carbamazepine) *(88)*. In general, however, for immediate-release drug products of BCS Classes II, III, and IV with low solubility or low permeability, food effects are most likely to result from a more complex combination of factors that influence the in vivo dissolution of the drug product and/or the absorption of the drug substance. In all cases, because the relative direction and/or the magnitude of food effects on formulation bioavailability are difficult to predict, and because the regulatory agency assesses the clinical implications of this change, a food-effect study is recommended for all new chemical entities, irrespective of their classification.

4.1.2. BIOEQUIVALENCE

Formulation factors are expected to play a minor role in bioavailability of Class I drug products because they rapidly dissolve in a wide pH-range environment and the drug is well absorbed. Although food can affect C_{max} and T_{max} by delaying gastric emptying and prolonging intestinal transit time or in certain instances increasing bioavailability, the food effect on these measures are expected to be similar for different formulations of the same Class I drug, provided they have a rapid and similar dissolution. As a result, these products should be bioequivalent under both fasted as well as fed conditions. Although an increase in exposure is observed for propranolol and metoprolol when concomitantly administered with meals, various immediate-release formulations were shown to be bioequivalent under both fasted and fed conditions. In the case of Class II, III, and IV drugs, excipients or interactions between excipients and the food-induced changes in gut physiology can contribute to food effects and consequently may influence the demonstration of bioequivalence *(89)*. When new formulations are developed with the intention of switchability, appropriate documentation of therapeutic equivalence *(90)* is therefore required.

4.2. Food Effects on Modified Release Formulations

4.2.1. BIOAVAILABILITY

Administration of a drug product with food may change the bioavailability by affecting either the drug substance or the formulation. In practice, it is difficult to determine the exact mechanism by which food changes the bioavailability of a drug product without performing specific mechanistic studies. The underlying BCS principles for food-effect expectations apply primarily to immediate-release formulations where the drug is released instantaneously from the dosage form. In these instances, solubility and permeability limit the rate of absorption. Unlike the conventional immediate-release formulations, modified-release products are specially designed in that the formulation and manufacturing variables control the release rate of the drug from the dosage form. As a consequence, these factors may play a key role in determining the outcome of a food-effect bioavailability study, irrespective of the BCS classification of the drug substance. Systemic availability of a drug from the modified-release product under fed conditions is complex. It consists of a combination of the physiological effects of meals on drug release (affecting disintegration, dissolution, degradation, or diffusion) from these dosage forms, as well as the effect of meals on drug absorption, once it is released from the modified-release product.

Modified-release oral dosage forms (e.g., sustained-release, delayed-release products) are predominantly designed to provide a therapeutic advantage over conventional immediate-release formulations such as curtailing frequent dosing intervals, minimizing peaks and troughs in plasma concentrations and overcoming the instability in the gastric pH. During the late 1970s to early 1980s, extensive experience with development of several modified-release dosage forms demonstrated that integrity of these products in the physiological environment of a fed state could present a challenge for formulation scientists. Theophylline is a noteworthy example for which a number of modified-release preparations were tested. Owing to its narrow therapeutic window of use, food effects on formulation robustness drew considerable attention of the scientific community. Although theophylline immediate-release formulation has a minimal food effect on the overall exposure, when formulated as modified-release formulations, these effects were formulation dependent. For instance, it was shown that rate as well as extent of absorption were increased when Theo-24 was administered with a high-calorie meal (about 800–1000 calories with 50% derived from fat), yet a light meal had a minimal effect. Temporal separation of meals and drug administration helped minimize the food effect. In another instance, although absorption from Theo-Dur sprinkles was reduced, food effect from Theobid-Duracap remained unchanged *(16)*.

Modified-release products may contain large amounts of drug, designed to be delivered over a prolonged period of time. Lack of formulation integrity or robustness may bear on its safe and effective use. Findings from modified-release theophylline studies during the 1970s and 1980s served as a testimony to this concern and re-enforced the need for thorough in vivo formulation evaluation before proceeding with further drug development. In fact, for regulatory purposes at the FDA, oral modified-release dosage forms are required to demonstrate lack of dose dumping, a phenomenon exemplifying the untimely release of an undesirable and unintended amount of drug from the modified-release dosage form *(91)*. To date, in vitro tests have not been consistently predictive of

either the extent of in vivo food effect or the dose dumping with the modified-release formulations. The FDA, therefore, recommends that a tangible in vivo food-effect study be conducted with all new modified-release formulations. This study serves to fulfill the regulatory requirement of a test for dose dumping. Sponsors of all modified-release dosage forms generally conduct one or more food-effect studies with the formulation under development. When food effect is identified, sponsors generally attempt to understand the source of interaction (i.e., whether food effect is owing to the drug substance or formulation). For certain drug products, insight into the temporal relationship between food and drug intake and impact of different meal types on drug exposure may be deemed clinically useful. The sponsors are encouraged to understand this relationship and when appropriate, to specify these in the dosage and administration instructions of the package inserts to optimize therapeutic benefits of the drug *(92,93)*.

4.2.2. BIOEQUIVALENCE

It has been demonstrated that various modified-release formulations of the same drug could exhibit different food effects. Some examples are theophylline and nifedipine modified-release formulations (refer to labels for Theo-24 and Uniphyl, labels for Adalat CC and Procardia) *(83)*. When new modified-release formulations are developed with the intention of switchability, it is critical to demonstrate bioequivalence under both fed and fasted conditions.

4.3. Regulatory Studies Under Fed Conditions

Concomitant food and drug intake could result in clinically significant effects that may warrant appropriate study design considerations in the clinical trials. Information on food administration in relation to drug intake also serves to optimize efficacy and safety once drugs are approved, by providing important and useful directions to patients regarding dosage and administration in package inserts. The FDA recommends that food-effect bioavailability studies be conducted for all new drugs and drug products during the Investigational New Drug (IND) period. The purpose of the study is to assess the effects of food on the rate and extent of absorption of a drug when the drug product is administered shortly after a meal as compared to administration under fasting conditions.

When generic equivalents of new drugs are developed, the manufacturer is required to submit an Abbreviated New Drug Application (ANDA). The FDA requires demonstration of switchability between the ANDA and the reference-listed drug (RLD). The bioequivalence studies in support of switchability are recommended under both fasted and fed states, with a few exceptions.

4.4. The Food-Effect Bioavailability and Fed Bioequivalence Studies Guidance

Study design variables are central to the outcome of a food-effect bioavailability study. Food effects on bioavailability are generally greatest when the drug product is administered shortly after a meal is ingested. Nutrient and caloric contents of the meal, meal volume, and meal temperature can cause physiological changes in the GI tract in a way that affects drug-product transit time, lumenal dissolution, drug permeability, and systemic availability. In general, meals that are high in total calories and fat content are more

likely to affect the GI physiology and thereby result in a larger effect on the bioavailability of a drug substance or drug product. A survey of food-effect studies in NDAs for immediate-release and modified-release products reviewed by FDA (survey conducted during 1991–1992 for drugs reviewed over the past 5–10 yr) revealed that important study design variables were not consistent in these studies and yet package inserts were not reflective of these irregularities. The FDA was also aware that the meal recommended for the food-effect bioavailability studies was of a higher caloric content than the fed bioequivalence study meal. These findings provided the impetus for harmonization through a formal guidance development from the regulatory agency addressing study design issues, data analysis, and labeling for studies under fed conditions.

The FDA published a guidance for industry in January 2003 *(94)* that provides recommendations on when food-effect bioavailability studies should be conducted as part of INDs and NDAs and when fed bioequivalence studies should be conducted as part of ANDAs. This guidance applies to both immediate-release and modified-release drug products and provides recommendations for food-effect bioavailability and fed bioequivalence study designs, data analysis, and product labeling.

4.4.1. Recommendations for Immediate-Release Drug Products

For INDs and NDAs, the guidance recommends that a food-effect bioavailability study be conducted for all new chemical entities during the IND period. These studies should be conducted early in the drug development process to guide and select formulations for further development. Food-effect bioavailability information should be available to design clinical safety and efficacy studies and to provide information for appropriate sections of product labels such as the ones entitled "Clinical Pharmacology" and "Dosage and Administration."

For ANDAs, in addition to a bioequivalence study under fasting conditions comparing the ANDA formulation to the RLD, a bioequivalence study under fed conditions is also recommended for all orally administered immediate-release drug products with the following exceptions: (a) when both test product and RLD are rapidly dissolving, have similar dissolution profiles, and contain a drug substance with high solubility and high permeability (BCS Class I), or (b) when the "Dosage and Administration" section of the RLD label states that the product should be taken only on an empty stomach, or (c) when the RLD label does not make any statements about the effect of food on absorption or administration.

4.4.2. Recommendations for Modified-Release Drug Products

The guidance recommends that food-effect bioavailability for NDAs and fed bioequivalence studies for ANDAs be performed for all modified-release dosage forms. This section provides general considerations for designing food-effect bioavailability and fed bioequivalence studies. Sponsors may choose to use alternative study designs with scientific rationale and justification. They may also consider additional studies for a better understanding of the drug product and to provide optimal labeling statements for dosage and administration (e.g., different meals and different times of drug intake in relation to meals). In studying modified-release dosage forms, consideration should be given to the possibility that coadministration with food can result in dose dumping, creating a potential safety risk for the study subjects.

4.4.2.1. General Design. The guidance recommends a randomized, balanced, single-dose, two-treatment (fed vs fasting), two-period, two-sequence crossover design for studying the effects of food on the bioavailability of either an immediate-release or a modified-release drug product. The formulation to be tested should be administered on an empty stomach (fasting condition) in one period and following a test meal (fed condition) in the other period. A similar, two-treatment, two-period, two-sequence crossover design is recommend for a fed bioequivalence study except that the treatments should consist of both test and reference formulations administered following a test meal (fed condition). An adequate washout period should separate the two treatments in food-effect bioavailability and fed bioequivalence studies.

4.4.2.2. Subject Selection. Both food-effect bioavailability and fed bioequivalence studies can be carried out in healthy volunteers drawn from the general population. Studies in the patient population are also appropriate if safety concerns preclude the enrollment of healthy subjects. A sufficient number of subjects should complete the study to achieve adequate power for a statistical assessment of food effects on bioavailability to claim an absence of food effect, or to claim bioequivalence in a fed bioequivalence study. A minimum of 12 subjects should complete the food-effect bioavailability and fed bioequivalence studies.

4.4.2.3. Dosage Strength. In general, the highest strength of a drug product intended to be marketed should be tested in food-effect bioavailability and fed bioequivalence studies. In some cases, clinical safety concerns can prevent the use of the highest strength and warrant the use of lower strengths of the dosage form. For products with multiple strengths in ANDAs, if a fed bioequivalence study has been performed on the highest strength, bioequivalence determination of one or more lower strengths can be waived based on dissolution profile comparisons *(90)*.

4.4.2.4. Test Meal. In evaluating the exposure changes of new drugs (INDs/NDAs) owing to food intake, the FDA seeks information on the "worst-case scenario" (i.e., the largest food effect likely resulting from coadministration of drugs with meals). This information is evaluated in the landscape of safety and efficacy of the drug and appropriate directions for use are incorporated in clinical trials and once the drug is approved these directions are provided in the labeling. Additional studies may be conducted if deemed useful. The FDA recommends that the fed bioequivalence study for ANDAs be conducted with a meal likely to provide maximal GI perturbation, as well.

The FDA recommends a high-fat (approx 50% of total caloric content of the meal) and high-calorie (approx 800 to 1000 calories) meal for food-effect bioavailability and fed bioequivalence studies. This test meal should derive approx 150, 250, and 500–600 calories from protein, carbohydrate, and fat, respectively. An example test meal would be two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of hash brown potatoes and 8 ounces of whole milk. Substitutions in this test meal can be made as long as the meal provides a similar amount of calories from protein, carbohydrate, and fat and has comparable meal volume and viscosity. In NDAs, it is recognized that a sponsor can choose to conduct food-effect bioavailability studies using meals with different combinations of fats, carbohydrates, and proteins for exploratory or label purposes. However, one of the meals for the food-effect bioavailability studies should be the high-fat, high-calorie test meal just described.

4.4.2.5. Administration.

Fasted Treatments: Following an overnight fast of at least 10 h, subjects should be administered the drug product with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 h post-dose. Water can be allowed as desired except for 1 h before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

Fed Treatments: Following an overnight fast of at least 10 h, subjects should start the recommended meal 30 min prior to administration of the drug product. Study subjects should eat this meal in 30 min or less; however, the drug product should be administered 30 min after start of the meal. The drug product should be administered with 240 mL (8 fluid ounces) of water. No food should be allowed for at least 4 h post-dose. Water can be allowed as desired except for 1 h before and after drug administration. Subjects should receive standardized meals scheduled at the same time in each period of the study.

4.4.2.6. Sample Collection. For both fasted and fed treatment periods, timed samples in biological fluid, usually plasma, should be collected from the subjects to permit characterization of the complete shape of the plasma concentration-time profile for the parent drug. It may be advisable to measure other moieties in the plasma, such as active metabolites *(90)*.

4.4.2.7. Data Analysis. Food-effect bioavailability studies may be exploratory and descriptive, or a sponsor may want to use a food-effect bioavailability study to make a label claim. The following exposure measures and pharmacokinetic parameters should be obtained from the resulting concentration-time curves for the test and reference products in food-effect bioavailability and fed bioequivalence studies:

Total exposure or area under the concentration-time curve ($AUC_{0\text{-inf}}$, $AUC_{0\text{-t}}$)
Peak exposure (C_{max})
Time to peak exposure (T_{max})
Lag-time (t_{lag}) for modified-release products, if present
Terminal elimination half-life ($t\frac{1}{2}\beta$)
Other relevant pharmacokinetic parameters

An equivalence approach is recommended for food-effect bioavailability (to make a claim of no food effects) and fed bioequivalence studies, analyzing data using an average criterion for AUC and C_{max}. Log-transformation of exposure measurements (AUC and C_{max}) prior to analysis is recommended. The 90% confidence interval for the ratio of population geometric means between test and reference products should be provided for $AUC_{0\text{-inf}}$, $AUC_{0\text{-t}}$, and C_{max} *(95)*. For IND or NDA food-effect bioavailability studies, the fasted treatment serves as the reference. For ANDA fed bioequivalence studies, the RLD administered under fed condition serves as the reference treatment.

5. DRUG PRODUCT LABELING ON FOOD EFFECTS

The results of food effect on drug exposure from food-effect bioavailability studies should be evaluated for clinical relevance and appropriately described in package inserts.

For an NDA, if the 90% confidence interval for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is not contained in the equivalence limits of 80–125% for either $AUC_{0\text{-inf}}$ ($AUC_{0\text{-t}}$ when appropriate) or

C_{max}, an absence of food effect on bioavailability is not established. In these situations, the sponsor should provide specific recommendations on the clinical significance of the food effect based on what is known from the total clinical database about dose–response (exposure–response) and/or pharmacokinetic–pharmacodynamic relationships of the drug under study. The sponsor should also indicate the clinical relevance of any difference in T_{max} and t_{lag}. The results of the food-effect bioavailability study should be reported factually in the "Clinical Pharmacology" section of the labeling and should form the basis for making label recommendations (e.g., *take only on an empty stomach*) in the "Dosage and Administration" section of the labeling. When important, other sections of the label may include pertinent information about interactions with meals. The following are two examples of general language for the package insert:

1. A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} and AUC were increased 57% and 45%, respectively, under fed conditions. This increase in exposure can be clinically significant, and therefore [the drug] should be taken only on an empty stomach (1 hour before or 2 hours after a meal).
2. A food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that the C_{max} was decreased 15% while the AUC remained unchanged. This decrease in exposure is not clinically significant, and therefore [the drug] could be taken without regard to meals.

An absence of food effect on bioavailability is indicated when the 90% confidence interval for the ratio of population geometric means between fed and fasted treatments, based on log-transformed data, is contained in the equivalence limits of 80–125% for AUC_{0-inf} (AUC_{0-t} when appropriate) and C_{max}. In this case, a sponsor can make a specific claim in the "Clinical Pharmacology" or "Dosage and Administration" section of the label that no food effect on bioavailability is expected provided that the T_{max} differences between the fasted and fed treatments are not clinically relevant. The following is an example of language for the package insert:

1. The C_{max} and AUC data from a food-effect study involving administration of [the drug product] to healthy volunteers under fasting conditions and with a high-fat meal indicated that exposure to the drug is not affected by food. Therefore, [the drug product] may be taken without regard to meals.

For an ANDA, bioequivalence of a test product to the RLD product under fed conditions is met with the following criteria. When the 90% confidence interval for the ratio of population geometric means between the test and RLD product, based on log-transformed data, is contained in the bioequivalence limits of 80–125% for AUC and C_{max}. Although no criterion applies to T_{max}, the T_{max} values for the test and reference products are expected to be comparable based on clinical relevance.

Historically, food-effect bioavailability studies have generated useful information on optimal dosing instructions for patients with regard to meals. The examples described in Tables 4–10 demonstrate the significance and utility of meal types, meal timing, and other general information on drug intake with meals. Note that these examples are some relevant excerpts from some approved labels; for complete information, refer to the respective package inserts.

Table 4
Videx Labeling Information

VIDEX® (didanosine) Chewable/Dispersible Buffered Tablets
VIDEX® (didanosine) Buffered Powder for Oral Solution
VIDEX® (didanosine) Pediatric Powder for Oral Solution
DOSAGE AND ADMINISTRATION
All VIDEX formulations should be administered on an empty stomach,
at least 30 minutes before or 2 hours after eating.

Table 5
Fosamax Labeling Information

FOSAMAX® (alendronate sodium) Tablets
DOSAGE AND ADMINISTRATION:
FOSAMAX must be taken at least one-half hour before the first food, beverage, or
medication of the day with plain water only. Other beverages (including mineral water),
food, and some medications are likely to reduce the absorption of FOSAMAX. Waiting
less than 30 minutes, or taking FOSAMAX with food, beverages (other than plain water)
or other medications will lessen the effect of FOSAMAX by decreasing its absorption
into the body.

Table 6
Retrovir Labeling Information

RETROVIR® (zidovudine)Tablets
RETROVIR® (zidovudine) Capsules
RETROVIR® (zidovudine) Syrup
Effect of Food on Absorption: RETROVIR may be administered with or without food.
The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine
was administered with food.
DOSAGE AND ADMINISTRATION
Adults: The recommended oral dose of RETROVIR is 600 mg per day in divided doses
in combination with other antiretroviral agents.

Table 7
Mepron Labeling Information

MEPRON® (atovaquone) Suspension
DOSAGE AND ADMINISTRATION
Dosage: *Prevention of PCP: Adults and Adolescents (13 to 16 Years)*: The recommended
oral dose is 1500 mg (10 mL) once daily administered with a meal.
Treatment of Mild-to-Moderate PCP: Adults and Adolescents (13 to 16 Years): The
recommended oral dose is 750 mg (5 mL) administered with meals twice daily for 21
days (total daily dose 1500 mg).
Note: Failure to administer MEPRON Suspension with meals may result in lower plasma
atovaquone concentrations and may limit response to therapy.

Table 8
Plendil Labeling Information

PLENDIL® (Felodipine) Extended-Release Tablets
DOSAGE AND ADMINISTRATION
PLENDIL should regularly be taken either without food or with a light meal.
PLENDIL should be swallowed whole and not crushed or chewed.

Table 9
Cognex Labeling Information

COGNEX® (Tacrine Hydrochloride) Capsules
DOSAGE AND ADMINISTRATION
Cognex® should be taken between meals whenever possible; however, if minor
GI upset occurs, Cognex® may be taken with meals to improve tolerability.
Taking Cognex® with meals can be expected to reduce plasma levels approxi-
mately 30% to 40%.

Table 10
Proscar Labeling Information

PROSCAR® (Finasteride) Tablets
DOSAGE AND ADMINISTRATION
PROSCAR may be administered with or without meals.

6. CONCLUSION AND RECOMMENDATIONS

Food-effect bioavailability studies provide insight into the exposure changes resulting from concomitant intake of drugs and meals. Exposure-response relationships translate these changes into clinical relevance, and guide clinical trial designs. This information also supports dosage and administration instructions for patients once drugs are approved, by providing directions in the package inserts on whether or not the drug could be taken with meals. Interactions with specific foods (e.g., grapefruit juice) and nutrients may need to be studied separately and are generally based on theoretical expectations of physico-chemical or physiological basis for interactions with specific drugs. Patients are more informed and concerned about drug–food interactions than ever before. Health care professionals must be aware of the potential for such interactions to provide patients with optimum oral drug therapy and to serve as a resource of drug information. The evolving literature and package inserts can offer information to help manage patients.

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8 Effects of Specific Foods and Non-Nutritive Dietary Components on Drug Metabolism

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1. INTRODUCTION

This chapter reviews the effects that specific components of foods have on the metabolism and actions of drugs in humans. The review focuses on examples of such interactions that are presently known, but it is not all-inclusive. Additional interactions are described in more detail in the chapter references.

Effects of diet on pharmacokinetics are most important clinically for drugs that have a narrow therapeutic window or index, and when the effect of a drug closely reflects its plasma concentration. For such drugs, a diet-induced change in kinetics may, at any given dosage level, alter plasma drug levels sufficiently to render the drug either ineffective or toxic. In contrast, a change in drug metabolism for a drug with a broad therapeutic window is less likely to have an effect on efficacy or safety. Attention to food–drug interactions is considered important by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO), which is an indication of their clinical relevance *(1)*.

2. BASIC APPROACH TO STUDY OF DIETARY EFFECTS ON DRUGS

2.1. Studies in Healthy Subjects and Observations in Patients

Some drug–nutrient interactions (DNIs) have been recognized in patients undergoing treatment for medical or psychiatric conditions. However, many clinically relevant DNIs are difficult to recognize and study in patients because effects of diet on drug metabolism may not be recognized, and may be attributed to other causes. Observations in patients are also likely to be confounded by underlying illness, organ dysfunction, alterations in fluid distribution, and exposure to multiple drugs. These concurrent confounding factors can limit recognition of effects of diet. Moreover, dietary variations are often complex and difficult to accurately determine in the clinical setting. Therefore, it is not surprising that many such effects have been first recognized in studies of healthy subjects under controlled experimental conditions. Studies in healthy subjects have also been important for documenting and explaining the underlying mechanisms for such interactions. Even

if it remains difficult to recognize specific occurrences of such interactions in individual patients, and such interactions are demonstrated mostly in healthy subjects, it is important to warn patients and health professionals of their potential for complicating drug therapy in clinical practice.

2.2. Drug Metabolic Pathways Likely To Be Affected by Diet

Foods—and vegetables in particular—are a complex mixture of chemicals, many of which are not recognized to provide nutritional value to the host. Nutritive components and non-nutritive chemicals may have unwanted effects on metabolic processes, including pathways of drug metabolism. Effects of some dietary substances resemble the more easily recognized effects of certain drugs on the metabolism of other drugs. Indeed, many drugs are derived from chemicals in plants. Therefore, it is not surprising that DNIs and drug–drug interactions have many common features and can be of similar magnitude *(2)*.

The cytochrome P450 (CYP) enzymes found in the endoplasmic reticulum of cells in the liver and intestinal mucosa are important for many drug–drug interactions because many drugs can either inhibit or induce one or more of these enzymes and thereby greatly influence the metabolism and clearance of other drugs. CYP enzymes are a large family of hemoproteins that oxidize both exogenous and endogenous chemicals. The enzyme reactions require both molecular oxygen and nicotinamide adenine dinucleotide phosphate. CYP-catalyzed reactions are termed mixed function oxidase or monooxygenase reactions because only one atom of the oxygen molecule is utilized for oxidizing the substrate, whereas the other oxygen atom reacts with protons to form water *(3)*.

Diets and their components may, like drugs, induce or inhibit these important enzymes. Effects of diet on drugs that are metabolized by CYP enzymes have been most studied in humans *(3)*. Effects on conjugating enzymes and P-glycoprotein (P-gp) are also important for some drugs and dietary factors. It is likely that many unknown effects of diet on drug metabolism remain to be discovered both by clinical observations and in careful metabolic studies. Additional studies are needed in the elderly and in patients with specific diseases that can affect diet and nutritional status *(4)*.

3. STUDIES IN ANIMALS AND HUMANS

Effects of diet and nutrition were initially recognized in animals, particularly rodents *(5,6)*. Some observations in animals have predicted effects of diet observed later in humans *(3)*. But it is difficult to extrapolate the conclusions of animal studies to humans because of the major differences between species in CYP and other drug-metabolizing enzymes. Additionally, differences in CYP enzymes between males and females are prominent in rodents and much less important in humans *(7)*.

In addition to being more relevant, studies in humans have other advantages. Human subjects are more compliant with dietary changes especially during short-term studies in supervised settings, making it possible to make a specific change in dietary composition without altering other components and total energy intake. Therefore, it is possible to observe effects of a change in diet without a confounding effect of a change in the total amount of energy consumed. Such studies are quite difficult in animals, without resorting to study design strategies such as pair feeding.

Effects of diet have been studied for only a small proportion of the drugs available for clinical usage. Many drugs are metabolized by several different CYP enzymes and also

by conjugating enzymes. Other pathways, such as transport by P-gp, may also be influenced by diet. Although effects of diet components on the metabolism of some drugs are well documented, it is not always evident which specific enzyme isoform is affected, and it remains difficult to extrapolate from one drug substrate to another.

3.1. Effects of Dietary Protein, Carbohydrate, and Fat

The first recognized effect of diet on human drug metabolism was seen in crossover studies in healthy male subjects. Dietary protein and carbohydrates were exchanged sequentially, while keeping fat and total energy constant *(8,9)*. Metabolic clearances of both antipyrine and theophylline were more rapid, and plasma levels of these drugs declined more rapidly, during the high-protein diet. These drugs were chosen for study because their clearances are dependent on metabolic tranformations by CYP enzymes in the liver. The metabolism of these drugs may especially reflect activity of hepatic CYP1A2 *(7)*.

In further studies, the addition of a pure protein supplement (100 g of sodium caseinate each day for 2 wk) to a calculated well-balanced diet in two subjects increased the rates of metabolism of antipyrine and theophylline, whereas in two other subjects, a supplement of carbohydrate (200 g of sucrose daily for 2 wk) had the opposite effect *(9)*. Increasing the protein content of the diet also accelerated the metabolism of propranolol *(10)* and perhaps aminopyrine and caffeine *(11)*. An effect of protein on theophylline and propranolol clearance has been shown to occur in both women and men *(10)*.

Further studies compared the effects of high-carbohydrate, high-fat, and high-protein diets on drug metabolism *(12)*. Composition of the three diets permitted observations on the effects of the isocaloric substitution of fat for carbohydrate while keeping protein constant at 10% of total calories, and the substitution of dietary protein for fat while keeping carbohydrate constant at 20% of total calories in the six healthy male subjects. As shown in Table 1, metabolic clearances for antipyrine and theophylline were greater during the high-protein dietary period than during the other two diets, as in previous studies, but there were no differences in the drug clearances between the high-fat and high-carbohydrate dietary periods. The conclusion was that the substitution of protein for either fat or carbohydrate can increase drug oxidation rates, whereas exchanging carbohydrate and fat has no major effect *(12)*.

The lack of an effect of carbohydrate and fat, including both saturated and unsaturated fats, were confirmed in an additional study in nine normal males *(12)*. Large isocaloric exchanges of carbohydrate for either unsaturated fat (corn oil) or saturated fat (butter) were accomplished while maintaining dietary protein constant at 15% of total calories. No significant changes in the metabolism of antipyrine and theophylline were observed *(12)*. Others have confirmed that substituting saturated and unsaturated fat in the diet of normal subjects has no effect on the metabolism of antipyrine *(13)*. Therefore, isocaloric exchanges of saturated fat, unsaturated fat, and carbohydrate do not appear to influence the metabolism of at least some substrates for CYP enzymes in humans. Changes in dietary fat can influence hepatic drug oxidations in animals *(5)*. It remains possible that some CYP enzymes or other enzymes important in drug metabolism may be influenced by dietary fat.

Thus, protein content of the diet appears to be more important for regulating oxidative drug metabolism in humans than carbohydrate or fat. Moreover, studies at different

Table 1
Drug Metabolism During Diets High in Protein, Carbohydrate, or Fat

	Diet Composition			Clearance	
	Protein	Fat	Carbohydrate	Antipyrine	Theophylline
Diet		(%)		(mL kg^{-1} min^{-1})	
High carbohydrate	10	10	80	0.57± 0.02	0.76± 0.06
High fat	10	70	20	0.59± 0.02	0.74± 0.04
High protein	50	30	20	0.71± 0.05[*†]	0.98± 0.08[¶]

Each calculated diet was consumed in the order shown by six normal male subjects, and antipyrine metabolism was studied on day 10 and theophylline metabolism on day 14 of each dietary period. Clearance values (means ± SE) during the high-protein dietary period were significantly different from the high carbohydrate dietary period ([*]$p < 0.005$), and the high fat dietary period ([†]$p < 0.01$, [¶] $p < 0.02$, paired t-test).
From ref. 12.

intakes of total calories indicate that dietary protein can influence drug-oxidation rates at levels of energy intake other than that needed to maintain body weight (14). Protein content of the diet may influence drug metabolism in patients with cirrhosis (15) as well as other clinical settings. For example, in hospitalized children with asthma, clearance of theophylline was greater during a high-protein diet than during two diets lower in protein content. Theophylline levels were higher and wheezing episodes and requirements for additional medications less frequent during a low-protein diet (Table 2) (16). In adults with obstructive pulmonary disease, theophylline concentrations were lower during a high-protein diet than during a high-carbohydrate diet (17).

The mechanism whereby dietary protein accelerates drug oxidation in humans is not established. Although human studies have mostly involved solid-food diets, it is unlikely that non-nutritive components of the diet were responsible for the effects ascribed to protein. The effects of feeding high-protein diets have been observed by different investigators that presumably were not uniform in terms of the solid foods in the experimental diets. Moreover, a protein supplement had the same effect as a high-protein diet in healthy subjects (9). Effects of dietary protein on drug metabolism in humans were corroborated by earlier studies of high-protein diets in rodents, although the results in rodents are more complex owing to marked differences between males and females that are not found in humans. Because the diets for the human studies were adequate in all essential nutrients, the substantial effects on drug metabolism were not a result of the correction of deficiencies in protein or other nutrients. Impaired gastrointestinal (GI) absorption or altered distribution after absorption of the test drugs has also not been a factor in such studies (18).

The mechanisms of protein effects on CYP enzymes in laboratory animals are also not known (3). High-protein intakes augment hepatic microsomal CYP content, liver weight, and mitotic indices in rodents (5,19). These effects are reminiscent of the inducing effects of phenobarbital. Certain amino acids such as tryptophan and oxidized sulfur may increase liver-protein synthesis and induce the mixed-function oxidase system in laboratory animals and in liver cell cultures (20–24).

The metabolism of steroid hormones occurs primarily in the liver and by CYP enzymes, microsomal reductases, and conjugating enzymes (25). Dietary effects on these enzymes might also be expected. Indeed, an increase in the protein-to-carbohydrate

Table 2

Theophylline Clearances and Serum Concentrations and the Total Number of Wheezing Episodes Occurring in Children With Asthma During Diets Differing in Protein Content

| | Diet Composition | | | | Theophylline Steady-State Serum | |
| Diet | Protein | Fat | Carbohydrate | Clearance $(L\ kg^{-1}\ min^{-1})$ | Concentration $(mg\ mL^{-1})$ | Wheezing Episodes |
	(%)					
Normal	6–8	35	57–60	0.059 ± 0.015	14.04 ± 3.97	22
High protein	14–20	20	60–66	$0.071 \pm 0.019^*$	10.66 ± 3.43	17
High carbohydrate	2–3	20	77–78	$0.048 \pm 0.016^*$	17.24 ± 5.68	9

After-steady state serum concentrations of theophylline of 10–20 µg/mL were achieved, children (age 7–14 yr) were fed the three test diets in the order shown, each for 12 d (with 2 d on a usual diet between each of the test diets). Values for theophylline clearance and concentration are means ± S.D.

Significantly different from results obtained during the normal diet ($p < 0.001$, paired *t*-test). (From refs. *16,139.*)

ratio of the diet can increase estrogen 2-hydroxylation *(26)* and decrease androgen 5α-reduction in healthy subjects *(27)*. The same dietary change may alter the plasma concentrations of testosterone and cortisol in a reciprocal fashion and produce parallel changes in the binding globulins for these steroids *(28)*. These effects mimic those induced by phenobarbital in humans *(29)*.

Dietary protein can also alter the disposition of drugs that are cleared primarily by the kidneys, by influencing renal plasma flow, creatinine clearance, and renal tubular transport *(30, 31)*. Renal tubular transport of basic drugs or drug metabolites may be especially reduced. For example, allopurinol is readily absorbed from the GI tract and rapidly converted by hepatic xanthine oxidase or aldehyde oxidase to its major metabolite, oxypurinol, which is then excreted largely unchanged in the urine. Berlinger et al. (1985) studied the pharmacokinetics of allopurinol in normal subjects during consumption of a high protein and low protein diets. A marked increase in area under the curve for oxypurinol and a decrease in renal clearance of this metabolite were demonstrated in healthy subjects during a low protein diet compared to a high protein diet. It was postulated that protein restriction produced an increase in the net tubular reabsorption of oxypurinol *(32)*. Therefore, in some patients treated with allopurinol, dietary restriction may enhance the retention of oxypurinol and increase the likelihood of adverse effects.

Protein and other specific food components in the diet can also enhance or interfere with the absorption of some drugs. For example, theophylline absorption has been reported to be faster after a high-protein meal than after a high-carbohydrate or high-fat meal *(32a)*. The buffering capacity of protein is greater than for carbohydrate and fat. Therefore, a high-protein diet may enhance the bioavailability of acid-labile drugs to a greater extent than a lower protein diet.

A dietary component can influence delivery of a drug to its central site of action. For example, a low-protein diet can benefit patients with Parkinson's disease during treatment with levodopa by reducing unpredictable fluctuations in response (the "on–off" phenomenon) *(33–35)*. Levodopa absorption and blood levels are not affected by protein

restriction, indicating that the effect occurs at a more central level *(36,37)*. Rather, a high-protein intake provides amino acids, especially large neutral amino acids, which inhibit the transport of levodopa across the blood–brain barrier (BBB) by the aromatic amino acid transporter *(38)*. This leads to reduced brain dopamine formation from exogenous levodopa *(39)*. A protein redistribution diet, with protein restriction during the day and unrestricted intake near bedtime was found to be beneficial in clinical studies *(36,40–42)*. But deficiencies may develop if intakes of protein or other nutrients are marginal prior to the dietary change *(43)*. A diet balanced in protein and carbohydrate has also been advocated *(44)*. As described later, efficacy of levodopa can also be affected by vitamin B_6 intake.

3.2. Cruciferous Vegetables

Cruciferous vegetables and alfalfa meal, when added to the diet of laboratory animals, were found to markedly induce chemical oxidation *(45–47)*. The inducing effects of cruciferous vegetables were accounted for primarily by indoles, including indole-3-carbinol and indole-3-acetonitrile *(48)*. Certain strains of cabbage and Brussels sprouts are particularly rich in these inducing substances. These vegetables and indoles have effects on the metabolism of environmental carcinogens such as aflatoxin B_1 and binding of their metabolites to DNA *(49–51)*.

These observations led to studies in humans. Drug oxidation and conjugation have been studied in normal subjects on calculated diets. Brussels sprouts and cabbage were substituted for other vegetables shown not to enhance mixed function oxidation in animals. The cruciferous vegetables significantly enhanced the oxidative metabolism of antipyrine and phenacetin (Tables 3 and 4) *(46)* and conjugation of acetaminophen *(52)*.

Cruciferous vegetables can complicate the use of warfarin and other coumarin anticoagulants. The vitamin K content of these vegetables and other foods can antagonize the anticoagulant effects of these drugs. Furthermore, a diet rich in Brussels sprouts can enhance the elimination rate of warfarin *(53)*. Coumarins in some herbal teas may enhance effects of coumarin anticoagulants *(1)*. Maintaining a reasonably constant intake of vitamin K and foods containing other substances that can influence the metabolism and effects of these anticoagulant drugs can help to keep the prothrombin time within the desired therapeutic range during long-term anticoagulation.

3.3. Grapefruit Juice

The effect of grapefruit juice on metabolism of drugs that are metabolized by CYP3A4 has become perhaps the best-known DNI, and is discussed in detail in the next chapter. The initial serendipitous observation of this effect occurred in 1989 when grapefruit juice was used as a vehicle in a study of the effects of alcohol on felodipine metabolism *(53a)*. It was noted that grapefruit juice decreased the oral clearance of this calcium channel blocker, and enhanced the area under the plasma concentration vs time curve. Because the bioavailability of the drug was increased, the systemic exposure and pharmacodynamic effects increased. Subsequently, interactions between a variety of drugs and grapefruit juice were studied *(54)* (*see* Chapter 9).

Grapefruit juice contains furanocoumarins and other substances that can inhibit CYP3A and to some extent other CYP isoforms. CYP3A inhibition by grapefruit juice occurs only in the small intestine. As a result, drugs that are substantially metabolized by

Table 3

Effects of Dietary Brussels Sprouts and Cabbage on Antipyrine Metabolism in Healthy Subjects

Diet	Antipyrine Clearance (L h^{-1})
Control (first time)	3.09 ± 0.31
Brussels sprouts and cabbage	3.44 ± 0.32*
Control (second time)	2.98 ± 0.33

Each diet was fed to 10 healthy subjects in the sequence shown. Values are means $\pm$ S.E.
*Significantly different from both control diet periods ($p < 0.002$, paired t-test). (From ref. *46.*)

Table 4

Effects of Dietary Brussels Sprouts and Cabbage on Phenacetin Metabolism in Healthy Subjects

Diet	Phenacetin AUC (μg h mL^{-1})
Control (first time)	5283 ± 1864
Brussels sprouts and cabbage	2718 ± 779*
Control (second time)	4391 ± 1506

Diets were fed to 10 subjects in the order shown. Values for area under the plasma concentration vs time curve (AUC) are means $\pm$ S.E. for 0–7 h.

* Plasma phenacetin concentrations were significantly lower at 3, 4, 5, and 7 h and plasma levels of total N-acetyl-p-aminophenol were significantly higher at 1, 2, and 7 h during the test diet period than during both control diet periods ($p < 0.05$–0.001, paired t-test). (From ref. *46.*)

CYP3A during absorption from the intestinal lumen are most notably affected by grapefruit juice. Drugs administered parenterally are not affected. Inhibition is both reversible and irreversible. Recovery from irreversible inhibition requires synthesis of new enzyme, and the limited information available suggests this may take up to 72 h after grapefruit juice exposure *(54)*. Inhibition by grapefruit juice is clinically important when drug response closely reflects plasma concentration, as is the case for calcium channel blockers.

Because this interaction occurs primarily with drugs that are subject to extensive first-pass metabolism by CYP3A in the intestine, there are many drugs that are not affected. As a result, it is often possible within a class of drugs to choose an alternative that is not subject to inhibition by grapefruit juice, or to predict whether this interaction might occur based on the known pharmacokinetic features and pathways of metabolism of a drug. Examples of drug groups where such choices can be made include calcium channel antagonists, β-hydroxy-βmethylglutaryl-CoA reductase inhibitors, sedative-hypnotics and anxiolytics, psychotropics, and antihistamines *(54)*. However, it must be kept in mind that inhibition of CYP3A4 may not be the only mechanism whereby grapefruit juice affects drug metabolism. Drug transporters such as P-gp in enterocytes may also be affected, and this mechanism may be more important than the CYP3A4 inhibition for some drugs such as cyclosporin *(54,55)*.

3.4. Herbs

Herbs represent complex and incompletely characterized mixtures of chemicals. Their effects on the metabolism and actions of drugs have received recent attention but remain largely unexplored. Reports of possible herb–drug interactions are often incomplete. Reviewers of this field have concluded that such interactions almost certainly occur and may put patients at risk, but further studies are needed *(56–59)*.

Interactions of herbs with warfarin, for example, are in general poorly documented *(59)*. Bleeding has been reported when warfarin is combined with ginkgo (*Ginkgo biloba*) *(59)*. However, a controlled prospective study failed to confirm such an effect *(60)*. Examples of other herbs reported to interact with warfarin to cause bleeding include dong quai (*Angelica sinensis*) *(61)* and danshen (*Salvia miltiorrhiza*) *(62)*.

St John's wort (*Hypericum perforatum*) can cause induction of CYP3A4 and 2E1 *(63)*, possibly 2C9 and 1A2, and P-gp, and decrease the blood concentrations or effects of drugs such as digoxin, theophylline, cyclosporin, protease inhibitors (e.g., indinavir and nevirapine), coumarin-derived anticoagulants, amitriptyline, and oral contraceptives *(56,64–66)*. The inducing effect on CYP3A4 is greater in females than in males *(63)*. Serotonin syndrome has been noted in patients who take St. John's wort along with serotonin-reuptake inhibitors, nefazodone, or triptans *(56,64,65)*. Garlic oil was found to reduce CYP2E1 in healthy subjects *(63)*.

Ginseng has been reported to induce mania in patients taking antidepressants *(56,67)*. Heavy betel nut (*Areca catechu*) consumption may precipitate extrapyramidal side effects with schizophrenic patients on neuroleptic drugs *(68)*. Yohimbine (*Pausinystalia yohimbe*) may increase risk of hypertension in patients taking tricyclic antidepressants *(56)*. Liquorice (*Glycyrrhiza glabra*) may potentiate oral and topical corticosteroids *(56)* and digitalis *(69)*. Heavy intake of licorice products can be an inapparent cause of hypertension that is resistant to drug therapy *(70)*.

Because herbal products in the United States are not subject to standardization and regulation of quality, their content is often variable and uncertain. Many of the chemical components of these plant products and their potentially significant effects on drug disposition and action remain unknown. Therefore, it is widely recommended that patients taking prescribed drugs should not take herbal remedies, unless authorized by their physicians *(56,65)*.

3.5. Methylxanthines

Methylxanthines such as caffeine (1,3,7-trimethylxanthine) are common natural, non-nutritive components of foods and especially beverages such as coffee and tea. Caffeine is added to many popular carbonated beverages. Theophylline (1,3-dimethylxanthine) is a drug used extensively as a bronchodilator in treating asthma and related pulmonary conditions.

CYP enzymes extensively metabolize these and other methylxanthines. When ingested regularly, these substances can also accumulate and influence drug metabolism. Effects on drug metabolism are complex, and may involve saturation and inhibition as well as induction of hepatic enzymes that metabolize methylxanthines and other drugs and chemicals. For example, with repeated doses, theobromine (3,7-dimethylxanthine), a major methylxanthine in chocolate, lowers its own metabolism by saturating or inhibiting hepatic enzymes; but several days after the last repeated dose, induction of theobro-

mine hepatic metabolism can be demonstrated *(71)*. Theobromine induction of its own metabolism was shown to occur in rats as well *(72)*. Theophylline also can induce its own metabolism in humans *(73)*. Studies in healthy subjects indicate that a pool of methylxanthines derived from the diet may compete with theophylline for common saturable metabolic pathways *(74)*.

Cola nuts, which are reported to contain 2.3% caffeine, are commonly chewed in Africa and elsewhere for stimulant effects. Antipyrine half-life was prolonged by cola-nut chewing in a cross-sectional study employing multiple regression analysis in Gambian villagers *(75)*. However, this effect was not seen in a controlled study in normal male volunteers in the United States *(76)*. This difference is not explained, but it is possible that other nutritional factors influenced metabolism of the test drug antipyrine in the West African study.

An interaction between caffeine and clozapine, both of which are CYP1A2 substrates, has been demonstrated in schizophrenic patients *(77)*. In seven subjects on monotherapy, clozapine concentrations were lower after they were changed to a caffeine-free diet for 5 d. Therefore, habitual caffeine intake can alter the metabolism of this drug. The findings suggest that caffeine intake should be medically supervised and levels of clozapine monitored in some schizophrenic patients *(77)*.

3.6. Food Preparation

Chemical changes in foods are induced during cooking at particularly high temperatures, and the chemical products may be absorbed and then influence drug-metabolic pathways. For example, charcoal broiling of meats leads to formation of polycyclic aromatic hydrocarbons similar to those found in cigarette smoke. Polycyclic aromatic hydrocarbons in cigarette smoke probably account for enhanced drug-oxidation rates in smokers *(78)*.

These chemicals are products of incomplete combustion, and are produced during charcoal broiling when drippings contact the hot coals, and are then volatilized and redeposited on the meat *(79)*. Oral administration of such compounds to rats increases benzo(*a*)pyrene hydroxylase activity in the intestine and liver. Moreover, feeding charcoal-broiled beef induces intestinal metabolism of phenacetin in the rat *(80)*.

Charcoal-broiled beef can have substantial effects on the metabolism of drugs such as phenacetin, theophylline, and antipyrine in healthy subjects *(81–83)*. Pharmacokinetics of these drugs were studied during periods of daily ingestion of standard portions of hamburger (8 ounces) and steak (6 ounces) that were broiled over charcoal and fed twice daily as part of a calculated test diet, and again during control diet periods, when aluminum foil was placed under the meat and drippings aspirated by hand to prevent their falling onto the burning charcoal. Phenacetin plasma concentrations were markedly reduced by consumption of charcoal-broiled beef, and the ratio of the major metabolite of phenacetin, *N*-acetyl-*p*-aminophenol (acetaminophen) to phenacetin was increased (Table 5) *(81)*. Therefore, both charcoal-broiled beef and cigarette smoking enhance phenacetin *O*-dealkylation in humans. In a separate study, clearance of antipyrine and theophylline were increased by consumption of charcoal-broiled beef *(82)*. Clinical usage of phenacetin has been largely replaced by acetaminophen, which is metabolized primarily by conjugation. Acetaminophen metabolism was not influenced by consumption of charcoal-broiled beef *(84)*.

Table 5
Effect of Charcoal-Broiled Beef on Phenacetin Metabolism in Healthy Subjects

Diet	Phenacetin AUC ($\mu g\ min\ mL^{-1}$)
Control (first time)	170 ± 40
Charcoal-broiled beef	37 ± 8*
Control (second time)	174 ± 53

Each diet was consumed by nine subjects in the order shown. Values for area under the plasma concentration vs time curve (AUC) are means $\pm$ S.E. for 0–7 h.

*Significantly different during the test diet than during control diet periods ($p < 0.01$, first time; $p < 0.025$, second time; paired t-test). (From ref. *81*.)

3.7. Tyramine and Related Substances

Hypertensive reactions may occur in patients taking monoamine oxidase inhibitors (MAOIs) after ingestion of foods containing tyramine, such as some highly flavored cheeses. These "tyramine reactions" or "cheese reactions" are among the best-known DNIs *(85)*. They began to be reported with use of the irreversible MAOIs from about 1961. By about 1965, the underlying mechanisms were understood to involve tyramine-provoked hypertension, and fairly simple dietary precautions could be recommended *(86,87)*. However, fear of these sometimes severe reactions persisted, and greatly limited the use of first generation, nonselective MAOIs as antidepressants, such as tranylcypromine, pargyline, phenelzine, selegiline, and isocarboxazide *(85,86)*.

Manifestations of these sudden and dramatic reactions may include hypertension with palpitation, nausea, vomiting, and headache. The potentially life-threatening hypertensive crises, which may occur within 1 h of ingestion of the tyramine-containing food, are described as resembling the paroxysmal symptoms of pheochromocytomas, which are neuroendocrine tumors that intermittently release catecholamines into the circulation *(85)*.

Tyramine and other phenylethylamines are formed from tyrosine owing to the actions of bacterial and fungal tyrosine decarboxylase. Monoamine oxidase in the intestine and liver normally oxidatively deaminates phenylethylamines that are absorbed from the diet. When monoamine oxidase is inhibited in these tissues by a drug, dietary phenylethylamines can be absorbed systemically and displace norepinephrine from storage vesicles in the nervous system. Large amounts of this neurotransmitter are then released into synapses, which can lead to severe acute hypertension, and additional complications such as myocardial infarction and thrombotic or hemorrhagic stroke *(1)*. Paradoxically, the interaction between cheddar cheese and tranylcypromine was used to therapeutic advantage in two patients with severe postural hypotension *(88)*.

Although highly flavored cheeses, such as cheddar, are most commonly associated with this adverse drug interaction, other high-protein foods that have started to ferment may also contain large amounts of tyramine or other phenylethylamines *(1)*. These include pickled herring, yeast preparations, broad beans, and certain wines (e.g., Chi-

anti) and beers *(89,90)*, Amounts of these substances in foods and beers can vary greatly from sample to sample. Tap lager beers prepared by bottom fermentation may contain amounts of tyramine that are significant even for moderate levels of beer consumption, and have been implicated in hypertensive reactions to MAOIs *(89)*.

Rates of absorption and delivery of dietary phenylethylamines to the systemic circulation can be greatly affected by other foods in the meal. Iron deficiency is said to increase susceptibility to these reactions. Concurrent sympathomimetic drugs may also exacerbate tyramine reactions. Reactions related to ingestion of broad beans (fava beans) may be due in part to their content of dopa or its amine derivative dopamine *(1)*.

Other drugs with weak monoamine oxidase-inhibiting properties, such as furazolidine (an antiprotozoal) and meperidine (a narcotic analgesic) have also been implicated in tyramine reactions *(1)*. Procarbazine has been reported to cause hypertension in patients consuming tyramine-containing foods while taking this drug for Hodgkin's disease *(91)*. Isoniazid (an antituberculosis drug) is a weak MAOI that may cause tyramine reactions in combination with tricyclic antidepressants *(92)*.

Strategies to avoid tyramine reactions in patients taking MAOIs have included dietary restrictions and development of new pharmaceutical products *(93)*. Based on analysis of phenylethylamine content of foods and case reports of diet-related hypertensive reactions, rational guidelines for diet planning and counseling of patients on MAOI drug regimens have been described. Some confidence in the safe use of these drugs may be provided by beginning dietary counseling before drug therapy, keeping tyramine intake below 5 mg, and recommending consumption of only fresh foods. Any food rich in aromatic amino acids can become high in tyramine with aging, or when microbial contamination is followed by prolonged storage or spoilage occurs *(87)*. It has been recommended that all tap (draft) beers should be avoided even at modest levels of consumption *(90)*. Dietary compliance should be monitored, and dietary restrictions continued 4 wk after completion of drug therapy *(87)*.

Altering the route of drug administration has been explored. For example, a selegiline transdermal system, when used for treating depression, apparently allows inhibition of central nervous system monoamine oxidase type A (MAO-A) and monoamine oxidase type B (MAO-B) enzymes while avoiding inhibition of intestinal and liver MAO-A enzyme. Transdermal administration of this drug to adults with major depression was reported to not significantly increase sensitivity to dietary tyramine *(94)*.

Pharmaceutical strategies of particular interest include combining MAOIs with tricyclic antidepressants and development of new selective and reversible MAOIs. Effectiveness of such approaches can be assessed by the tyramine pressor test *(93)*. Selegiline is approved as adjunctive treatment of Parkinson's disease using lower doses (e.g., 10 mg/d by mouth) than is used for depression. When used in this manner, selegiline does not inhibit intestinal and hepatic MAO-A, and is therefore a selective, irreversible cerebral MAO-B inhibitor without significant risk of the tyramine reaction *(95,96)*. However, this dose-dependent selectivity is not absolute, and a few hypertensive reactions have been reported even at the recommended doses for Parkinson's disease, and there is some selectivity retained at higher doses as well *(97,98)*. Rapidly reversible MAO-A inhibitors, such as moclobemide, a novel benzamide, are reported to carry less risk of a hypertensive reaction and yet appear to be effective antidepressants *(97,99)*, but with doses above 900 mg/d the risk of interaction with dietary tyramine may be significant *(100)*.

3.8. Alcohol

Adverse reactions develop soon after alcohol is consumed in patients treated with tetraethylthiuram disulfide (disulfuram). For this reason, the drug has been used in alcohol treatment programs as an adjunctive means of encouraging abstinence. The unpleasant manifestations of this food–drug interaction may include flushing, headache, nausea, vomiting, weakness, vertigo, hypotension, blurred vision, and seizures. The drug inhibits the enzyme aldehyde dehydrogenase, which oxidizes acetaldehyde that is derived from alcohol. Cyanamide is a disulfiram-like drug that has been used for the management of alcoholism in some countries such as Japan, but has been associated with adverse effects on the liver *(101)*. The disulfiram reaction has been reproduced using acetaldehyde, and has therefore been termed the "acetaldehyde syndrome." It can occur with ingestion of foods cooked with wine, wine vinegar, or wine-containing desserts *(102)*.

Other drugs have been found to cause disulfuran-like reactions in association with alcohol *(1)*. These drugs, some of which are aldehyde dehydrogenase inhibitors, include cyanamide, metronidazole, sulfonylureas *(103)*, griseofulvin *(104)*, procarbazine, some cephalosporin antibiotics, and possibly ketoconazole *(105)*. Some mushrooms contain inhibitors of aldehyde dehydrogenase and may cause such reactions *(106,107)*. Inhibitors of this enzyme may be found in other foods, such as cabbage *(108)*.

The potential for metronidazole to cause a disulfiram-like reaction has been questioned, based on lack of convincing case reports or evidence for inhibition of hepatic alcohol dehydrogenase *(109,110)*. This drug may increase acetaldehyde production in the colon, at least in rats *(111)*.

Cephalosporin antibiotics have differing effects on the liver alcohol dehydrogenase and circulating acetaldehyde levels *(112,113)*. Those reported to cause disulfiram-like reactions include cefoperazone, moxalactam, ceftriaxone, cefonicid, and cefmetazole *(114–116)*. Reactive metabolites rather than the parent drugs are thought to be responsible for the enzyme inhibition *(117)*. Drugs with an *N*-methyltetrazolethiol side chain in the 3' position, and certain other side chains are particularly associated with this reaction. Drugs with these structural features can also inhibit vitamin K epoxide reductase and cause coagulopathies (hypoprothrombinemia and bleeding), particularly in patients with vitamin K deficiency *(114,118–121)*. Vitamin K administration can prevent this drug-induced coagulopathy.

3.9. Vitamins

A number of vitamin deficiencies alter hepatic mixed-function oxidations in laboratory animals *(5,6,122)*. Therefore, it is likely that ingestion of vitamins may alter drug metabolism in humans by correcting evident or subtle vitamin deficiencies in patients. But there are few studies in humans, and the observations in animals are difficult to translate to human populations owing to marked species differences in drug metabolism. There is also some potential for large doses of vitamins to alter drug metabolism in subjects without vitamin deficiencies.

The effects of vitamin C have been most studied in humans. Several species, including humans, guinea pigs, and other primates, as well as some strains of rats, are unable to synthesize vitamin C, and therefore require small amounts in the diet. Interrelationships between vitamin C and CYP enzymes were examined in some detail in early studies *(123)*. Depletion of this vitamin in the guinea pig and in a rat strain unable to synthesize

ascorbic acid impairs oxidative drug metabolism and reduces CYP and most associated enzyme activities *(124,125)*. Amounts of ascorbic acid required for optimal induction of CYP by exogenous chemicals (e.g., polychlorinated biphenyls) exceed the amounts required to maintain induced levels of mixed-function oxidase activities *(125)*.

Observations in a few patient populations suggest that vitamin C deficiency impairs drug metabolism in humans. For example, antipyrine half-lives were longer in liver disease patients with low leukocyte ascorbate levels than in patients with higher ascorbate levels *(126)*. Ascorbic acid supplementation of elderly patients *(127)* and diabetics *(128)* with low initial leukocyte or serum ascorbate levels resulted in shortening of antipyrine half-lives. It is possible that additional nutritional deficiencies contributed to impaired drug metabolism in these studies.

Studies in healthy subjects have not found a substantial effect of vitamin C deficiency. For example, subclinical vitamin C deficiency of short duration in five male volunteers had no significant effect on antipyrine metabolism *(129)*. In 10 elderly subjects who underwent ascorbate depletion for 4 wk, no significant change in caffeine metabolism was reported *(130)*. It is possible that effects on drug metabolism occur in humans only with more severe deficiency of vitamin C than was induced in these experiments.

Large doses of vitamin C can decrease monooxygenase activities in animals *(131)*. Such effects have been little studied in humans. Vitamin C administered in large doses increased antipyrine clearance in one study *(132)* but not in another *(133)*. A small influence on warfarin disposition was not considered clinically significant *(134)*. Large doses of this vitamin may have effects on nonoxidative pathways of drug metabolism. For example, the vitamin may reduce sulfate conjugation of drugs such as salicylamide and acetaminophen by competing for available sulfate *(135,136)* (*see* Chapter 1).

Administration of vitamin B_6 can enhance the peripheral conversion of levodopa to dopamine by dopa-decarboxylase, a pyridoxine-requiring enzyme, such that less is available to cross the BBB for conversion there to dopamine. Dopamine itself does not cross the BBB. Carbidopa, an inhibitor of peripheral dopamine decarboxylase, which enhances the efficacy and reduces side effects of levodopa, also prevents the reduction in efficacy of levodopa by exogenous vitamin B_6 *(137)*.

4. CONCLUSION AND IMPLICATIONS

It is apparent that the variety of macronutrients and micronutrients found in foods can have major effects on the metabolism and clinical effects of some drugs. There is incomplete understanding of many of these interactions, because experimental and clinical observations are incomplete. It is likely also that there are many specific effects of dietary components on drug metabolism and actions that remain to be discovered. Given the complex mixture of chemicals found in foods and the large number of new drugs that come to market yearly, interactions between dietary components and drugs will require continued attention from investigators and health professionals in the future.

Studies in healthy subjects indicated that diet may explain part of the intraindividual variations in drug metabolism rates that occur over time *(138)*. Further studies in relevant patient populations on the effects on drug metabolism of naturally occurring dietary variations are needed. As knowledge of these interactions increases, there will be an increasing need for physicians, pharmacists, and drug manufacturers to provide informa-

tion on DNIs to patients. It must be kept in mind that public understanding of diet and nutrition is less than desirable, and compliance with dietary recommendations is often not satisfactory. Compliance is particularly difficult for individuals who are physically or mentally impaired, or do not normally prepare their own food. Therefore, monitoring strategies may be considered for some drugs that are particularly affected by changes in diet.

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9 Grapefruit Juice–Drug Interaction Issues

David G. Bailey

1. INTRODUCTION

Medications and food are often taken together. Linking drug administration to a regular event like a meal can improve the patient's adherence to the treatment regimen, especially in the elderly *(1)*. However, concomitant drug and food intake create the opportunity for an interaction that may change (increase or decrease) drug benefit or toxicity.

The response to a drug is largely dependent on its concentration at the cellular site of action (drug receptor). Increased drug concentration generally causes enhanced magnitude and duration of effect, whereas decreased drug concentration produces the opposite result. The concentration at the drug receptor of an orally administered medication is determined by the net result of oral bioavailability (rate and fraction of the oral dose of drug absorbed into the systemic blood circulation), distribution from the circulation to the drug receptor, and removal from the drug receptor.

For most medications, absorption from the gastrointestinal (GI) tract occurs in the proximal portion of the small intestines (duodenum). This is mainly owing to much greater surface area and blood flow compared to the stomach. Before gaining access into the systemic circulation, drugs must pass through the gut wall, enter the portal blood circulation, and pass through the liver (Fig. 1). Mechanisms in both the gut wall and the liver are capable of reducing drug bioavailability. This can occur by enzymatic conversion of drug to derivatives (metabolites) at these sites, a process known as presystemic or first-pass drug metabolism. Oral drug bioavailability is commonly determined by measuring the systemic plasma drug concentration–time profile. A change in its rate (as indicated by peak drug concentration [C_{max}] and time to C_{max} [t_{max}]), or extent (as determined by the area under the drug concentration–time curve [AUC]), can have important implications for pharmacotherapy.

More than 10 years ago, our group observed that grapefruit juice markedly increased the rate and extent of oral bioavailability of the dihydropyridine calcium channel antagonist, felodipine. It was originally suggested from a secondary finding in an ethanol–drug interaction study *(2)*. In this investigation, grapefruit juice had been chosen to mask the taste of the ethanol. Results showed that plasma drug concentrations were not different
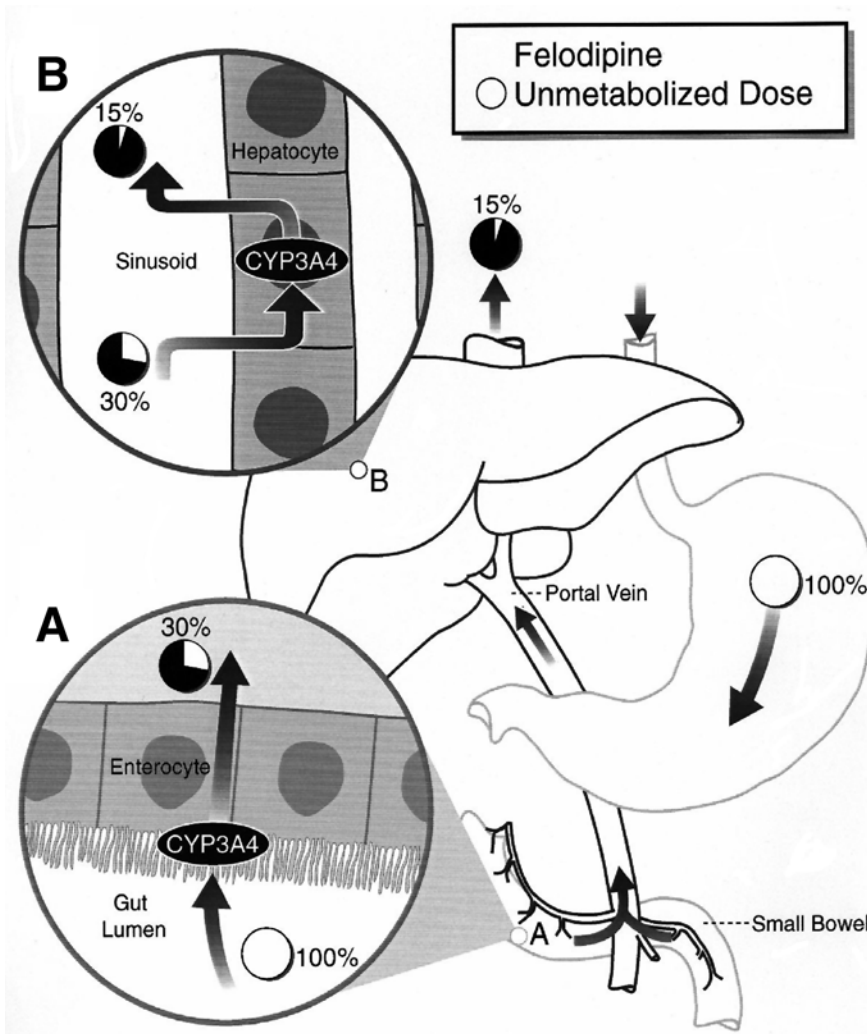
Fig. 1. Sequential presystemic felodipine metabolism by CYP3A4 in apical enterocytes of the small bowel (**A**) and then the hepatocytes of the liver (**B**). The percent of unmetabolized felodipine is presented before and after passage through the gut wall and the liver.

between felodipine plus ethanol (in grapefruit juice) or felodipine alone (with grapefruit juice). However, both groups had concentrations that were several-fold higher than those observed in other pharmacokinetic investigations in which the same dose of felodipine was given with water. A systematic examination for obvious possible causes, such as incorrect dose or drug assay problems, did not resolve this discrepancy. This eventually resulted in a pilot project in a single volunteer to judge the possible role of the juice. Plasma felodipine concentrations were more than fivefold higher with grapefruit juice compared to those with water *(3)*. Subsequently, the interaction was established in a formal clinical study involving patients with untreated borderline hypertension *(4)*. This finding represented a new type of food–drug interaction and critically illustrated the importance of unexpected observations in research.

2. REVIEW OF BASIC SCIENCE

Felodipine has been the most extensively studied probe for grapefruit juice–drug interactions. Normally, felodipine is completely absorbed from the GI tract following oral administration *(5)*. Thus, grapefruit juice did not act by improving drug dissolution or other pharmaceutical property of the drug formulation. However, felodipine has low inherent oral bioavailability averaging 15% (ranging from 4 to 36% among individuals) from high presystemic metabolism *(5,6)*. An enzyme belonging to the family of cytochrome P450 (CYP) mixed-function oxidases is responsible. CYPs account for the majority of oxidative biotransformations of drugs. This usually produces a metabolite(s) that is (are) pharmacologically inactive or less active and more readily eliminated from the body in urine. More than 50 different human CYPs have been identified. The nomenclature of CYPs is determined by similarity of amino acid composition. For example, the enzyme CYP3A4 belongs to family 3 (40% identical amino acid sequencing) and subfamily 3A (55% identical amino acids).

CYP3A4 metabolizes felodipine *(7–9)* and many other medications. It is involved in the metabolism of approx 60% of drugs that are oxidized *(10)*. The location of CYP3A4 in the small intestine and liver makes it well suited to play a significant role in presystemic drug metabolism *(3,11)*. Intestinal CYP3A4 is found in apical enterocytes and varies 11-fold in protein content among individuals *(12)*. Hepatic CYP3A4 content is much higher and varies 20-fold among individuals. Intestinal and hepatic CYP3A4 content appear to be regulated independently of each other *(13)*.

The first report showed that felodipine C_{max} and AUC with grapefruit juice were threefold those compared with orange juice or water *(4)*. However, felodipine elimination half-life ($t_{1/2}$), i.e., rate of drug removal from the systemic circulation, was not different among treatments. Also, intravenous pharmacokinetics of felodipine with grapefruit juice were not changed *(14)*. Thus, grapefruit juice primarily inhibited presystemic, rather than systemic, metabolism of felodipine.

Small intestinal enterocyte CYP3A4 protein content with grapefruit juice was reduced by a mean 62% *(15)*. Subjects with the highest enterocyte content of CYP3A4 before grapefruit juice had the largest reduction of this enzyme and greatest increase in felodipine C_{max} with the juice. In contrast, liver CYP3A4 activity, as measured by the erythromycin breath test, was not altered. Intestinal content of other drug metabolizing enzymes (CYP2D6, CYP1A1) was not affected. Thus, grapefruit juice appeared to inhibit intestinal CYP3A4 activity selectively.

Decreased expression of intestinal CYP3A4 implied that the interaction was not the result of just competition between felodipine and substrate(s) in grapefruit juice for metabolism. Because the content of enterocyte CYP3A4 mRNA was not changed, the interaction likely did not result from decreased production of CYP3A4 protein *(15)*. Rather, it indicated that the inhibitory effect was caused by enhanced degradation of this enzyme. This effect could have been caused by a substance(s) in grapefruit juice that was initially metabolized by CYP3A4 to a reactive intermediate(s) and then bonded covalently to the enzyme, a process termed "suicide" or "mechanism-based" inhibition *(3)*. The structurally modified and inactivated CYP3A4 might then be expected to undergo rapid proteolysis within the cell. Consequently, the return of CYP3A4 activity would require de novo enzyme synthesis. Because reduced intestinal CYP3A4 protein by grapefruit juice

did not cause increased CYP3A4 mRNA, it indicated that there was not an effective feedback mechanism within the enterocyte to up-regulate CYP3A4 synthesis. Thus, it might be predicted that return of CYP3A4 activity would require enterocyte replacement. This could cause prolonged inhibition of CYP3A4-mediated drug metabolism by grapefruit juice.

The duration of inhibitory activity of grapefruit juice has been evaluated. In the initial study, consumption of a single glass (200 mL) of grapefruit juice at various time intervals before felodipine administration showed that the pharmacokinetic interaction was maximal between simultaneous and 4 hour previous juice consumption *(16)*. Then, the extent of the interaction declined slowly with increasing time interval. The half-life of disappearance of inhibitory effect of grapefruit juice on CYP3A4-mediated drug metabolism was estimated at 12 h. Increased felodipine C_{max} was still evident when this volume of grapefruit juice was consumed 24 h beforehand. Subsequently, two other studies using two other drug probes, nisoldipine or simvastatin, confirmed the long duration of effect of grapefruit juice *(17,18)*. In the case of nisoldipine, increased drug AUC was observed up to 72 h after a 7-d pretreatment period of grapefruit juice (200 mL) three times daily *(17)*.

Because grapefruit juice produced a long duration of inhibition of intestinal CYP3A4 activity, repeated administration of juice might be expected to cause a cumulative increase in magnitude of pharmacokinetic interaction. Under single dose conditions, mean felodipine C_{max} and AUC with a glass of grapefruit juice (250 mL) were 3.5-fold and 2.7-fold, respectively, of those compared to with water *(15)*. During repeated juice consumption, grapefruit juice (250 mL three times daily for 5 d) further increased felodipine C_{max} and AUC to 5.4-fold and 3.5-fold, respectively, of those relative to single dose administration of felodipine with water. Thus, repeated administration of grapefruit juice under certain conditions can cause a cumulative increase in the magnitude of the pharmacokinetic drug interaction.

3. CLINICAL EVIDENCE

3.1. Medications Studied for an Interaction With Grapefruit Juice

Many drugs from a broad range of therapeutic categories have been examined for a possible interaction with grapefruit juice Those drugs that have increased oral bioavailability with grapefruit juice are listed in Table 1 *(4,9,19–78)*. Medications without enhanced bioavailability are shown in Table 2 *(79–100)*. Comparisons between these tables supported the concept that medications interacting with grapefruit juice have low to intermediate inherent oral bioavailability (<5 to 60%) and undergo presystemic metabolism mediated primarily by CYP3A4. In general, drugs with lower bioavailability have greater magnitude of interaction.

3.2. Adverse Effects With Grapefruit Juice

3.2.1. TORSADE DE POINTES

The antiarrhythmic agents, amiodarone and quinidine, and the antimalarial drug, halofantrine, can produce QTc interval prolongation and associated risk of developing the life-threatening cardiac ventricular arrhythmia, torsade de pointes. Other medications that produce this serious drug effect include the nonsedating antihistamines, astemizole and terfenadine, and the GI prokinetic agent, cisapride. These latter medications have

Table 1
Drugs With Increased Oral Bioavailability With Grapefruit Juice

Anti-Infective Agents
　　Albendazole *(19)*
　　Artemether *(20)*
　　Erythromycin *(21)*
　　Halofantrine *(22)*
　　Praziquantil *(23)*
　　Saquinavir *(24)*

Anti-Inflammatory Agents
　　Methyprednisolone *(25)*

Antilipemic Agents
　　Atorvastatin *(26)*
　　Lovastatin *(27–29)*
　　Simvastatin *(18,30)*

Cardiovascular Agents
　　Amiodarone *(31)*
　　Carvedilol *(32)*
　　Felodipine *(4,9,14–16,33–39)*
　　Nifedipine *(40–42)*
　　Nimodipine *(43)*
　　Nicardipine *(44)*
　　Nisoldipine *(17,45)*
　　Nitrendipine *(46,47)*
　　Sildenafil *(48)*
　　Verapamil *(49–51)*

Central Nervous System Agents
　　Buspirone *(52)*
　　Carbamazepine *(53)*
　　Diazepam *(54)*
　　Midazolam *(55,56)*
　　Scopolamine *(57)*
　　Sertraline *(58)*
　　Triazolam *(59,60)*

Estrogens
　　Ethinylestradiol *(61)*

Gastrointestinal Agents
　　Cisapride *(62–64)*

Histamine H_1 Antagonists
　　Astemizole *(65)*
　　Terfenadine *(66–69)*

Immunosuppressive Agents
　　Cyclosporine *(70–77)*
　　Tacrolimus *(78)*

been removed from the market because of this concern. The risk of developing this arrhythmia appears to be increased in conditions where plasma concentrations of these drugs are elevated.

Mean oral bioavailability of amiodarone is normally variable among individuals (range: 20–80%) as a result of extensive first-pass metabolism *(101)*. *N*-desethylamiodarone (N-DEA) is the major metabolite formed by CYP3A4 *(102)*. This metabolite appears to have significant anti-arrhythmic properties. Mean amiodarone C_{max} and AUC with grapefruit juice (300 mL at 0 h, 3 h, and 9 h relative to drug administration) were 1.8-fold and 1.5-fold those compared to amiodarone alone *(31)*. This resulted in plasma amiodarone concentrations that exceeded recommended therapeutic levels. Plasma N-DEA concentrations were decreased to undetectable levels and prolongation of QTc interval was less with concomitant grapefruit juice. Inhibition of N-DEA production might decrease the beneficial action of amiodarone or conversely it might reduce the unwanted proarrhythmic effects linked to QTc prolongation. Because the clinical outcome is not clear, consumption of grapefruit juice should be avoided in patients receiving amiodarone.

Table 2
Drugs Without Increased Oral Bioavailability With Grapefruit Juice

Antiasthmatic Agents	*Antilipemic Agents*
Theophylline *(79)*	Pravastatin *(26)*
Anticoagulants	*Cardiovascular Agents*
Acenocoumarin *(80)*	Amlodipine *(88,89)*
Warfarin *(81)*	Diltiazem *(90,91)*
	Propafenone *(92)*[a]
	Quinidine *(93,94)*[a]
Anti-Infective Agents	*Central Nervous System Agents*
Amprenavir *(82)*	Alprazolam *(95)*
Clarithromycin *(83)*	Clomipramine *(96)*
Indinavir *(84)*	Clozapine *(97)*
Itraconazole *(85,86)*	Haloperidol *(98)*
Quinine *(86)*	Phenytoin *(99)*
Anti-Inflammatory Agents	*Estrogens*
Prednisone *(74)*	17β-Estradiol *(100)*

[a]See text for discussion of concern for potential interaction.

Quinidine has relatively high absolute oral bioavailability (about 70%) but it is has a narrow therapeutic range of effective and safe plasma drug concentrations. In one single dose study, grapefruit juice (240 mL) did not change mean quinidine C_{max} or AUC; however, it decreased 3-hydroxyquinidine AUC compared to water *(93)*. In another study, chronic consumption of grapefruit juice (250 mL twice daily) reduced the oral clearance of quinidine and 3-hydroxy and *N*-oxide metabolites to 0.85, 0.81, and 0.73 of those with water *(94)*. Thus, grapefruit juice appears to have a small effect on mean pharmacokinetics of quinidine. However, modestly elevated plasma quinidine concentrations have the potential to cause serious side effects. Thus, it seems reasonable to avoid grapefruit juice consumption during therapy with quinidine until proven safe.

Halofantrine has an oral bioavailability of 10% and is metabolized to the less cardiotoxic metabolite, *N*-debutylhalofantrine, by CYP3A4 *(105–107)*. When it was administered as a single dose after grapefruit juice (250 mL once daily for 3 d and once at 12 h before drug), halofantrine C_{max} and AUC were 3.2-fold and 2.8-fold, respectively, those with water *(22)*. *N*-debutylhalofantrine AUC was decreased to 0.4-fold that observed after water. Maximum QTc interval prolongation with halofantrine was increased to a mean 31 ms with grapefruit juice compared to 17 ms with water. It was concluded that consumption of grapefruit juice should be contraindicated during administration of halofantrine.

3.2.2. RHADOMYOLYSIS

β-hydroxy-βmethylglutaryl-CoA (HMG-CoA) reductase inhibitors belong to an important class of cholesterol-lowering medications. However, they can cause significant toxicity. Unwanted effects range from diffuse myalgia and elevated creatine phosphokinase to severe skeletal muscle degeneration (rhabdomyolysis) and associated acute renal failure. These effects can occur when plasma concentration of HMG-CoA reductase inhibitor is markedly elevated.

Atorvastatin, lovastatin, and simvastatin have low oral bioavailability as a result of presystemic metabolism by CYP3A4. Atorvastatin is active and has a mean absolute oral bioavailability of 12% *(108)*. Simvastatin and lovastatin are prodrugs that are converted by esterases to the corresponding active acid derivative. However, an alternative primary metabolic pathway mediated by CYP3A4 is normally responsible for the inactivation of the majority of lovastatin and simvastatin. This results in an absolute oral bioavailability that is less than 5% *(27,109)*. Although grapefruit juice augmented the plasma concentrations of atorvastatin, lovastatin, and simvastatin and active metabolites, the magnitude of pharmacokinetic interaction was different. Atorvastatin AUC with grapefruit juice was a mean 2.5-fold of that compared with water *(26)*. In contrast, lovastatin and simvastatin AUCs with grapefruit juice were at least 15-fold those observed with water *(27,30)*. Active metabolites were also increased. Thus, HMG-CoA reductase inhibitors with lower inherent oral bioavailability from presystemic metabolism by CYP3A4 may have greater risk of serious adverse effects with grapefruit juice. Regardless, it is recommended that consumption of grapefruit juice should be avoided during therapy with atorvastatin, lovastatin, or simvastatin.

Pravastatin is metabolized by CYP3A4 to only a minor extent and shown not to interact with grapefruit juice *(26)*. Fluvastatin has essentially complete oral bioavailability and is predominantly metabolized by CYP2C9. Thus, it would be predicted not to interact with grapefruit juice. Pravastatin and fluvastatin might be considered as alternative agents when there is concern for a potential interaction with grapefruit juice.

3.2.3. SYMPTOMATIC HYPOTENSION

Dihydropyridine calcium channel antagonists are selective arteriolar vasodilators that are often employed in the management of hypertension or other cardiovascular disorders. Adverse clinical consequences of excessive vasodilatation from elevated plasma concentration of dihydropyridines include headache, ankle edema, and facial flushing. Although these effects are generally not considered to be serious, they could be sufficiently unpleasant to decrease patient compliance to the treatment regimen and to negate drug benefit. At the other extreme, adverse drug events from excessive vasodilatation may result in symptomatic hypotension or myocardial infarction.

Several dihydropyridines have low inherent oral bioavailability and are inactivated, at least in part, by CYP3A4-mediated metabolism. In middle-aged subjects with untreated borderline hypertension, mean felodipine AUC with grapefruit juice was 2.8-fold that compared with water *(4)*. This was associated with enhanced diastolic blood pressure reduction, heart increase and frequency of vasodilatation-related side events. In healthy elderly individuals (70–83 yr of age), mean oral felodipine AUC with grapefruit juice was 2.9-fold that compared with water, supporting the importance of intestinal CYP3A4-mediated drug metabolism in this age group *(37)*. In contrast with the effect in middle-

age individuals, there was enhanced reduction of both systolic and diastolic blood pressure in the elderly. Although some tachycardia was apparent in both age groups, lower systolic blood pressure in only the elderly may have resulted from attenuated baroreceptor reflex responsiveness that is known to occur with aging *(110)*. This likely also explains the greater blood pressure-lowering effects of felodipine in the elderly *(111)*. Because the elderly appear more susceptible to hypotension-related adverse events, the interaction between felodipine and grapefruit juice seems particularly relevant.

Other dihydropyridines that interact with grapefruit juice include nifedipine *(40–42)*, nicardipine *(44)*, nimodipine *(43)*, nisoldipine *(17,45)*, and nitrendipine *(46,47)*. Average dihydropyridine C_{max} and AUC with grapefruit juice ranged from 1.5-fold to 4.0-fold those with water under single dose conditions. In contrast, amlodipine has a negligible pharmacokinetic interaction with grapefruit juice *(88,89)*. Because amlodipine has inherently high (80%) oral bioavailability, this appears to be the major reason.

Sildenafil is used to treat erectile dysfunction by causing vasodilatation of smooth muscle of the corpus cavernosa. At therapeutic drug concentration, sildenafil inhibits a form of phosphodiesterase (PDE5) to increase intracellular cyclic guanosine monophosphate (cGMP) concentration selectively in this tissue. At higher drug concentration, the selectivity of sildenafil for PDE5 is lost and other forms of PDE are inhibited, resulting in a generalized increase in intracellular cGMP and systemic vasodilatation. Nitrates can also increase intracellular cGMP concentration but this is by a mechanism involving stimulating cGMP production. The combined effects of sildenafil and nitrates can be sufficient to cause symptomatic hypotension, myocardial infarction or sudden death. Sildenafil has intermediate oral bioavailability (mean: 41%, range: 25%–63%) and is cleared extensively through metabolism mediated by CYP3A4 *(112,113)*. The primary metabolite (*N*-desmethylsildenafil) is approx 50% as potent as the parent drug. Sildenafil and desmethylsildenafil AUCs with grapefruit juice (250 mL) given before (1 h) and together with drug were a mean 1.2-fold those compared to water in a single dose study *(48)*. Mean decrease in systolic and diastolic blood pressure and increase in heart rate were not different between treatments. However, sildenafil AUCs with grapefruit juice ranged from 0.8-fold to 2.6-fold those compared to water among individuals. The authors concluded that the small increase in the mean oral bioavailability of sildenafil and active metabolite by grapefruit juice would probably not produce more enhanced therapeutic or adverse effects. However, variability in the extent of the pharmacokinetic interaction among individuals, in the amount of CYP3A4 inhibitors among brands and batches of grapefruit juice and in the volume of juice consumed make the effect less predictable. It was recommended that the combination of sildenafil and grapefruit juice should be avoided.

3.2.4. DYSRRHYTHMIA

Verapamil depresses atrioventricular conduction and myocardial contractility and dilates arteriolar smooth muscle. Verapamil is a racemic mixture of *S*- and *R*-enantiomers. The *S*-enantiomer is more pharmacologically active. Verapamil undergoes stereoselective first-pass metabolism involving CYP3A4 that results in variable bioavailability of 13–34% for the *S*-enantiomer and 33–65% for the *R*-enantiomer among individuals. In one study, administration of a single glass of grapefruit juice (200 mL) to 10 hypertensive patients receiving chronic short-acting verapamil resulted in increased

AUC ratio of racemic parent drug to major active dealkylated metabolite, norverapamil, indicative of inhibition of verapamil metabolism *(49)*. However, the absolute pharmacokinetic values for verapamil and norverapamil were not changed. In a second study, grapefruit juice (200 mL twice daily for 5 d) increased steady-state plasma concentrations of both *S*- and *R*-enantiomers of verapamil compared to orange juice control *(50)*. Mean AUC and C_{max} of *S*-verapamil with grapefruit juice were 1.4-fold and 1.6-fold those with orange juice, respectively. The effect was similar for *R*-verapamil. Considerable intersubject variability in the magnitude of the pharmacokinetic interaction was apparent. No change in the mean pharmacodynamics of verapamil (blood pressure, heart rate, PR interval <350 ms) was observed. In the third study, grapefruit juice (1 L per day for 3 d) augmented the steady-state plasma concentration of *S,R*-verapamil administered in the prolonged release drug formulation *(51)*. Mean verapamil AUC and C_{max} with grapefruit juice were 2.5-fold and 2.6-fold of those compared with water. The increases were slightly greater for verapamil than for norverapamil. Prolongation of PR interval above 350 ms occurred in two of the 24 individuals in the group receiving grapefruit juice. The results of these studies show that a pharmacokinetic interaction can occur with verapamil under most conditions of concomitant grapefruit juice administration. However, a pharmacodynamic interaction was evident only during chronic verapamil and repeated high-volume grapefruit juice consumption. Nevertheless, the high variability of the pharmacokinetic interaction among individuals suggests that a clinically relevant interaction may occur with verapamil under single-dose and more usual volumes of grapefruit juice administration.

3.2.5. Loss of Drug Efficacy

Losartan antagonizes the vasoconstrictor and aldosterone stimulating effects of angiotensin II. It undergoes substantial first-pass metabolism resulting in a mean absolute oral bioavailability of 33%. Losartan is partially converted by CYP3A4 and CYP2C9 to the active carboxylic acid metabolite, E-3174, that is responsible for the majority of angiotensin II receptor antagonism. E-3174 AUC with grapefruit juice was reduced compared to that with water, suggesting that the therapeutic effectiveness of losartan may be decreased by grapefruit juice *(114)*.

Carvedilol combines nonselective β-receptor and α-1 receptor blockade in a single racemic drug. β-Receptor blockade is attributed to the *S*-enantiomer, whereas α-1 receptor blockade is present in equal potency in both enantiomers. Because heart failure can worsen when β and α receptor blockade are excessive, care must be taken in situations where plasma *S,R*-carvedilol concentrations are increased. Although racemic carvedilol is well absorbed from the GI tract, it has only a 25–35% absolute oral bioavailability because of presystemic metabolism. This process is stereoselective and results in plasma concentrations of *S*-carvedilol that are twofold to threefold lower than those of *R*-carvedilol. Glucuronidation and oxidation by CYP2D6 and CYP2C9 appear to be the major pathways of drug elimination. Consequently, it might be predicted that grapefruit juice would not significantly interact with carvedilol. Results of a clinical investigation showed that mean AUC of *S,R*-carvedilol with grapefruit juice (300 mL) was 1.2-fold that of water under single dose conditions *(32)*. Unfortunately, the magnitude of the interaction among individuals and the effect on each enantiomer was not reported. Because dosage and effect of carvedilol must be carefully individualized and closely monitored by a physician expe-

rienced in the treatment of heart failure, this makes a recommendation about grapefruit juice use in this setting unclear. For no other reason than to eliminate factors that might prevent establishment of a stable dose–response relationship, it seems reasonable to indicate that patients with heart failure receiving carvedilol should avoid grapefruit juice intake

3.3. Potential Beneficial Effects With Grapefruit Juice

3.3.1. DRUG COST SAVINGS

Cyclosporine is an immunosuppressive agent useful in preventing organ rejection following transplantation. It is crucial that plasma cyclosporine concentrations are maintained within a narrow range so as to have adequate drug concentration to prevent transplant rejection but not to have sufficiently high concentration to cause renal toxicity. Cyclosporine is very expensive and must be taken on a daily basis for many years. Cyclosporine has a 30–40% oral bioavailability. Theoretically, increasing cyclosporine bioavailability could result in reduced drug dose and associated cost. Cyclosporine is metabolized by CYP3A4. Thus, grapefruit juice might be useful in this situation. Several investigations have shown that grapefruit juice can increase cyclosporine bioavailability *(70–77)*. However, the effect was variable among studies. Also, there is the absolute need for consistency of effect among batches and suppliers of the juice. Practically, it may not be possible to maintain a uniform effect on cyclosporine bioavailability. Thus, grapefruit juice is currently not recommended as a means to reduce drug cost in this circumstance.

3.3.2. MAINTENANCE OF DRUG EFFECTIVENESS

Artemether is an antimalarial drug with fast onset of action, few side effects, and good activity against multidrug-resistant parasites. However, it has a high relapse rate during monotherapy. Because there is marked reduction in plasma drug concentrations on repeated administration, induction of its own metabolism (autoinduction) is considered the cause of loss of efficacy. Artemether undergoes high presystemic metabolism by CYP3A4. During single dose administration, grapefruit juice increased the oral bioavailability of artemether compared to water *(115)*. After 5 d of concomitant grapefruit juice administration, higher plasma artemether concentrations were observed compared to those with 5 d of water. However, both grapefruit juice and water produced decreased oral bioavailability of artemether over this time period. Thus, grapefruit juice improved the oral bioavailability of artemether under conditions of single and repeated administration. However, grapefruit juice did not totally abolish the autoinduction of artemether. Nevertheless, it prolonged effective plasma drug concentrations. Oral treatment with artemether may be more effective when the medication is taken with grapefruit juice.

3.3.3. ENHANCED DRUG EFFICACY

Protease inhibitors are antiretroviral drugs used in the treatment of HIV-1 infection. Saquinavir has very low oral bioavailability (1–2%) and is a substrate for CYP3A4. Because it does not have toxicity at high plasma drug concentration, any increase in saquinavir bioavailability has the potential to produce only enhanced drug benefit. Saquinavir AUC with grapefruit juice was twofold that with water *(24)*. Although saquinavir with grapefruit might produce some therapeutic benefit compared to saquinavir alone, the extent of the interaction was minor compared to the 58-fold increase seen with ritonavir *(116)*.

Table 3
Drugs That May Interact With Grapefruit Juice

Inhibition of Intestinal CYP3A4
    Clopidogrel
    Ergotamine
    Propafenone
    Repaglinide
    Sibutramine

Inhibition of Intestinal P-glycoprotein
    Eprosartan
    Telimisartan
    Valsartan

Inhibition of Intestinal Organic Anion
Transporting Polypeptides
    Etoposide
    Celiprolol

4. LIMITATIONS OF THE DATA

4.1. Incomplete List of Interacting Drugs

A substantial number of drugs have been assessed for an interaction with grapefruit juice. However, many more medications have not been studied. Nevertheless, it is possible to predict the likelihood of an interaction for other drugs. Because grapefruit juice enhances oral drug bioavailability, the suspected medication should have an inherent absolute bioavailability that is normally low or intermediate (<60–70%). Additionally, there should be accompanying data to indicate that the drug is extensively metabolized by CYP3A4. Drugs with such a potential to interact with grapefruit juice are listed in Table 3.

The antiplatelet agent, clopidogrel, is an irreversible inhibitor of adenosine 5'diphosphate-induced platelet aggregation and is used for secondary prevention of vascular events in patients with history of symptomatic atherosclerotic disease. It is rapidly converted to at least one active metabolite, which results in plasma clopidogrel concentration that is normally not detectable following oral administration. Although the active metabolite(s) has not been identified, recent findings have shown that concomitant administration of a CYP3A4 inhibitor, erythromycin or troleandomycin, attenuated platelet aggregation inhibition; whereas, pretreatment with a CYP3A4 inducer, rifampin, enhanced platelet aggregation inhibition *(117)*. Consequently, the active metabolite(s) of clopidogrel is (are) likely formed by CYP3A4. Because clopidogrel has negligible oral bioavailability, extensive presystemic metabolism by intestinal CYP3A4 might be expected. Consequently, grapefruit juice could reduce formation of the active metabolite(s) and attenuate the therapeutic benefit of clopidogrel.

Ergotamine is an alkaloid used to treat migraine headache. Serious toxicity can occur during therapy. Ergotism is a syndrome referred to as "St Anthony's Fire" and is characterized by vascular ischemia and neurological compromise as a result of excessive

ergotamine concentration. Cases of gangrene and stroke have been reported that have resulted in amputation or death. Ergotamine appears to have low oral bioavailability and is a substrate of CYP3A4 *(118)*. Toxicity has occurred in patients concomitantly receiving standard doses of ergotamine with the CYP3A4 inhibitors, clarithromycin, ritonavir, or triacetyloleandomycin *(119)*. Thus, an interaction between ergotamine and grapefruit juice appears probable and this combination should be avoided. Alternatively, better options for the treatment of migraine headache include the class of drugs known as triptans. There does not appear to be an interaction between most drugs of this class and grapefruit juice.

Propafenone undergoes presystemic metabolism resulting in an absolute oral bioavailability that ranges from 3 to 40%. Normally, the major route of elimination is metabolism by CYP2D6 and the minor route involves metabolism by CYP3A4. However, the activity of CYP2D6 varies markedly among individuals. Genetic mutations can result in CYP2D6 activity that is markedly reduced or absent, a phenomenon known as "genetic polymorphism." The frequency–activity distribution curve of CYP2D6 is divided into two basic populations classified as extensive (EM) or poor (PM) metabolizers. The incidence of CYP2D6 PM is 5–10% in Caucasians and about 1% in Asians. Preliminary data indicate that CYP3A4 inhibitors, erythromycin, ketoconazole, or grapefruit juice, can increase plasma propafenone concentrations in individuals who are CYP2D6 PM *(92)*. Symptoms of propafenone overdose include bradycardia, hypotension, conduction disturbances, ventricular tachycardia and/or fibrillation, somnolence, or convulsions. This may explain the adverse interaction in a patient taking propafenone for 4 yr who experienced convulsions 2 d after starting treatment with the CYP3A4 inhibitor, ketoconazole *(120)*. Thus, grapefruit juice may potentially cause propafenone toxicity in individuals who are CYP2D6 PM.

Repaglinide is an oral antidiabetic agent that reduces blood glucose by stimulating insulin release from pancreatic β-cells. It has a mean absolute oral bioavailability of about 50% and is inactivated by metabolism involving CYP3A4. Four days pretreatment with the CYP3A4 inhibitor, clarithromycin, produced repaglinide C_{max} and AUC that were 1.7-fold and 1.4-fold those without clarithromycin *(121)*. Although insulin concentration was elevated, blood glucose concentration was not altered. Concomitant use of grapefruit juice might enhance plasma repaglinide concentrations and increase the risk of hypoglycemia. This may be particularly important for the elderly who are particularly susceptible to the hypoglycemic action of glucose-lowering drugs and who are the major consumers of grapefruit juice.

Sibutramine reduces body weight by enhancing satiety and inducing thermogenesis through inhibition of neuronal reuptake of serotonin and noradrenaline. Sibutramine appears to undergo extensive CYP3A4-mediated presystemic metabolism to active metabolites. Concomitant administration of the CYP3A4 inhibitors, ketoconazole or erythromycin, produced mean sibutramine C_{max} that were twofold or threefold, respectively, those compared to sibutramine alone *(122)*. The C_{max} of at least one active metabolite was also increased. Systolic and diastolic blood pressures and heart rate were increased compared to sibutramine alone. Because caution is recommended for administration of sibutramine with CYP3A4 inhibitors, it may also be appropriate to include avoidance of grapefruit juice. As patients might consider the "grapefruit diet" as an adjunct to weight reduction, this precaution appears particularly relevant.

5. FUTURE RESEARCH NEEDS

5.1. Inhibition of Drug Transport Mediated by P-Glycoprotein

Transporters are increasingly recognized as important determinants of drug disposition and resulting clinical response. The best-characterized drug transporter is P-glycoprotein (P-gp). P-gp was first observed in tumor cells where it caused drug resistance to chemotherapeutic agents. Subsequently, P-gp was shown to play an important physiological role. P-gp is an adenosine 5'-triphosphate-dependent efflux pump located on the luminal surface of epithelial cells of the small intestine, the bile canalicular membrane of the liver, and the proximal tubule of the kidney. It is also located on endothelial cells that comprise the blood–brain and blood–testes barriers. P-gp affects the disposition of drugs by limiting their absorption from the gut, by facilitating their removal through secretion into bile and urine, and by reducing their entry into brain and testes (*see* Chapter 3).

The effect of grapefruit juice on P-gp has not been as extensively documented compared to its effect on CYP3A4. In one study, repeated administration of grapefruit juice (250 mL three times daily for 5 d) did not appear to alter enterocyte P-gp content in humans *(15)*. However, a nonspecific antibody for detecting P-gp had been used. Thus, it is currently not clear whether grapefruit juice can decrease enterocyte P-gp expression as it does for CYP3A4 expression *(15)*. Other results suggest that grapefruit juice can modulate P-gp activity. This conclusion is based on the effect of grapefruit juice relative to that of Seville (sour) orange juice. In one investigation, both juices decreased enterocyte CYP3A4 content and augmented the oral bioavailability of felodipine, a drug metabolized by CYP3A4 but not transported by P-gp *(39)*. In another study, only grapefruit juice increased the oral bioavailability of cyclosporine, a medication metabolized by CYP3A4 and transported by P-gp *(123)*. Thus, grapefruit appeared to increase drug bioavailability by an additional mechanism to inactivation of intestinal CYP3A4 that may involve inhibition of P-gp. In contrast, grapefruit juice increased (9%, $p = 0.01$) the oral bioavailability of the nonmetabolized P-gp substrate, digoxin, in humans *(124)*. This prompted the authors to conclude that grapefruit juice did not relevantly inhibit intestinal activity of P-gp in humans. However, digoxin normally has an oral bioavailability of 70–80%. Thus, inhibition of P-gp in the GI tract would not be expected to enhance the absorption of digoxin. Furthermore, data from other sources support an effect on P-gp activity. For example, grapefruit juice increased plasma concentrations of the nonmetabolized P-gp substrate, talinolol, following oral administration to rats *(125)*. Also, grapefruit juice inhibited P-gp-mediated drug transport in certain in vitro studies *(126,127)*. On the other hand, grapefruit juice was reported to activate this transporter in one in vitro study *(128)*. However, the authors later attributed this finding to equipment artifact *(39)*. Thus, information from a number of different sources imply that grapefruit juice can inhibit intestinal P-gp activity. However, the clinical relevance of this effect requires further investigation.

The angiotensin II receptor blockers, eprosartan, telmisartan, and valsartan, have low absolute oral bioavailability reported as 13, 43, and 23%, respectively. Although they are excreted essentially unchanged, biliary clearance is important for the systemic elimination of these drugs. Because P-gp in the liver plays an important role in the canalicular secretion of drugs into bile, P-gp in the GI tract may be responsible for the low oral bioavailability of these angiotensin II receptor blockers. Consequently, grapefruit juice might augment the oral bioavailability of candesartan, eprosartan, telmisartan, or valsartan.

5.2. Inhibition of Drug Transport by Organic Anion Transporting Polypeptides

Drug absorption from the GI tract and distribution into tissues are generally considered to be mediated primarily by passive diffusion. However, recent findings indicate that a family of drug uptake transporters known as organic anion transporting polypeptides (OATPs) might play an important role for certain medications. In the small intestine, OATP transporters are located on the luminal membrane of enterocytes and enable drug uptake from the GI tract into the portal circulation. In the liver, they are found on the sinusoidal membrane and facilitate the movement of drug from portal circulation into hepatocytes.

Grapefruit, orange, and apple juices were recently shown to reduce markedly the oral bioavailability of the nonmetabolized antihistamine, fexofenadine, a substrate for both P-gp and OATPs *(129)*. In vitro studies demonstrated that these juices and certain constituents (furanocoumarins and bioflavonoids) were much less potent inhibitors of P-gp compared to OATPs. These initial findings appear to represent a new mechanism for food–drug interactions involving inhibition of drug uptake transporters by grapefruit or other fruit juices. It may help explain the recent observations that the oral bioavailability of etoposide and celiprolol were decreased by grapefruit juice *(130,131)*.

6. CONCLUSION AND CLINICAL RECOMMENDATIONS

Drug-related issues such as pharmacokinetics, mechanism of elimination, and toxicity play critical roles when assessing potential risk of an interaction with grapefruit juice. If a medication has low oral bioavailability from high presystemic metabolism mediated by CYP3A4 and can produce serious overdose toxicity, it appears mandatory to advise against concomitant consumption of grapefruit juice. Although this may not cause altered drug response in most instances, it is often difficult to predict. Consequently, avoiding the combination will definitely prevent toxicity. Also, alternative medications that don't interact with grapefruit juice are often available.

Patient-related issues affect the clinical importance of the interaction. The magnitude of pharmacokinetic interaction is normally markedly variable. For example, felodipine AUC with grapefruit juice can range from no change to eightfold that with water among individuals *(9,15,33)*. This difference appears dependent on intestinal CYP3A4 content such that patients with the highest amount of CYP3A4 before consuming grapefruit juice are the ones that show the greatest increase in drug concentration *(15)*. Unfortunately, there are no routine clinical tests available to estimate the extent of pharmacokinetic interaction before exposure. Pre-existing medical conditions can also affect clinical response. For example, dihydropyridines produce an antihypertensive effect dependent on pretreatment blood pressure. The greatest reduction in blood pressure occurs in patients with the highest pretreatment blood pressure *(111,132)*. These patients are likely at greater risk of developing cardiovascular ischemic symptoms with the combination of a dihydropyridine and grapefruit juice. Age appears to affect susceptibility to drug interactions. For example, elderly patients have demonstrated enhanced antihypertensive effect to dihydropyridines compared to younger individuals *(4,37)*. As mentioned previously, this may result from reduced autonomic responsiveness from age-related decreased baroreceptor sensitivity *(110)*. Because the elderly are the group most often prescribed

medications and are major consumers of grapefruit juice, the potential for a relevant unwanted grapefruit juice–drug interaction in this population appears substantial.

Administration-related issues require consideration as well. First, grapefruit juice appears to have the potential to interact only with drugs that are administered orally *(14,70)*. Second, commercial white grapefruit juice from frozen concentrate, diluted from concentrate or fresh frozen has been shown to interact with felodipine *(4,9,14–16,33–37,39)*. Segments from unprocessed grapefruit can do the same *(38)*. Thus, any form of grapefruit should be considered to produce a drug interaction. Third, consumption of a single glass of a normal amount of regular-strength grapefruit juice (200 mL) can produce a clinically relevant increase in oral drug bioavailability *(14,16,34)*. Because administration of the same volume of double-strength juice did not substantially enhance this effect, it appears that as little as 200 mL of regular-strength grapefruit juice can produce near maximal acute pharmacokinetic interaction *(34)*. Fourth, chronic consumption of grapefruit juice several times daily should be considered to produce a cumulative inhibitory effect on intestinal CYP3A4 and enhanced the magnitude of the drug interaction *(15)*. Fifth, high consumption of grapefruit juice may also inhibit hepatic CYP3A4 *(60)*. Sixth, the amount of active ingredient(s) in grapefruit may vary among batches and lots that may affect reproducibility of the interaction. Seventh, grapefruit juice has a very long duration of action *(16–18)*. A glass of grapefruit juice consumed one day has the potential to augment the oral bioavailability of drug administered the next day. Thus, it is recommended that grapefruit juice consumption should best be avoided entirely during pharmacotherapy, rather than just for concomitant juice and drug administration, when there is a concern for drug toxicity from excessive plasma drug concentration.

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10 Nutrients That May Optimize Drug Effects

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1. INTRODUCTION

Drug–nutrient interactions (DNIs) are often the result of physical and chemical interactions between drugs and nutrients. These interactions are influenced by several factors that can be defined as either physical–chemical properties (e.g., pH, dissolution, disintegration, binding) or physiological determinants (e.g., absorption and elimination process, gastrointestinal [GI] transit time, GI secretions, splanchnic blood flow, liver enzyme inhibition, or induction) *(1,2)*. Clinically significant DNIs may result in therapeutic failure, drug toxicity, or nutrient deficiency. Less commonly considered, DNIs may even enhance drug effect. This chapter focuses on some clinically relevant DNIs that result in a beneficial increase of drug effect or reduction of drug toxicity.

2. EFFECTS OF FOOD ON DRUG ABSORPTION

2.1. Albendazole

Albendazole is a broad-spectrum anthelmintic agent effective against larval and adult stages of trematodes and cestodes *(3)*. Albendazole is available in oral tablets. Owing to its low aqueous solubility, albendazole is poorly absorbed from the GI tract. However, administration with a fatty meal enhances albendazole solubility and increases its bioavailability.

Fatty meals increase the oral bioavailability of albendazole up to fivefold as compared to fasting. Maximal plasma concentrations of albendazole sulfoxide (primary active metabolite) were achieved in 2–5 h with albendazole 400 mg doses during treatment of patients with hydatid disease *(4)*. In a study that assessed the bioavailability of albendazole in six hydatid disease patients, mean plasma albendazole concentrations were 4.5 times higher when albendazole was administered with breakfast as compared to fasting *(5)*. In another study of adult patients with onchocerciasis, plasma albendazole sulfoxide concentrations increased fourfold when albendazole was administered with breakfast (43.1 g of fat) instead of on an empty stomach *(6)*. However, when given with 20 mL of olive oil in 100 mL of milk to four adult volunteers, plasma albendazole sulfoxide concentrations increased 3.5-fold in one subject, whereas only small changes occurred in the other three subjects *(7)*.

Albendazole absorption is significantly increased when taken with food. Albendazole should be administered with fatty meals to increase albendazole concentrations within tissues and hydatid cysts *(4)*. However, administration of albendazole on an empty stomach is preferable when albendazole intraluminal effects are desired to treat susceptible intestinal parasites *(3,5)*.

2.2. Atovaquone

Atovaquone is an antiprotozoal agent available in oral suspension form. Atovaquone is used as second-line agent for treatment and prophylaxis of mild to moderate *Pneumocystis carinii* pneumonia in patients who are intolerant to trimethorpim-sulfamethoxazole. The lipohilic and low aqueous solubility of atovaquone makes it slowly and irregularly absorbed on an empty stomach. However, atovaquone bioavailability is enhanced when taken with a fatty meal. The previously marketed atovaquone tablet resulted in irregular absorption and subtherapeutic plasma concentrations. As such, manufacturing of atovaquone tablets (Mepron®) was discontinued since the suspension became available. Atovaquone suspension had a twofold increase in bioavailability as compared to the tablet *(8)*, resulting in increased atovaquone area under the concentration-time curve (AUC) and increased peak plasma concentrations (C_{max}) *(9)*.

In a prospective open-label crossover study of 10 healthy volunteers, a single 750 mg dose of atovaquone suspension resulted in significantly increased atovaquone bioavailability when administered following breakfast (fat content 21 g) or following an oral liquid nutrition supplement (Sustacal Plus®: fat content 28 g). Atovaquone AUC following breakfast (103.8 μg.h/mL) and Sustacal Plus® (118.8 μg.h/mL) were significantly greater as compared to fasting (43.4 μg.h/mL) ($p < 0.0001$). This corresponds to a mean increase in atovaquone bioavailability by 502% and 505% following breakfast and Sustacal Plus®, respectively *(10)*.

Two studies investigated the effect of food on the pharmacokinetics of atovaquone suspension in patients infected with the human immunodeficiency virus (HIV) *(11,12)*. In an open-label, dose-escalation study including 22 HIV-infected patients, administration of atovaquone with breakfast (23 g fat) increased average atovaquone steady-state plasma concentrations by 1.3- to 1.7-fold as compared to fasting *(11)*. Similarly, a single- and multiple-dose pharmacokinetic study in HIV-infected patients showed food to increase atovaquone bioavailability by 1.4-fold. However, increased incidence of rash was observed when higher plasma atovaquone concentrations were achieved with the 1000 mg twice-daily dose taken with food *(12)*.

In summary, the rate and extent of atovaquone absorption are significantly increased when taken with food, especially fatty meals. As such, atovaquone should be administered with meals to increase its absorption and improve its therapeutic effects *(8)*.

2.3. Cefuroxime

Cefuroxime is a broad-spectrum β-lactam antibiotic belonging to the second-generation cephalosporins. Cefuroxime has a broad activity against susceptible bacteria causing infections of the upper and lower respiratory tract, skin and soft tissues, and the genitourinary tract *(13)*. Cefuroxime is available as the prodrug cefuroxime axetil in oral suspension and tablet dosage forms, and as cefuroxime for intravenous administration *(14)*. Cefuroxime axetil is rapidly absorbed from the GI tract and is hydrolyzed to active cefuroxime once in the bloodstream *(13–15)*. The oral tablet and suspension forms of

cefuroxime axetil are not bioequivalent and cannot be used interchangeably *(14)*. The safety and efficacy of oral cefuroxime tablet and suspension were established in separate clinical trials, and the dosage forms have different therapeutic indications *(13,14)*. Since cefuroxime axetil oral tablet form became available, it has been reformulated several times due to absorption problems *(15)*. Food *(16–18)* and milk *(19)* have been shown to enhance cefuroxime axetil bioavailability, but the exact mechanism of this effect remains unknown.

In a randomized, crossover, open-label study that evaluated the effects of food and fasting on cefuroxime bioavailability in healthy volunteers, mean cefuroxime absolute bioavailability during fasting was 32–35%. There was a 34% increase in relative bioavailability when cefuroxime axetil was taken with food (AUC: 50 µg·h/mL) as compared to fasting (AUC: 36.4 µg·h/mL). Compared to fasting, food also resulted in increases of the C_{max} (13.9 µg/mL vs 9.9 µg/mL) and the time to peak concentration (T_{max}: 2.7 h vs 2.1 h, respectively). Cefuroxime elimination half-life was not significantly changed *(16)*. In another study, similar food effects on cefuroxime absorption were observed. A single 500 mg dose of cefuroxime axetil taken with food resulted in increased absolute cefuroxime bioavailability from 36 to 52%, corresponding to a relative increase in cefuroxime bioavailability by 45%. There was also a linear correlation between cefuroxime single doses ranging from 125–1000 mg given with food and both the AUC ($r^2 = 0.958$) and C_{max} ($r^2 = 0.943$) *(17)*.

A study evaluated the effects of food and increased gastric pH (with administration of ranitidine and sodium bicarbonate) on cefuroxime absorption in six healthy volunteers. Cefuroxime administration with food resulted in increased cefuroxime bioavailability despite the anticipated negative effects of increased gastric pH on cefuroxime absorption. Cefuroxime bioavailability significantly increased with food as compared to fasting (AUC: 39.8 ± 2.9 µg·h/mL vs 23.4 ± 2.9 µg·h/mL, $p < 0.05$). The T_{max} was significantly longer when cefuroxime was taken with food as compared to fasting (13.6 ± 1.0 h vs 7.3 ± 0.8 h, $p < 0.05$). The C_{max} was slightly higher in the fed state, but this was statistically significant *(20)*.

In a study that evaluated the effects of food on serum cefuroxime concentrations and the minimum inhibitory concentration (MIC), serum cefuroxime concentrations were at or above the MIC of common respiratory pathogens for the majority of the dosing interval *(18)*. This suggests that administration of cefuroxime axetil with food achieves adequate serum levels for the effective treatment of susceptible organisms *(13,18)*.

There are pharmacokinetic differences between the cefuroxime tablet and suspension forms *(13–21)*. In one study, the AUC and C_{max} for cefuroxime suspension averaged 91 and 71% of that for the tablet, respectively *(13)*. In another study, cefuroxime administration with meals resulted in significantly lower AUC for oral cefuroxime suspension as compared to the tablet (10.22 µg·h/mL vs 14.02 µg·h/mL, respectively; $p = 0.001$). Food also resulted in significantly lower C_{max} with cefuroxime suspension as compared to the tablet (2.48 µg/mL vs 4.04 µg/mL, respectively; $p = 0.001$). Despite these differences, serum cefuroxime bactericidal activities were not affected and remained similar with both dosage forms *(21)*.

In summary, cefuroxime axetil tablets should preferably be administered with food or milk to enhance absorption. Oral cefuroxime suspension provides an alternative to the tablet, especially in those who cannot swallow the tablet. Patients with elevated intragastric pH should take cefuroxime tablets with food to enhance absorption.

2.4. Griseofulvin

Griseofulvin is an oral antifungal agent used for treatment of tinea infections. Because of its low aqueous solubility, griseofulvin absorption is slow, irregular, and incomplete, especially when taken on an empty stomach *(22)*. However, griseofulvin absorption increases by twofold when griseofulvin is taken with fatty meals *(23)*. Food appears to increase griseofulvin absorption by increasing its disintegration and de-aggregation *(24)*.

In a study of 12 adult volunteers who received a single 500 mg tablet of griseofulvin, a significant increase by 70 and 120% in griseofulvin bioavailability occurred following intake of a low-fat (29.3% calories from fat) and high-fat (52.4% calories from fat) meal, respectively, as compared to fasting ($p < 0.01$) *(25)*. One study, however, concluded that fatty meals increase the rate but not the extent of griseofulvin absorption, and that griseofulvin follows a circadian rhythm of absorption regardless of dietary fat content *(26)*.

Griseofulvin absorption also varies with the dosage form used. A crossover study of four healthy volunteers compared the absorption of two different dosage forms consisting of microsize and ultramicrosize griseofulvin tablets taken with or without food. When taken on an empty stomach, griseofulvin C_{max} of the ultramicrosize formulation was about 70% of the microsize formulation. When taken with food, griseofulvin C_{max} was 136% of the microsize formulation and about twice the C_{max} for the ultramicrosize formulation. The rate and extent of griseofulvin bioavailability were similar for both formulations when taken with food *(24)*.

In summary, optimal plasma griseofulvin concentrations are attained when griseofulvin is administered with a high-fat meal. As such, taking griseofulvin with meals maximizes its absorption and enhances therapeutic drug effect.

2.5. Isotretinoin

Isotretinoin is a synthetic analog of vitamin A available in oral capsules. Isotretinoin is primarily used for treatment of cystic acne. Isotretinoin is a highly lipophilic drug with maximal isotretinoin absorption achieved when administered with a fatty meal *(27)*.

The effects of food and fasting on isotretinoin bioavailability were evaluated in a randomized crossover study of 20 healthy male volunteers. An 80 mg oral dose of isotretinoin was administered either during a complete fast, 1 h before a standard breakfast, with a standard breakfast, or 1 h after a standard breakfast. Each treatment was separated by a washout period. Study results showed that isotretinoin bioavailability increased by about 1.5- to 2-fold when isotretinoin was administered 1 h before, with, or 1 h after breakfast, as compared to fasting. Mean C_{max} increased 1.6- to 2.4-fold in the presence of food but T_{max} was slightly delayed by 0.8–1.6 h. The investigators related the positive effects of food on isotretinoin absorption to increased bile flow that enhances isotretinoin solubility *(28)*.

In summary, isotretinoin bioavailability is increased when the drug is taken with food. Consistent intake of isotretinoin with meals is recommended in order to maximize isotretinoin clinical effects.

2.6. Itraconazole

Itraconazole is a triazole antifungal used for treatment of superficial and systemic fungal infections. Itraconazole is available in oral solution and capsule, and as an injectable form for intravenous administration. Each itraconazole dosage form has specific indications *(29)*. Itraconazole is a highly lipophilic, extremely weak base that is almost

insoluble in water and requires an acidic medium for optimal oral absorption *(30,31)*. The bioavailability of oral itraconazole also depends on the dosage form and the presence or absence of food. Whereas food enhances itraconazole capsule dissolution and absorption *(32,33)*, oral itraconazole solution is already in the dissolved form and is better absorbed when taken on an empty stomach *(34)*. Also, the formulation of oral itraconazole solution with cyclodextrin significantly improved its bioavailability *(35,36)*.

In one study, the bioavailability of itraconazole capsules increased from 40% with fasting to 102% when administered with meals *(32)*. In another study of 27 healthy volunteers, a 200 mg, single oral dose itraconazole capsule was administered with or without food. Pharmacokinetic parameters were analyzed for itraconazole and its active metabolite hydroxyitraconazole. The AUC for itraconazole and its active metabolite hydroxyitraconazole (3423 ± 1154 ng.h/mL; 7978 ± 2648 ng.h/mL, respectively) were higher when itraconazole was administered with food as compared to fasting (2094 ± 905 ng.h/mL; 5191 ± 2489 ng.h/mL, respectively). The C_{max} for itraconazole with fasting was 59% that with food (140 ± 65 ng/mL and 239 ± 85 ng/mL, respectively), and C_{max} for hydroxyitraconazole with fasting was 72% that with food (286 ± 101 ng/mL and 397 ± 103 ng/mL, respectively) *(29)*.

The absorption of oral itraconazole capsules is reduced when gastric acidity is decreased. This typically occurs in patients treated with gastric acid suppressants (antacids, H_2-receptor antagonists, proton pump inhibitors). In hypochlorhydric patients, coadministration of oral itraconazole capsules with an acidic beverage (e.g., cola) increased itraconazole bioavailability *(37,38)*. Following the administration of a single 100 mg dose of itraconazole capsules with 325 mL of water or an acid cola beverage (pH 2.5), the AUC for itraconazole was significantly higher with cola (2.02 ± 1.41 µg·h/mL) than with water (1.12 ± 1.09 µg·h/mL) ($p < 0.05$). The C_{max} of itraconazole was also significantly higher with cola (0.31 ± 0.18 µg/mL) than with water (0.14 ± 0.9 µg/mL) ($p < 0.05$). Additionally, the T_{max} was longer with cola (3.38 ± 0.79 h) than with water (2.56 ± 0.62 h) ($p < 0.05$) *(38)*.

In contrast to itraconazole capsules, itraconazole oral solution does not require food or acidic medium to increase its absorption. Significantly higher itraconazole and hydroxyitraconazole AUC and C_{max}, and shorter T_{max} occur when itraconazole oral solution is taken on an empty stomach rather than with food *(30)*. Following administration of oral itraconazole solution at a dose of 200 mg/d, respective mean itraconazole and hydroxyitraconazole concentrations were 43 and 38% higher when itraconazole was taken with food as compared to fasting *(34)*. The AUC with a single 100 mg dose of itraconazole oral solution was significantly higher when administered during fasting (2379 ± 1353 ng-h/mL) as compared to the fed state (1713 ± 741 ng-h/mL). The C_{max} was also significantly higher in the fasting state (349 ± 239 ng/mL) as compared to the fed state (147 ± 74 ng/mL) ($p = 0.006$). Additionally, the T_{max} was significantly shorter during fasting (1.7 ± 0.5 h) as compared to the fed state (3.8 ± 1.4 h) ($p = 0.0001$) *(30)*.

In summary, oral itraconazole capsules should be taken with a full meal for maximal absorption. However, oral itraconazole solution is better absorbed when taken on an empty stomach. Oral itraconazole solution provides an alternative to itraconazole capsules in patients who have difficulty swallowing the capsule or in those whose oral intake is restricted *(29,33)*. The optimal serum itraconazole and hydroxyitraconazole concentrations are not known, however, itraconazole oral solution is associated with higher

serum drug concentrations compared to oral capsules *(39)*. Administration of itraconazole with cola enhances itraconazole capsule absorption in patients receiving acid suppression therapy *(37)*. Oral itraconazole solution should be taken on an empty stomach, at least 2 h before or 2 h after a meal, to optimize oral absorption and bioavailability. Patients receiving medications that alter gastric pH should take itraconazole oral capsules with a cola beverage.

2.7. Mebendazole

Mebendazole is a broad-spectrum, anthelmintic agent available in oral chewable tablets. Mebendazole is poorly absorbed form the GI tract, but its absorption is increased when administered with food *(3)*. When used for treatment of echinococcosis, systemic bioavailability and intracystic mebendazole concentrations are essential to achieve therapeutic effect.

Administration of mebendazole with a fatty meal to three healthy volunteers resulted in an eightfold increase in plasma mebendazole concentrations. Plasma mebendazole concentrations remained below 17 nmol/L in two subjects and a maximum concentration of 17 nmol/L was achieved in the third subject. When the same dose was administered with a standard breakfast (two slices of ham, two fried eggs, 10 g butter, jam, bread, and coffee), plasma mebendazole concentrations rose within 2–4 h to 91 nmol/L, 112 nmol/L, and 142 nmol/L in the three subjects, respectively *(40)*. Mixing mebendazole with olive oil also increased the drug's bioavailability to a greater level than giving the tablets or suspension with a standard breakfast *(41)*. A wide variability in mebendazole absorption was reported in patients treated for hydatid cysts. Although plasma mebendazole concentrations were higher when mebendazole was given with food, the difference was not found statistically significant *(42)*.

When taken with food, higher plasma mebendazole concentrations are achieved. This is a desirable effect in treatment of hydatid cysts. Mebendazole tablets can be chewed, swallowed as a whole, or crushed and mixed with food *(43)*.

2.8. Misoprostol

Misoprostol is a prostaglandin E_1 analog that is primarily used for preventing gastric ulceration in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Misoprostol is available in oral tablets. GI side effects such as diarrhea and abdominal pain are common with misoprostol therapy. Diarrhea is dose-related and may sometimes require discontinuation of misoprostol therapy. The incidence of diarrhea with 800 μg/d of misoprostol in patients treated with NSAIDs ranges between 14 and 40%. Administration of misoprostol after meals slows misoprostol absorption rate and thus reduces the frequency of diarrhea *(44)*.

In a randomized, open-label, crossover study of 12 healthy volunteers, misoprostol absorption was studied when taken with a high-fat meal or during fasting. Study results showed food to decrease misoprostol absorption rate without significantly affecting the amount and extent of misoprostol absorption. Food significantly increased misoprostol T_{max} (64 ± 79 min) as compared to fasting (14 ± 8 min) ($p < 0.05$). Food, however, decreased misoprostol C_{max} (303 ± 176 pg/mL) as compared to fasting (811 ± 317 pg/mL) ($p < 0.05$). Because achieving a rapid high C_{max} of the active misoprostol metabolite (misoprostol acid) may result in increased side effects (diarrhea and abdominal pain), these effects can be minimized when misoprostol is taken with food *(45)*.

The effects of misoprostol on bowel motility were evaluated in a double-blind, cross-over study of 12 healthy volunteers. Study results showed that orocecal transit time (measured by H_2 breath test following lactulose administration) was shortened by 57 and 18% when misoprostol was administered before and after meals, respectively. The mean orocecal transit time was significantly shorter when misoprostol 400 μg was given before meals compared to after meals ($p < 0.001$) and to placebo ($p < 0.001$). Although other parameters such as stool frequency, fecal fat and bile acids, and fecal weight showed differences between treatments, these differences were not found statistically significant *(46)*.

In summary, administration of misoprostol before or after meals decreases the C_{max} of the active metabolite misoprostol acid without affecting misoprostol bioavailability *(45)*. Misoprostol should then be taken with food to reduce the incidence of diarrhea *(44)*.

2.9. Nitrofurantoin

Nitrofurantion is a broad-spectrum bactericidal agent that exerts its effects by possibly interfering with bacterial carbohydrate metabolism *(47,48)* or cell-wall synthesis *(49)*. Nitrofurantoin is used for treatment of uncomplicated urinary tract infections caused by susceptible microorganisms. Nitrofurantoin is available in different formulations including nitrofurantoin monohydrate (75%) with macrocrystals (25%) in oral capsules (Macrobid®), nitrofurantoin macrocrystalline oral capsules (Macrodantin®), and microcrystalline oral suspension (Furadantin®) *(50–52)*. A tablet formulation was previously manufactured but is no longer available.

Oral nitrofurantoin is absorbed in the small intestines. Because serum nitrofurantoin concentrations are usually low or undetectable in patients with normal renal function *(47,53,54)*, urinary nitrofurantoin levels are typically used to assess nitrofurantoin absorption *(55)*. Macrocrystalline nitrofurantoin has slower dissolution and absorption rate than nitrofurantoin monohydrate. Food, however, improves nitrofurantoin bioavailability by about 40% *(50)* and substantially increases the duration of therapeutic nitrofurantoin urine concentrations *(47)*.

The effects of food on nitrofurantoin absorption in macrocrystalline and microcrystalline tablets were evaluated in a study of four healthy volunteers. Nitrofurantoin 100 mg single dose was administered either following an 8 h overnight fasting or immediately after breakfast. Serial urinary specimens were collected to measure nitrofurantoin urine concentrations. Study results showed that food delayed nitrofurantoin absorption in the macrocrystalline form but did not have a significant effect on the absorption rate of the microcrystalline form. Food also resulted in increased maximum urine excretion rate of macrocrystalline nitrofurantoin but did not have a significant effect on the excretion rate of the microcrystalline form. Compared to fasting, food increased nitrofurantoin bioavailability by an average of 30 and 80% of the microcrystalline and macrocrystalline form, respectively *(56)*.

Another study compared the effects of food on the oral bioavailability of nitrofurantoin in three different microcrystalline tablets, a macrocrystalline capsule, and an aqueous microcrystalline suspension. The percent of a single 100 mg oral dose recovered in the urine was significantly greater when administered with food compared to the fasting state for the microcrystalline tablets ($p < 0.05$) and the macrocrystalline capsule ($p < 0.05$). Food increased the bioavailability of the tablets and the macrocrystalline capsule by 23–400% and 85%, respectively. Although the bioavailability of the microcrystalline

suspension was also increased with food, this was not statistically significant. Compared to fasting, food also significantly increased the mean duration of therapeutic urinary concentrations of nitrofurantoin macrocrystalline capsule ($p < 0.05$). Compared to fasting, food also increased the duration of therapeutic urinary concentrations of the microcrystalline suspension but the difference was not statistically significant. Nitrofurantoin administration with food also improved the uniformity of nitrofurantoin absorption and decreased the coefficients of variation. It was hypothesized that by decreasing the rate of gastric emptying, food increases nitrofurantoin residence in the stomach, thereby increasing drug dissolution that makes nitrofurantoin more readily absorbed in the small intestines *(57)*.

In summary, food delays nitrofurantoin absorption thereby increasing its absorption and reducing its peak plasma concentrations *(52,57)*. Nitrofurantoin macrocrystals are more slowly absorbed than the microcrystals *(55,58)*. As such, nitrofurantoin macrocrystals are better tolerated and are associated with less nausea and vomiting *(59–61)*. Nitrofurantoin should be administered with food to enhance its absorption, increase the duration of nitrofurantoin urinary concentrations, and improve GI tolerance *(50)*.

2.10. Saquinavir

Saquinavir is an antiretroviral agent used for treatment of HIV infection. Saquinavir is available in oral capsules as saquinavir mesylate (Invirase®), and in soft capsules as saquinavir (Fortovase®). The two dosage forms are not bioequivalent and cannot be used interchangeably. Fortovase has better bioavailability as compared to Invirase. Following administration of single 600 mg doses of saquinavir, the relative bioavailability of Fortovase was 331% as compared to Invirase. Food, however, substantially increases saquinavir absorption in either of the dosage forms *(62,63)*. Administration of saquinavir with food was reported to have increased saquinavir bioavailability by 1800% *(64)*.

In a study of six healthy volunteers who received saquinavir in a single 600 mg dose, a 6.7-fold increase in AUC was reported when saquinavir was administered with food as compared to fasting. Mean 24-h saquinavir AUC increased from 24 ng.h/mL with fasting to 161 ng.h/mL following breakfast (1006 kcal, 57 g fat, 48 g protein, 60 g carbohydrate). The 24-h AUC and C_{max} were on average twofold higher following a higher calorie and fat meal (943 kcal, 54 g fat) than a lower calorie and fat meal (355 kcal, 8 g fat) *(62)*. In another study of 12 healthy volunteers who received a single 800 mg dose of Fortovase, the mean 12-h AUC increased from 167 ng.h/mL with fasting to 1120 ng.h/mL when saquinavir was taken with breakfast (1006 kcal, 57 g fat, 48 g protein, 60 g carbohydrate) *(63)*.

In summary, food increases saquinavir bioavailability by increasing drug dissolution and disintegration *(65)*. As such, Fortovase and Invirase should be taken with food or within 2 h after a meal *(62,63)*. Owing to its improved absorption, Fortovase should be used as the saquinavir formulation of choice of an antiretroviral regimen.

3. EFFECTS OF SPECIFIC NUTRIENTS ON DRUG ABSORPTION

3.1. Ascorbic Acid and Iron

Iron deficiency anemia can affect all age groups especially children and women of childbearing age. There are two forms of iron in the diet including heme iron (from meat) and non-heme iron (from cereals, fruits, and vegetables). Heme iron accounts for about 10–15% of iron intake when consuming a meat-rich diet, whereas most of the remaining

dietary iron is in the non-heme form. Factors that increase (e.g., ascorbic acid) or decrease (e.g., phytates) non-heme iron absorption do not, however, affect heme iron absorption *(66)*. On the other hand, ferrous iron (Fe^{2+}) is better absorbed than ferric iron (Fe^{3+}). Most dietary iron is in the ferric state, but factors such as gastric acidity, dietary ascorbic acid, and other reducing substances convert ferric iron to ferrous iron. When considering oral iron supplements, the amount of iron absorbed depends on the type of iron salt used (sulfate vs fumarate vs gluconate), iron dose administered, and body iron stores. For instance, 10–35% of an oral iron dose is normally absorbed, whereas a greater amount of iron is absorbed in patients with iron deficiency anemia *(67)*.

Iron absorption is significantly reduced by the presence of phytate in the diet. Phytates, or hexaphosphates, are natural components of vegetables and cereals that bind iron in the GI tract to form insoluble and unabsorbable compounds. Ascorbic acid inhibits iron chelation to phytates and also reduces iron to the ferrous form, making it more available for absorption *(67)*. The amount of ascorbic acid needed to inhibit phytate binding to iron depends on the amount of phytate present *(68,69)*. The higher the phytate amount the more ascorbic acid is required to reverse the inhibition. With meals containing no phytates, ascorbic acid increases iron absorption by about 60% *(70)*. When phytates were added into wheat rolls at 2 mg, 25 mg, and 250 mg, iron absorption was inhibited by 18%, 64%, and 82%, respectively. When 50 mg of ascorbic acid was given, absolute iron absorption was highest when the rolls contained no phytates and was lowest when the rolls contained 250 mg of phytates. It is estimated that about 80 mg of ascorbic acid are needed to counteract the effects of 25 mg of phytates, and a few hundred milligrams of ascorbic acid are required to counteract the effects of 250 mg of phytates *(71)*. The average North American person consumes about 750 mg of phytates daily, although wide individual and geographical variations exist *(72)*.

Iron absorption was increased two- to threefold when 50 mg of ascorbic acid were added twice daily to each meal *(66–69)*. The first 50–100 mg doses of ascorbic acid appear to have the most significant effects on iron absorption. Higher doses have little additional effects *(70)*. Administration of ascorbic acid at doses of 500 mg twice daily after meals for 2 mo significantly improved iron status in strict vegetarians *(73)*. However, there was no significant effect on serum ferritin levels when higher ascorbic acid doses of 1 g twice daily were given to adults consuming a well-balanced diet. The lack of significant response with high ascorbic acid doses may indicate that iron reserves are maintained under tight control regardless of the mechanisms that enhance iron bioavailability *(74)*. Also, ascorbic acid supplementation may have little effect on improving iron absorption in well-nourished, non-iron-depleted subjects.

Ascorbic acid effects on iron retention were also evaluated in premenopausal women following induction of iron depletion by a low-iron diet and phlebotomy. Women in this study consumed a low-iron diet that provided 5 mg of elemental iron per 2000 calories for 67–88 d. At the end of the low-iron diet period, subjects were divided into three groups to receive a diet containing either 13.7 mg of iron per 2000 calories, or supplemental ascorbic acid 500 mg three times daily with meals, or a placebo supplement for 5.5 wk. Study results showed significant improvement in apparent iron absorption (defined as the difference between dietary and fecal iron) with ascorbic acid supplementation compared to placebo. Blood analysis at the end of 5 wk showed ascorbic acid to have also improved hemoglobin, serum iron concentration, and erythrocyte protoporphyrins. Ascorbic acid

had no effect on improving serum ferritin, transferrin saturation, hematocrit, or total iron-binding capacity *(75)*.

Ascorbic acid effect on iron absorption was also reported in children. In a study that evaluated ascorbic acid effect on iron absorption in 54 preschool Indian children with iron deficiency, ascorbic acid supplementation at a dose of 100 mg twice daily given with meals for 60 d resulted in significant improvement in hemoglobin ($p < 0.001$) and red cell morphology as compared with placebo ($p < 0.01$) *(76)*. In another study of 65 Chinese children with mild iron deficiency anemia who were consuming a predominantly vegetarian diet, daily ascorbic acid supplementation at 50 mg, 100mg, and 150 mg had nearly the same effects on improving iron status *(77)*.

The fraction of iron in ferritin and ferric hydroxide that enters the non-heme dietary iron is also influenced by diet composition. One study compared the absorption of iron from ferritin iron and ferric hydroxide in 35 multiparous women. When administered in water, the geometric mean iron absorption was 0.7 and 2.4% from ferritin iron and ferric hydroxide, respectively. With the presence of 100 mg ascorbic acid in dietary maize porridge, iron absorption increased to 12.1% for ferritin and 10.5% for ferric hydroxide, compared to 0.4% for both compounds with maize porridge without ascorbic acid *(78)*.

Ascorbic acid in fruit juices and vegetables is as effective as equal amounts of synthetic ascorbic acid in enhancing iron absorption *(69)*. In a study that evaluated the effect of fruit and fruit juices on iron absorption from a rice diet containing 0.4 mg of iron, juices of citrus fruits with higher ascorbic acid content resulted in higher amounts of iron absorbed *(79)*.

Iron supplements are commercially available in different salt forms (gluconate, fumarate, sulfate) providing different elemental iron amounts *(80)*. Iron sulfate is the most widely prescribed oral iron supplement usually given in one to three daily doses. Coadministration of 100–200 mg/d of ascorbic acid with iron supplements enhances iron absorption especially in anemic patients *(67)*. Patients who poorly absorb iron, such as those with gastrectomy, would most benefit from ascorbic acid supplementation during oral iron therapy *(81)*. Various combinations of commercial iron and ascorbic acid formulations can also be found such as Fero-Grad-500® (timed-release tablet containing ferrous sulfate 105 mg with sodium ascorbate 500 mg), Vitelle Irospan® (timed-release tablet and capsule containing ferrous sulfate exsiccated 65 mg with ascorbic acid 150 mg), Hemaspan® (containing ferrous fumarate 110 mg with ascorbic acid 200 mg), and Cevi-Fer® (timed-release capsule containing ferrous fumarate 20 mg with ascorbic acid 300 mg). Slow-release formulations of iron may result in portions of the dose bypassing the intestinal sites of absorption.

4. EFFECTS OF SPECIFIC NUTRIENTS ON REDUCING DRUG TOXICITY

4.1. Pyridoxine and Isoniazid

Isoniazid is an antimycobacterial agent used for treatment and prophylaxis of *Mycobacterium tuberculosis* infections. Peripheral neuropathy is the most common side effect of isoniazid therapy *(82)*. Peripheral neuropathy is dose-related and occurs mainly in "slow-acetylators," chronic alcoholics, malnourished, uremic, and diabetic patients. Signs and symptoms of peripheral neuropathy include paresthesias of the feet and hands, muscle

weakness, and diminished or exaggerated reflexes. The mechanism of isoniazid-induced peripheral neuropathy is likely related to isoniazid-induced pyridoxine deficiency or to isoniazid-blocking effect of pyridoxal phosphate synthesis by inhibition of pyridoxine kinase activity *(83,84)*. Vitamin B_6 occurs in the body as pyridoxine, pyridoxal, and pyridoxamine *(85)*. Pyridoxine kinase is the enzyme that converts pyridoxal to pyridoxal phosphate *(83,84)*. Pyridoxal phosphate is the active byproduct of pyridoxal metabolism that acts as a coenzyme in the metabolism of neurotransmitters. Reduced pyridoxal phosphate availability during isoniazid therapy is believed to cause reduction in neurotransmitter synthesis that eventually leads to peripheral neuropathy *(84)*.

The incidence of peripheral neuropathy correlates with the isoniazid dose and the presence or absence of patient-specific factors. Peripheral neuropathy occurs in about 1–2% of patients treated with the usual isoniazid doses of 3–5 mg/kg/d *(82)*. The incidence of peripheral neuropathy increases to 40% with isoniazid doses of 20 mg/kg/d *(83)*. In malnourished patients, even low isoniazid doses of 4–6 mg/kg/d may cause peripheral neuropathy in up to 20% of patients *(84)*. Peripheral neuropathy does not usually appear until 6 mo of isoniazid therapy *(82)*, but could appear earlier in malnourished patients or those with preexisting pyridoxine deficiency *(86)*.

It is a common practice to supplement pyridoxine at doses of 15–50 mg/d during the course of isoniazid therapy. Higher pyridoxine doses of 100 mg/d are required in patients treated with hemodialysis. Increased pyridoxine requirement during hemodialysis is likely resulting from reduced pyridoxine metabolism to active pyridoxal phosphate and increased dialysis clearance of pyridoxal phosphate *(87)*. Pyridoxine has also been used to prevent or treat isoniazid-induced psychosis *(85,88)* and seizures *(89,90)*. Seizures are the major toxic reactions of isoniazid overdose *(82)*. In case of isoniazid overdose, intravenous pyridoxine doses of 1 g for each 1 g of isoniazid dose ingested were used without evidence of pyridoxine toxicity *(90,91)*.

In summary, peripheral neuropathy rarely occurs in well-nourished patients treated with isoniazid doses up to 5 mg/kg/d *(92)*. Adult patients treated with isoniazid, especially those at high-risk for peripheral neuropathy, should receive prophylactic oral pyridoxine at doses of 50 mg/d *(82)*. Although high pyridoxine doses can possibly reduce isoniazid activity *(93)* or even cause neuropathy *(94)*, doses of 100–200 mg/d have been safely used to treat isoniazid-induced peripheral neuropathy *(84,93)*. The practice of avoiding pyridoxine prophylaxis in children receiving isoniazid should be discouraged especially in malnourished children *(95)*. Children treated with isoniazid may be supplemented with oral pyridoxine at dose of 1–2 mg/kg/d *(96)*.

4.2. Folic Acid and Methotrexate

Methotrexate is an antineoplastic antimetabolite used for treatment of certain cancers. Methotrexate is also used for treatment of psoriasis and rheumatoid arthritis (RA). Methotrexate use in RA is based on its anti-inflammatory, immunosuppressive, and antiproliferative effects. A low-dose methotrexate of 5–25 mg/wk is usually used for short- and long-term treatment of adults with RA *(97,98)*. Higher doses are exceptionally used when efficacy is not achieved at low doses. Significant toxicities, especially bone marrow suppression, occur at methotrexate doses exceeding 20 mg/wk *(99)*. Dose-related hematological, GI, hepatic, and pulmonary toxicities frequently lead to cessation of methotrexate therapy *(100,101)*.

Methotrexate is structurally similar to folic acid. Methotrexate inhibits the dihydrofolate reductase enzyme that reduces folic acid to tetrahydrofolic acid. This results in decreased intracellular levels of reduced folates and inhibition of DNA synthesis and cellular replication (100,101). The resultant folate depletion and inhibition of folate-dependent enzymes contribute to methotrexate toxicities in nontarget tissues. Diarrhea, stomatitis, and leukopenia are manifestations of methotrexate toxicity that mimic the symptoms of folic acid deficiency (102). Thus, adequate folate supplementation is crucial to reduce methotrexate toxicity.

Leucovorin (folinic acid) is a chemically active reduced folate derivative that is clinically used as a folate rescue to counteract methotrexate toxicity. Low oral doses of leucovorin at 2.5-5 mg/wk are used in combination with low-dose methotrexate (103). Low leucovorin doses reduce methotrexate toxicity without altering its efficacy. However, higher leucovorin doses (45 mg/wk) may counteract methotrexate efficacy and result in worsening of RA (104). As such, folic acid has been investigated as a possible substitute for leucovorin. Compared to methotrexate, folic acid has a lower affinity to the dihydrofolate reductase enzyme. This gives folic acid the advantage of reducing methotrexate toxicity without counteracting its efficacy.

Low plasma and erythrocyte folate and high homocysteine levels were reported in patients treated with methotrexate without folate supplementation (105,106). Plasma homocysteine levels decreased following folic acid or folinic acid supplementation (106). Reducing homocysteine levels may have a long-term cardiovascular protective effect because hyperhomocysteinemia may be a risk factor for cardiovascular disease (107).

The optimal dose and timing of folic acid supplementation in relation to methotrexate therapy are still debatable. Although weekly folic acid doses of 1 mg (108) and 5 mg (100) were shown to reduce low-dose methotrexate toxicity, higher doses were suggested to sufficiently prevent methotrexate toxicity (109). The effects of folic acid on reducing low-dose methotrexate toxicity were evaluated in a double-blind, placebo controlled trial of 79 patients with RA. Oral folic acid doses of either 1 mg/d (5 mg/wk) or 5.5 mg/d (27.5 mg/wk) were given 5 d a week on days not coinciding with methotrexate administration. Study results showed that either folic acid dose resulted in lower toxicity scores compared to placebo ($p < 0.001$). Also, neither folic acid dose interfered with methotrexate efficacy as assessed by joint indices and grip strengths (101). However, results of another study using folic acid doses at 5 mg/d for 13 consecutive days along with weekly intramuscular methotrexate showed alterations in methotrexate pharmacokinetics. There was a significant decrease in plasma methotrexate concentrations and increased total methotrexate clearance. The investigators concluded that decreased plasma methotrexate concentrations were possibly due to folic acid-induced increased cellular methotrexate uptake (110). Based on these results, the question remains about the optimal folic acid dose that reduces methotrexate toxicity without interfering with its efficacy.

A meta-analysis of seven double-blind randomized controlled studies was conducted to evaluate the effects of folic acid or folinic acid on the toxicity of low-dose methotrexate (< 20 mg/wk) in patients with RA. Results of the meta-analysis showed a 79% reduction in methotrexate-induced mucosal and GI toxicity with folic acid supplementation. A clinically but not statistically significant 42% reduction of the same side effects was seen with folinic acid. Similar effects were also achieved with low- and high-dose folic acid (1-27.5 mg/wk) or folinic acid (1-20 mg/wk). However, high folinic acid doses were

associated with increased tender and swollen joint count, a possible indication of decreased response to methotrexate *(100)*. The protective effects of folic acid reported in the meta-analysis *(100)* were not, however, replicated in a later individual study. In a 48-wk multicenter, randomized, double-blind, placebo-controlled study, folic acid at 1 mg/d and folinic acid at 2.5 mg/wk reduced the incidence of elevated liver enzymes without affecting the incidence, severity, or duration of other toxicities including mucosal and GI side effects *(112)*.

Based on available data, folic acid supplementation appears to reduce low-dose methotrexate toxicity *(109)* and results in less frequent interruption of methotrexate therapy *(112)*. Relying on dietary folic acid intake alone may not be sufficient to prevent methotrexate toxicity *(113)*. Because folic acid supplements are safe, effective, and less expensive than folinic acid *(114)*, weekly oral folic acid supplementation given on non-methotrexate days appears an appropriate substitute to leucovorin. Although there is no unanimity on the optimal folic acid dose, clinical studies reported weekly folic acid doses of 1 mg, 5 mg, and 27.5 mg to be safe and effective in reducing low-dose methotrexate toxicity *(100)*. Baseline patient folate status, methotrexate dose, and duration of methotrexate therapy appear to play a role in determining the optimal protective dose of folic acid. Reports of possible liver protective effects of folic acid are encouraging and require further exploration *(115)*.

4.3. Folic Acid and Fluorouracil

Fluorouracil (5-FU) is a fluorinated pyrimidine antineoplastic antimetabolite used in the palliative management of colorectal, stomach, pancreatic, breast, ovarian, and head and neck cancers. 5-FU exerts its effects primarily through its active metabolite fluorodeoxyuridine monophosphate that inhibits thymidylate synthase, a key enzyme in pyrimidine synthesis. Leucovorin, a modulator of 5-FU activity, is typically administered intravenously in combination with 5-FU to enhance 5-FU activity. Leucovorin enhances thymidylate synthase inhibition through increasing the intracellular pool of folates that stabilizes the thymidylate synthase–fluorodeoxyuridine monophosphate complex *(116,117)*. Because reduced folate metabolites enhance 5-FU antitumor activity, folic acid has been proposed as an alternative to leucovorin as long as it generates the same plasma metabolite levels. Animal studies have shown potential modulating effects for folic acid in mice with lymphocytic leukemia treated with 5-FU *(118)*. However, human studies evaluating the role of folic acid as a possible modulator of 5-FU activity are limited.

A crossover, randomized pharmacokinetic study evaluated the metabolism of folic acid and its ability to yield reduced folates. The study included 10 adult volunteers who were divided into two groups. One group received folic acid at doses of 25 mg/m^2 and the other group received 125 mg/m^2. After a 2-wk washout period, the same group received the same folic acid dose by the alternative route. Serial blood samples were collected over 24 h following folic acid administration. Plasma samples were analyzed for folic acid and for reduced folate metabolite concentrations. Study results showed a twofold increase in plasma-reduced folate concentrations with the higher oral folic acid dose as compared to the lower dose. In comparison with other studies using leucovorin, the same reduced folate metabolites were generated following folic acid administration. Folic acid at 125 mg/m^2 was at least as effective as leucovorin in increasing plasma-

reduced folate concentrations. However, folic acid metabolites accumulated at a slower rate and persisted longer than leucovorin metabolites. Based on these results and considering the short half-life of 5-FU, the study concluded that folic acid offers a potential therapeutic alternative to leucovorin in modulating 5-FU efficacy. It was also concluded that giving folic acid 4–6 h before 5-FU allows enough time for effective accumulation of reduced folate metabolites *(119)*.

However, a clinical study combining 5-FU and high-dose folic acid yielded disappointing results. The study included 22 patients with metastatic colorectal cancer who received a weekly dose of 5-FU 600 mg/m^2 (maximum 1 g) administered 1 h after an intravenous folic acid dose. The starting folic acid dose was 40 mg/m^2 escalated based on tolerance to the maximum dose of 140 mg/m^2. Study results showed a low response rate and severe toxicities with the combination therapy of folic acid and 5-FU, as compared to 5-FU alone. Only four patients had partial responses for a mean duration of 4 mo, but no patient had complete response. Severe diarrhea requiring hospitalization was reported in 12 patients and also caused 3 patients to drop out of the study. Two patients developed leukopenia and died later from sepsis. The study concluded that the use of folic acid with 5-FU could not be justified and that further studies were still needed. There was no clear explanation for the low response rate and high toxicities encountered in this study. The 5-FU dose was within the usual recommended dose. Mean serum folate concentrations at 1 h after folic acid administration were 11 nmol/L higher than the in vitro optimal levels for stabilization of the thymidylate synthase–fluorodeoxyuridine monophosphate complex. However, interpretation of these levels is difficult because serum folate levels do not necessarily correlate with intracellular folate concentrations. Also, it was unknown whether folic acid or the folic acid dose could have contributed to these effects, or even if patients with colorectal cancer are more sensitive to the combination therapy *(120)*. For instance, severe GI toxicities (e.g., stomatitis and diarrhea) are more commonly seen in patients with colorectal cancer who are treated with leucovorin and 5-FU, as compared to 5-FU alone. For safety reasons, it is generally recommended that patients who develop GI toxicity should not be initiated or continued on leucovorin therapy with 5-FU, and that patients should be monitored closely until diarrhea resolves *(121)*.

At present, intravenous leucovorin remains the agent of choice for modulation of 5-FU effect. The safety, efficacy, optimal dose, and dosing schedule for folic acid as a modulator of 5-FU activity remain unknown. Studies comparing leucovorin to folic acid are needed before folic acid can be recommended as a safe and effective modulator of 5-FU effect in the treatment of cancer.

5. EFFECTS OF SPECIFIC NUTRIENTS ON ENHANCING DRUG EFFECT

5.1. Plant Stanols and Statins

The management of dyslipidemia combines drug therapy and lifestyle modifications. β-Hydroxy-β-methylglutaryl-CoA reductase inhibitors ("statins") are the most widely prescribed agents to lower low-density lipoprotein (LDL) cholesterol. Besides reducing cholesterol intake, an alternate or adjunct approach in managing hypercholesterolemia is inhibiting cholesterol absorption with dietary inclusion of plant sterols and stanols. Plant sterols and stanols block dietary and biliary cholesterol absorption in the small intestines and cause reduction of serum cholesterol and LDL levels *(122,123)*.

Plant sterols (phytosterols) are naturally occurring plant constituents. They are C-28 (campesterol) and C-29 (sitosterol, stigmasterol) sterols. They are mainly found in edible oils, nuts, and seeds. Plant stanols are saturated derivatives of plant sterols with sitostanol being the most common stanol. Sitostanol is found mainly in wood pulp, tall oil, and to a lesser extent in soybean oil.

Western diets provide about 100–300 mg/d of plant sterols and 20–50 mg/d of plant stanols. Plant stanols and sterols have been incorporated into various food products including margarine and salad dressing and are more used in Europe than in the United States. Although plant stanols and sterols have shown to be equally effective in reducing cholesterol levels *(122)*, the compounds have inherent differences. For instance, plant stanols are preferable over plant sterols because they are relatively unabsorbed from the GI tract. Although plant sterols are poorly absorbed, daily sterols intake of 3.24 g increase serum sitosterol and campesterol by 40 and 70%, respectively. Because of concerns that plant sterols and their byproducts may initiate the development of atherosclerosis, plant stanols appear safer substances especially during long-term consumption *(124)*.

Plant stanols have been used in adjunct therapies with statins to manage hypercholesterolemia. Because statins inhibit cholesterol synthesis and stanols block cholesterol absorption, an additive effect of combining the two agents would be anticipated to further lower serum cholesterol levels. The combined effects of statins and plant stanols are equivalent to a one- to twofold increase in statin dose *(125)*. A double-blind, placebo-controlled study evaluated the effects of adding dietary plant stanol esters (esterified plant stanols) to statin therapy. One-hundred-sixty-seven adults with serum LDL-cholesterol concentrations of 130 mg/dL or higher and total cholesterol concentrations of 350 mg/dL or lower who had been receiving a stable dose of a statin for at least 90 d were included in the study. Subjects were randomized to receive either dietary canola oil based-spread in three servings that provided 5.1 g/d of plant stanol ester (equivalent of 3 g/d of plant stanols) or placebo for a period of 8 wk. Study results showed plant stanols in combination with statins significantly reduced serum total cholesterol (12 vs 5%, $p < 0.0001$) and LDL levels (17 vs 7%, $p < 0.0001$), as compared to placebo. There were no changes in serum triglyceride or high-density lipoprotein concentrations. Plant stanols were well tolerated *(126)*.

When considering statin therapy alone or in combination with stanols, doubling the statin dose would reduce serum LDL levels by an additional 6%, whereas a 10% reduction in LDL levels is achieved when statins are combined with stanols. Also, doubling the statin dose carries the risk of hepatic and muscle toxicity. As such, adding plant stanols to statin therapy appears a safer alternative *(125,126)*. However, a possible limiting factor to stanol efficacy alone is related to the liver upregulation of its LDL receptor activity to increase LDL synthesis in response to decreased cholesterol levels in liver cells *(127)*. The magnitude of this compensatory effect remains unknown.

A commercial product containing plant stanol esters (Benecol®) is available in spreads and softgels. It is usually taken with meals in two to three daily servings and appears to be well tolerated. However, the overall efficacy of plant stanols and sterols on lowering serum cholesterol remains modest especially with the associated compensatory increase in liver cholesterol synthesis *(127)*. Also, the relatively high cost of plant stanol and sterol products and the need to consume them several times daily makes them less appealing to the consumer.

Table 1
Summary of Relevant Drug–Nutrient Interactions That May Optimize Drug Effect

Drug	Diet/Nutrient	Proposed Mechanism	Relevant Effects of Interaction	Recommendations
Albendazole	Fatty meal	Increased solubility and absorption	Increased plasma and tissue drug concentrations Enhanced therapeutic effect	Should be taken with food when treating systemic infections
Atovaquone	Fatty meal	Increased solubility and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Cefuroxime axetil (tablets)	Meals, Milk	Increased absorption with decreased gastric pH	Increased plasma concentrations However, bactericidal activity not affected	Preferably taken with food or milk
Fluorouracil (5-FU)	Folic acid	Increased levels of reduced folate metabolites	Possible reduction of 5-FU toxicity and modulation of 5-FU activity	Efficacy and safety not established
Griseofulvin	Fatty meal	Increased disintegration and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food
Iron	Ascorbic acid	Inhibition of iron chelation to phytates Reduction of iron to the ferrous form	Increased iron absorption	Coadminister ascorbic acid (100–200 mg/d) with iron in patients who are poor absorbers
Isoniazid	Pyridoxine	Increased pyridoxal phosphate availability	Prevention of isoniazid-induced peripheral neuropathy	Coadminister prophylactic pyridoxine to adults (50 mg/d) and children (1–2 mg/kg/d) receiving isoniazid
Isotretinoin	Meals	Increased solubility and absorption	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food

(continued)

Table 1 *(continued)*

Drug	Diet/Nutrient	Proposed Mechanism	Relevant Effects of Interaction	Recommendations
Itraconazole (capsules)	Meals, acidic beverages	Increased solubility and absorption in acidic medium	Increased plasma concentrations Enhanced therapeutic effect	Should be taken with food or an acidic beverage (e.g., cola) Itraconazole oral solution should be taken on empty stomach
Mebendazole	Meals	Increased absorption	Increased target drug concentrations Enhanced therapeutic effect	Should be taken with food when treating systemic infections
Methotrexate	Folic acid	Increased levels of reduced folate metabolites	Reduced low-dose methotrexate toxicity in the treatment of rheumatoid arthritis	Weekly folic acid doses of 1 mg, 5 mg, and 27.5 mg have been used with low-dose methotrexate regimens
Misoprostol	Meals	Reduced absorption rate Reduced peak plasma concentrations	Reduced frequency of diarrhea	Should be taken with food
Nitrofurantoin	Meals	Increased dissolution and absorption	Increased duration of urinary concentrations, Reduced peak plasma concentrations Improved gastrointestinal tolerance	Should be taken with food
Saquinavir	Meals	Increased dissolution, disintegration and absorption	Increased therapeutic effect	Should be taken with food or within 2 h after a meal
Statins	Plant Stanols	Blockage of cholesterol absorption	Reduced serum cholesterol and low-density lipoprotein levels	Use stanols two to three times a day in diet or as adjunct to lipid-lowering therapy

Selective cholesterol absorption inhibitors have been under investigation. Ezetimibe (Zetia®) is a selective cholesterol absorption inhibitor that recently became available. Ezetimibe has been shown to reduce LDL cholesterol levels by about 17% as a monotherapy agent *(128)*, and by 25% when combined with statins *(129)*. Ezetimibe offers the advantages of significantly reducing LDL levels with a once daily dose of 10 mg taken without regard to meal or time of the day *(130)*.

6. CONCLUSION

DNIs can cause increased or decreased drug effect. Beneficial DNIs either enhance therapeutic drug effect or reduce drug toxicity. Clinicians should be aware of these interactions and should counsel patients about the appropriate nutrient intake to improve the safety and efficacy of drug therapy.

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11 Dietary Supplement Interactions With Medication

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1. INTRODUCTION

Routine, self-initiated supplementation with nutritional, herbal, and other related products is common among individuals in the Western world *(1,2)*. Among the most likely users of dietary supplements include middle-aged Caucasian women and elderly with preexisting medical conditions or chronic diseases often requiring medication. Therefore, the potential for drug–nutrient interactions (DNIs) is high and the resulting adverse reactions can be serious. Given the recent tragedies and reports implicating the use of dietary supplements *(3–11)*, the potential risks and adverse effects of these products, ostensibly for health benefit, cannot be underestimated.

This chapter discusses the topic of dietary supplements and their interactions with commonly used prescription medications. It defines dietary supplements, describes the interactions of dietary supplements with prescription drugs focusing on some of the most commonly used supplements, describes the limitations in characterizing these interactions, and offers suggestions for clinicians to help identify, monitor, and avoid these interactions. It addresses the effects and mechanisms of nutrient-containing, herbal-containing, and non-nutrient/nonherbal-containing dietary supplements on the pharmacokinetics and pharmacodynamics of prescription medications. Following a general discussion, the focus is on the five most popular selling non-nutrient, dietary supplement ingredients (ginseng, St. John's wort [SJW], garlic, ginkgo, and echinacea) and vitamin supplementation.

The ideal and the most organized way to approach DNIs would be to neatly characterize these supplement interactions with prescription medications into the four mechanism-based categories (Table 1). However, the complexity of products, paucity of clinical trials, void of product standardization, and lack of product dose reproducibility limits the ability to accurately delineate, characterize, and quantify these interactions *(12)*. The reader should keep in mind that this chapter is not intended to serve as an all exhaustive review

Table 1
Mechanism-Based Interactions

Category	Description
Type I	Ex vivo bioinactivation
Type II	Absorption
IIA	Metabolism
IIB	Transport
IIC	Complexation
Type III	Physiologic disposition
Type IV	Elimination

From ref. *12*.

of potential herb–drug interactions, but is more intended to serve as a reference for the mechanism of major herb–drug and vitamin–drug interactions that are currently the most clearly studied and defined.

1.1. Definition of Dietary Supplements

In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA) which amended the Food, Drug, and Cosmetic Act, changing the framework for regulating dietary supplements as a unique entity. DSHEA defines a dietary supplement as *(13)*:

..a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients: a vitamin, mineral, herbs or other botanicals, amino acids, a dietary substance used by man to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, constituent, extract, or combination of any ingredient described above; and intended for ingestion in the form of a capsule, powder, softgel, or gelcap, and not represented as a conventional food or as sole item of a meal or diet.

The stimulus for these changes was the thought that the people of the United States recognized that these products may benefit their health. Although the intent was to increase availability of products and information about those products, in effect, this act eliminated the premarket safety evaluations for dietary supplements that apply to food ingredients. Under this act and the current regulations, dietary supplements are not required to undergo the rigorous testing for safety and efficacy before being marketed, including identification of interactions, which is currently required of all prescription medications. Also, the Food and Drug Administration (FDA) does not monitor the manufacturing practices of the companies marketing these products, and leaves the manufacturer responsible for data supporting any product claims in the labeling. The FDA does not generally review statements made on the labeling of dietary supplements. Thus, the DSHEA places the burden of proof on the government if it wishes to take regulatory action against a supplement. The government must show that the supplement presents a "significant or unreasonable risk of illness or injury" under the conditions recommended or suggested in labeling (or under ordinary conditions of use if the labeling is silent). DSHEA's regulatory framework, unlike the system involved in drug regulation requiring extensive premarketing evaluation of safety and efficacy, is primarily a "postmarket"

program similar to the bulk of food regulation. Whether the recent tragic events involving a number of dietary supplements will change the government's regulatory approach remains to be determined. Regulations for Good Manufacturing Practices of dietary supplements have been recently proposed by the FDA *(14)*.

1.2. Prevalence of Dietary Supplement Use

As a result of the DSHEA, use and sales for dietary supplements in the United States have increased dramatically. The Vitamins and Lifestyle study found that 75% of the study cohort (35,000 men and 40,000 women in Washington State) had used at least one dietary supplement in the last 10 years *(1)*. Similarly, a survey conducted in 2000 involving 1183 respondents from the members of the Dutch Health Care Consumer Panel revealed that at least 36% of the respondents took echinacea-containing supplements and at least 52% took multivitamin and mineral supplements *(2)*. In 1996, more than $6.5 billion was spent in the United States on dietary supplements *(15)*. Total sales of these products grew to more than $12 billion in 1998 and more recently this sum has grown to more than $17.6 billion in 2001 in the United States *(15,16)*. This figure accounts for products containing vitamins, minerals, and other nutrients, to herbal products, sport products, and specialty type products. Considering the results of a survey of Americans conducted in 1999 that estimated that 9.6% of those studied, or more than 19 million Americans, have turned to herbal medicine as a form of alternative medicine second only to prayer, herbal products have a strong foothold for use in the United States *(17)*. A separate random survey of the noninstitutionalized population in the United States found that approx 81% of participants used at least one prescription or over-the-counter medication in the previous week, and 16% of patients using prescription products also reported using one or more herbal products or supplements *(18)*. A recent survey conducted in 979 preoperative patients undergoing anesthesia showed that 17.4% reported current use of herbal or selected dietary supplements *(19)*. In reality, the actual number of patients using dietary supplements may be underrepresented in these studies because not all patients readily report to their physicians and other health care providers the use of these products. Additionally, patients tend to underreport use of these products on written questionnaires *(20)*. Because such a large number of people are using herbal supplementation concomitantly with prescription medication, the stage is set for significant and potentially dangerous interactions that may result from the use of these products simultaneously.

2. BASIC SCIENCE

2.1. Confounding Issues With Dietary Supplements

A potential problem for documenting interactions with dietary supplements and prescription products is that the labeling of these products may not reflect the actual ingredients present in the formulation. A wide array of compounds were found in the products ranging from undeclared pharmaceuticals such as ephedrine and chlorpheniramine, to toxic levels of heavy metals including lead and arsenic in some Asian patent medicinal products sold in California *(21)*. A review of 25 commercially available ginseng preparations found that although the labeled plant products were in fact present in the preparation, the concentrations of these compounds, however, differed from labeled amounts *(22)*. Also, a study of steroid-containing supplements found a disparity between the

labeled amount of steroids in the product and the actual quantity within it. One product tested even contained testosterone, which is a class II controlled substance in the United States *(23)*. Not only do potential safety concerns exist when undisclosed drugs appear in these products, but questionable purity and accuracy of labeling further confound health care professionals, making their jobs more difficult in identifying and managing potential interactions and adverse reactions associated with FDA-approved medications. For example, a documented interaction between a supplement product and a medication may be the result of a poorly formulated product rather than to the labeled active ingredient per se. These issues are unlikely to be changed unless a significant revision or amendment to DSHEA takes place.

2.2. Type of Data Available

Because of the difficulties associated with studying herbal products, the literature currently available to classify these interactions is quite limited and consists mainly of case reports and anecdotal evidence. Like other types of drug–drug interactions, dietary supplements may act as the precipitant agent and thus can affect the pharmacokinetics and pharmacodynamics of prescription medications (object drugs). From the pharmacokinetic standpoint, dietary supplements can have profound effects on the absorption, distribution, elimination or clearance of the object drug through metabolic inhibition or induction of specific enzymes and transporters. A considerable number of herbs and supplements have been identified as potent inhibitors of the cytochrome P450 (CYP) enzyme system, the most important phase I enzyme family responsible for the biotransformation of many biogenic amines, steroids, cholesterol, and most prescription drugs used in the United States *(24)*. Some herbs and nutrient supplements also affect the functions of cell membrane transporters. For example, SJW induces intestinal P-glycoprotein (P-gp) *(25,26)*. P-gp is an adenosine-5'triphospate (ATP)-dependent efflux pump encoded by the multidrug resistant gene-1, which is located on chromosome 7. It belongs to the ATP-binding cassette transporter family and is highly expressed in the gastrointestinal tract, renal tubule, the blood–brain barrier, the liver, and several other tissues. P-gp is particularly highly expressed and functionally active in the intestinal epithelial tissues. Its primary function involves active transport of specific xenobiotics, drugs, chemicals, or even certain food substances that have already been absorbed by the epithelial cells back into the gut lumen *(27,28)*. This is likely an intrinsic defense mechanism of the human body to decrease the exposure to xenobiotics (in other words, "foreign" compounds). Many drugs, especially those with low oral bioavailability, are substrates of P-gp and modulation of intestinal P-gp activity can directly alter their absorption. Cyclosporine, digoxin, most dihydropyridine calcium channel blockers, and a number of protease inhibitors are examples of P-gp substrates. Induction of P-gp by SJW can decrease the systemic absorption of digoxin leading to subtherapeutic serum concentrations and potentially treatment failure. SJW also induces CYP3A4, an enzyme responsible for the elimination of indinavir, a protease inhibitor *(29–31)*. This decreases the oral absorption and increases the metabolic elimination of indinavir potentially leading to treatment failure for human immunodeficiency virus (HIV). On the contrary, some supplements may interact with an object drug by potentiating their pharmacological effects on specific receptors *(32)*. Therefore, dietary supplements can play a very important role in the study of drug interactions complicating a patient's medication regimen and may have a profound effect on the patient's treatment outcome (*see* Chapter 3).

Table 2
Ten Most Commonly Used Non-Nutrient Dietary Supplements

1. Ginseng	6. Echinacea
2. Ginkgo	7. Lecithin
3. Garlic	8. Chondroitin
4. Glucosamine	9. Creatine
5. St. John's wort	10. Saw palmetto

From ref. *18.*

3. CLINICAL EVIDENCE

3.1. Ginseng

The 10 most commonly used dietary supplements are listed in Table 2 *(18)*. Ginseng is one of the most popular herbal supplements in the United States. There are a number of different species of ginseng. However, the most studied forms of ginseng include just three species: *Panax ginseng* (Asian ginseng), *Panax quinquefolius* (American ginseng), and *Panax japonicus* (Japanese ginseng) *(33)*. These species can be found in many dosage forms including alcoholic extracts, fresh root, teas, capsules, and in combination products with other mineral, vitamin, and herbal ingredients *(34)*. Ginseng has been used therapeutically for thousands of years in Asia for a variety of illnesses and ailments. Some of these uses vary from more traditional ones such as to increase general well-being to more present-day uses such as to improve vitality, immune function, cognitive function, cardiovascular function, physical performance, sexual performance, and even the treatment of cancer *(35)*. Compounds known as the ginsenosides are thought to be responsible for the therapeutic activity of ginseng. However, because of the complexity of actions of these compounds as well as the activity of non-ginsenoside compounds contained within the herb, the overall activity of the herb is very complex *(33)*. The potential interactions with prescription medications are even less well understood and explained mainly by case reports.

Currently, there is one published case report of an interaction between ginseng and the oral anticoagulant agent warfarin *(36)*. In this case, a 74-yr-old man with a mechanical heart valve was being anticoagulated with warfarin with International Normalized Ratios (INRs) within the therapeutic range for more than 5 yr before deciding to begin taking ginseng capsules. All of his other medications and diet remained the same. Two weeks after taking the ginseng capsules, the patient's INR dropped to a subtherapeutic level. On discontinuation of the ginseng product, the patient's INR returned to the therapeutic level and continues to remain within the therapeutic range. Doses of warfarin were not adjusted. A study in rats examining the interaction with warfarin and ginseng found conflicting results *(37)*. This study found no impact of ginseng on warfarin pharmacokinetics and dynamics when the two were concomitantly administered. Although the data are sparse and conflicting, more vigilant monitoring or the avoidance of ginseng in patients treated with warfarin may be warranted.

Similar to the cases of warfarin and ginseng, the human experience with an interaction between ginseng and phenelzine is only documented in case report form. Phenelzine is a monoamine oxidase inhibitor with many known food and drug interactions. It is used

for the treatment of depression. In the cases reported, upon addition of ginseng products to therapy with phenelzine, patients developed tremulousness, headache, and sleeplessness *(38,39)*. The symptoms improved with discontinuation of the ginseng. While still being treated with phenelzine, one of these patients was inadvertently rechallenged with ginseng many years later and experienced similar results *(40)*.

A case report by Becker suggested that a ginseng product containing germanium may decrease the diuretic effect of furosemide. However, it is important to point out that exposure to germanium, a heavy metal, may itself lead to renal failure. It is, therefore, unclear, based on this case report, whether a true drug–herb interaction was present *(41)*.

An increase of plasma nifedipine concentrations was observed following the use of ginseng, although the clinical significance of pharmacodynamic responses (e.g., blood pressure, heart rate) was not documented. Furthermore, this investigation involved the use of three different dietary supplements (i.e., SJW, ginseng, and ginkgo). The subjects received all three supplements in a sequential order with a 14-d washout period between each phase. Because the mechanisms of interactions were not known, it is unclear whether the 14-d washout period was sufficient. Therefore, the study results could have been confounded by the presence of multiple drug interaction *(42)*.

3.2. St. John's Wort

Of all the herbal products currently marketed in the United States, SJW is probably the most formally studied and reported in terms of the potential to cause specific interactions with prescription medications. Its scientific name is *Hypericum perforatum*. It is so called SJW because its flowers bloom by the end of June, which is the time of the feast of St. John the Baptist. This herb has been used for thousands of years topically for many ailments, including minor burns and wounds and in more recent times as an oral extract to treat mild depression. SJW is a perennial plant that can be found throughout Europe, Asia, North Africa, and in North America *(43)*. The product tends to be standardized in terms of its hypericin content, but as with other herbal products, there have been published reports of discrepancies between labeled content and actual content assayed *(44)*. In addition to hypericin, a number of its derivatives and metabolites, such as hyperforin, chlorogenic acid, and quercetin, may also contribute to its clinical effect.

The dramatic ability of SJW to alter the concentrations of concomitantly administered medications is thought to occur through two major mechanisms. First, SJW has the ability to induce intestinal transporter (e.g., P-gp) activity. Second, the herb can increase the activity of CYP3A4 and CYP2B6 through pregnane X receptor activation *(24–26,30,31,45,46)*. CYP3A4 is an enzyme responsible for the metabolism of a majority of prescription agents and its induction has important clinical implications. Although CYP2B6 activity is also increased by hyperforin, there are very few medications identified to be CYP2B6 substrates. Therefore, the clinical relevance of CYP2B6 induction remains to be determined. In the human small intestine, CYP3A4 and P-gp function as a coupled system to reduce xenobiotic exposures by the host. This coupling system has the most significant influence on the absorption of substances that are substrates of both CYP3A4 and P-gp. Drug molecules that "escape" the initial extraction by the intestinal CYP3A4 enzymes and are absorbed into the epithelial cells can be excreted back into the gut lumen by P-gp, potentially re-exposing them to gut-wall metabolism multiple times. Induction of both P-gp and CYP3A4 by SJW may lead to a dramatic reduction in oral bioavailability of drugs

and can have grave implications for narrow therapeutic index agents. Decreased oral absorption may lead to subtherapeutic serum concentrations of medicinal agents resulting in treatment failure.

Even the induction of CYP3A4 alone may have grave complications for narrow therapeutic index agents. SJW may cause up to a sixfold induction of CYP3A4 activity. CYP3A4 is the most important phase I oxidative enzyme in humans accounting for the metabolism of more than 50% of prescription drugs currently used. CYP3A4 is ubiquitous with the most significant concentrations found in a variety of tissues including the liver and intestinal epithelium *(47)*. However, in terms of drug metabolism, the most significant locale for CYP3A4 is the liver and intestine. An induction of CYP 3A4 in the intestinal epithelium can increase the presystemic metabolism of medicinal agents preventing their absorption. This can lead to an overall decrease in the total bioavailability of an orally administered agent. Also, an induction of CYP3A4 in the liver will increase the systemic elimination of medicinal agents primarily metabolized by this enzyme system. This could lead to a decrease in the systemic exposure of the agent and potentially lost efficacy. Like P-gp, this effect is especially true for narrow therapeutic index agents.

In addition to pharmacokinetic studies, a number of clinical trials and case reports have corroborated the interaction between SJW and prescription medication with a narrow therapeutic index that are substrates for P-gp, CYP3A4, or both. These trials are summarized in Table 3. Most notably, there is literature published with SJW in combination with indinavir *(31)*, digoxin *(25)*, cyclosporine *(48,49)*, tacrolimus *(50)*, irinotecan *(51)*, fexofenadine *(52)*, and simvastatin *(53)*. It has also been reported that the serum concentration of norethindrone, a progestin-derivative used in some oral contraceptive preparations, can be decreased by SJW. This reduction in norethindrone concentration was associated with increased incidence of breakthrough bleeding. However, it is not known whether the contraceptive efficacy is negatively affected by SJW *(54)*. Ongoing investigations are currently underway to further assess the risks and clinical implications of this drug–herb interaction. All these results confirm that SJW may alter therapeutic effects and drug concentrations. The alteration in therapeutic concentrations in some cases potentially has very deleterious and dangerous consequences for affected patients. For example, a decrease in the therapeutic concentrations of indinavir, a protease inhibitor used in the treatment of HIV disease, may lead to an increase in HIV viral load or viral resistance indicating treatment failure. Additionally, subtherapeutic concentrations of cyclosporine or tacrolimus, medications used by organ transplant recipients to prevent rejection, can lead to organ rejection and significant morbidity or even mortality for these patients.

Because of the potential for SJW to induce P-gp and CYP 3A4, it is probably prudent to avoid using SJW in patients treated with prescription medications that are substrates of these two enzyme systems. Most importantly, it would be imperative to avoid narrow therapeutic index agents transported by P-gp or metabolized by CYP3A4 in order to avoid a dangerous interaction. Table 4 is a compilation of the agents that should be used with extreme caution with SJW. However, keep in mind that any agent that is affected by these two pathways has the potential to be influenced by SJW and should probably be avoided concomitantly with SJW. Patients should be carefully counseled about the potential risks of initiating therapy with SJW and health care professionals should be vigilant about the potential risks associated with this herbal product.

Table 3
Summary of Documented Drug Interactions With St. John's Wort

Interacting Medication	Type of Report	Reported Results
Indinavir	Open-label trial	Reduced mean AUC by 57%
Digoxin	Placebo-controlled parallel study	After 10 d of therapy with SJW, mean AUC reduced by 25%
Cyclosporine	Case report (two patients)	Acute heart transplant rejection, subtherapeutic cyclosporine concentrations
Cyclosporine	Case report	Kidney transplant recipient with subtherapeutic cyclosporine concentrations
Tacrolimus	Case report	Kidney transplant recipient with decreased tacrolimus levels. Levels returned to baseline upon discontinuation of SJW
Irinotecan	Randomized crossover	Formation of active metabolite decreased by 42%. Less myelosuppression in SJW-treated patient
Fexofenadine	Open-label trial	Single-dose SJW increased C_{max} by 45% and decreased oral clearance by 20%
Simvastatin	Double-blind crossover	Significant decrease in the active metabolite simvastatin hydroxy acid

AUC, area under the concentration-time curve; SJW, St. John's wort.
From refs. *25,31,48–53.*

Outside the realm of pharmacokinetic interactions, SJW may also interact with a number of medications based on pharmacodynamic properties. The agents that are particularly at risk for causing this type of reaction are antidepressants, including selective serotonin reuptake inhibitors (SSRIs), namely paroxetine and sertraline, and agents such as trazodone or nefazodone. There have been a number of cases of the combination of these agents with SJW causing symptoms consistent with that of excess serotonin or serotonin syndrome *(55,56).* Serotonin syndrome is generally characterized by mental status changes, tremor, autonomic instability, myalgias, and motor restlessness *(57).* This reaction is thought to occur because of hyperforin, a component of SJW that may inhibit the reuptake of serotonin. This, in combination with a prescription SSRI or other prescription agent that inhibits the reuptake of serotonin, may have an additive effect and predispose one to the serotonin syndrome. The potential for dangerous complications owing to

Table 4
Drugs That Should Be Used With Caution With SJW Based on Pharmacokinetic Interactions

CYP 3A4 Substrates	P-gp Substrates

Antiarrhythmics
    amiodarone, quinidine
	Antiarrhythmics
	    digoxin, quinidine, amiodarone

Calcium channel blockers
    diltiazem, verapamil,
    nifedipine
	Calcium channel blockers
	    diltiazem, verapamil

Immunosuppresants
    cyclosporine, tacrolimus
	Immunosuppresants
	    cyclosporine, tacrolimus

Protease Inhibitors
    ritonavir, indinavir,
    saquinavir, nelfinavir
	Protease Inhibitors
	    amprenavir, indinavir,
	    nelfinavir, saquinavir

Antiepileptics Carbamazepine	

serotonin syndrome cannot be understated and deaths have occurred as a result of this syndrome. Patients who are currently being treated with SSRIs or other antidepressants that increase the concentrations of serotonin should be warned of this potential interaction and should be advised not to use SJW with these prescription medications.

3.3. Garlic

Along the lines of potential CYP and P-gp interactions with herbal products and prescription medication, there is some evidence emerging that may suggest garlic (*Allium sativum*) might also have an effect on these two systems *(58–60)*. Used for centuries as a flavoring ingredient in food, garlic is also believed to carry many other beneficial effects. In the ancient world, garlic was used for a variety of reasons, including to treat common ailments, headaches and body weakness, epilepsy, and even hemorrhoids to clean the arteries *(61)*. This is very much in line with some of the more modern therapeutic uses of garlic, which include use as an antihypertensive, a cholesterol-lowering agent, to improve circulation, as an antiatherosclerotic, and even as a blood thinner *(62)*. The active component in garlic is thought to be allicin, which is only formed when garlic is crushed. Cooking or heating destroy the necessary enzymes for the formation of allicin. However, there still are a number of other components found within garlic products with potential activity.

In vitro data indicates that garlic may have an inhibitory effect on CYP2C9, 2C19, 2D6, and 3A isoenzymes *(58)*. In contrast, an in vivo study in nine healthy volunteers, which examined the chronic administration of garlic (greater than 3 wk), showed that garlic decreased the systemic exposure and maximum concentrations of saquinavir, a protease inhibitor that is a known substrate of the CYP3A4 *(59)*. However, the exact mechanism of the decrease was not able to be determined from this trial. Furthermore, garlic had a bimodal effect on the serum concentrations of subjects tested. Six subjects

showed a decreased saquinavir systemic exposure, measured by the area under the concentration-time curve (AUC) during treatment with garlic, which later returned to just below their baseline upon discontinuation of garlic. The AUC of the three other subjects was unchanged while on garlic, but dropped significantly after the discontinuation of garlic. The reason for this bimodal distribution in subjects was not able to be determined. Because the overall maximal plasma concentration (C_{max}) and AUC were decreased, the data imply that chronic ingestion of garlic may have an induction effect on CYP3A4 in the intestinal mucosa. However, because saquinavir is also a P-gp substrate, an effect on P-gp at this time cannot be ruled out. Another trial that evaluated the effect of a variety of herbal products, including garlic, on substrates of various different CYP isoenzymes in healthy volunteers found that garlic had no significant effect on the CYP3A4 isoenzyme but did indeed have an inhibitory effect on the CYP2E1 metabolic pathway *(60)*. Because no effect of CYP3A4 was seen in this study, the authors argue that there may be varying components of different garlic preparations and garlic's effect on the CYP enzyme system might be product-dependent. Until garlic's mechanism for interacting with CYP or P-gp is further evaluated, clinicians should pay particular attention to patients using garlic while concomitantly taking prescription agents that are CYP or P-gp substrates.

3.4. Ginkgo

Ginkgo is a popular herb that is derived from the dried leaves of *Ginkgo biloba* or maidenhair, a tree that is native to China, but can be cultivated in Europe, Asia, and North America. Use of this herb dates back to the very beginnings of ancient Chinese medicine. Today, the herb can be found used for a variety of purposes including cognition, memory, cerebral vascular disease, peripheral vascular disease, and multiple sclerosis, to name a few. The active components of *Ginkgo biloba* are extracted from the leaves, which contain ginkgolides A, B, C, J, and M, and bilobalide *(63)*.

In terms of specific drug interactions with ginkgo, there are a number of case reports documenting possible interactions between ginkgo and the anticoagulants warfarin and aspirin *(64,65)*. In the reported cases, bleeding seems to be the most common result of the concomitant use of ginkgo with other anticoagulant agents. This reaction may in part be exacerbated by the fact that various ginkolides are capable of inhibiting platelet-activating factor *(66)*. There have been a number of case reports of ginkgo attributed to an increased risk of serious bleeding events *(67)*. It may be possible that the cumulative effects of ginkgo's inhibition of platelet-activating factor with other anticoagulants are responsible for the reaction. Because of the possible potential for ginkgo to increase the risk of bleeding, clinicians should recommend patients avoid the use of this herb with any anticoagulant therapy or prior to any scheduled surgery.

Metabolically, there are conflicting results regarding the potential for ginkgo to affect CYP. A published abstract reported that ginkgo had an inhibitory effect on CYP3A4 in healthy volunteers reporting a 53% decrease in mean nifedipine (a CYP3A4 substrate) concentration at peak time 0.5 h after 18 d of ginkgo therapy compared to nifedipine alone *(68)*. However, a published trial examining ginkgo's effects on a number of different CYP substrates found the herb had no significant effect on any of the CYP isoenzymes tested including CYP3A4, 2D6, 1A2, and 2E1 *(60)*. The authors of this paper argue that different formulations of ginkgo with differing concentrations of phytochemicals and different bioavailability might be responsible for the discrepancy between studies *(60)*.

Once again, until the metabolic profile of ginkgo is better understood it would be reasonable to recommend not using the agent concomitantly with other prescription agents that are substrates for CYP or P-gp.

3.5. Echinacea

Echinacea is one of the most popular herbal remedies used to treat or prevent the common cold and respiratory or urinary tract infections. During the winter months, when cold and flu tend to be more prevalent, the demand for echinacea in retail pharmacies and other supplement retailers across the country seems to increase. Also, echinacea can be found incorporated into a number of throat lozenges or cough drops intended to mitigate the symptoms of a cold. Products are generally composed of one or a combination of three echinacea species, *E. purpurea*, *E. angustifolia*, and *E. pallida (69)*. Specific drug interactions associated with the use of echinacea have not been reported. However, there is in vitro data suggesting that echinacea may have an inhibitory effect on the CYP3A4 enzyme *(70)*. Although this data is in vitro and no in vivo data have yet confirmed the findings, those patients taking CYP3A4 metabolic substrates for medicinal purposes would be advised to avoid the use of echinacea. Further study in vivo is certainly warranted to further delineate the magnitude of this potential interaction.

Additional interactions between dietary supplements and medications have been proposed or are being actively investigated. These include not only herbal products but nutrient supplements as well (Table 5).

3.6. Vitamin Supplements and Drug Interactions

Although it is well known that a number of drugs have the potential to cause hypovitaminosis, it is less appreciated that vitamin supplementation may affect drug disposition. Other nutrients may also interact with drugs—altering absorption, metabolism, and pharmacodynamic effects. Unfortunately, most of the data are obtained from case reports including single patients, animal models, or from in vitro investigations (Table 6). The two better documented vitamins include folic acid and vitamin E (α-tocopherol).

It has been established that patients receiving chronic therapy with phenytoin carry a 50% risk of folate deficiency. Ironically, supplementation of 1 mg/d folic acid may lead to a significant decrease in serum phenytoin concentrations in 15–50% of the patients. This interaction between folic acid and phenytoin may involve the bilateral interdependent transport and possible metabolic processes *(71)*. Although the exact mechanism is unknown, pharmacokinetic analysis of phenytoin suggests that folic acid may increase the affinity of the metabolic enzyme(s) involved in the elimination of the phenytoin without causing overall enzymatic induction *(72)*. Although it is important to monitor for any signs of folic acid deficiency (such as megaloblastic anemia) in patients receiving long-term phenytoin therapy, it is as important to closely follow their serum phenytoin concentration should folate supplementation be deemed necessary in order to avoid breakthrough seizures secondary to subtherapeutic serum phenytoin concentrations.

The mechanism of interactions with drugs caused by vitamin E is of particular interest. The enhanced oral absorption of cyclosporine by water-soluble vitamin E was first reported in pediatric patients after liver transplantation *(73,74)*. Subsequently, a more formal observation trial took place in liver transplant recipients. In 26 patients who failed to achieve therapeutic blood cyclosporine concentrations despite prolonged intravenous

Table 5
Some Additional Proposed Interactions Between Dietary Supplements and Drugs

Supplement Ingredient (Precipitant)	Medication (Object)	Comment
S-Adenosyl-methionine	Serotonergic agents	Risk for serotonin syndrome
Calcium	Thyroid hormone	May interfere with drug absorption
Coenzyme Q	Warfarin	May antagonize drug effect
Dong quai	Warfarin	May potentiate drug effect
Echinacea	Immunosuppressants	Potential for altered drug effectiveness
Fennel	Fluoroquinolones	Reduced drug bioavailability
Feverfew	NSAIDS	Additive inhibition of prostaglandin production
Folic acid	Phenytoin	Reduced circulating drug concentrations
Ginseng	Oral hypoglycemics	Additive hypoglycemic effects
5-Hydroxytryptophan	Carbidopa	May cause scleroderma-like syndrome
Iron	ACE-inhibitors	May interfere with drug absorption
Iron	Levodopa/Carbidopa	May interfere with drug absorption
Kava	Benzodiazepines	Potential for additive CNS depression
Minerals (divalent)	Fluoroquinolones	Reduced drug bioavailability
Valerian	Barbiturates	May potentiate sedative effects
Vitamin E	Aspirin	Additive antithrombotic effect possible

NSAIDs, nonsteroidal anti-inflammatory drugs; ACE, angiotensin-converting enzyme; CNS, central nervous system.

From ref. 79.

administration or provision of daily oral cyclosporine doses higher than the normally recommended range (>10 mg/kg/d for adults, and >30 mg/kg/d for children), concurrent administration of 6.25 IU/kg of vitamin E liquid (D-α-tocopheryl-polyethylene-glycol-1000 succinate [TPGS]) before each oral dose of cyclosporine led to a significant improvement in cyclosporine absorption. TPGS coadministration resulted in a reduction of daily cyclosporine dose by 28.3% in 19 adult patients and 31.7% in 7 pediatric patients. Steady-state, whole-blood cyclosporine trough concentrations were all significantly increased. Patients who previously required intravenous administration of cyclosporine were all successfully converted to oral therapy (75).

Although it was initially thought that TPGS acted as a vehicle to allow lipophilic drugs, such as cyclosporine, to be more readily absorbed, subsequent investigation showed that TPGS is a P-gp inhibitor (76,77). This mechanism implies that coadministration of vitamin E liquid may increase the absorption of a significant number of drugs. However, what has not yet been determined is whether vitamin E capsule (α-tocopheryl acetate) may cause a similar magnitude of drug interactions. It is reasonable to conclude, however, that vitamin supplementation may not appear to be completely without risks.

Table 6
Dietary Factors That Modulate CYP Activity

Parameters	Species	Tissue	CYP Activity
Protein supplementation	Human	Whole body	↑ CYP1A2
Protein deficiency	Human	Whole body	↓ CYP1A2
MCT oil supplementation	Rat	Liver	↑ CYP1A2
Corn oil supplementation	Rat	Liver	↑ CYP2B1, CYP2E1 CYP3A
Vitamin A supplementation	Rat	Skin	↓ CYP1A1, CYP1A2
		Liver	↑ CYP2A1, CYP3A2
			↓ CYP2C6, CYP2C11
Vitamin A deficiency	Rat	Liver	↓ CYP2C11
Thiamin deficiency	Rat	Liver	↑ CYP2E1
Vitamin C deficiency	Guinea pig	Liver	↓ CYP1A2
	ODS-rat	Liver	↑ CYP1A2↓ CYP3A
Vitamin E supplementation	Rat	Liver	↑ CYP2C11
Iron deficiency	Rat	Intestine	↓ total CYP
Starvation	Rat	Liver	↓ CYP1A2, CYP2C11
			↑ CYP2B, CYP2E1, CYP3A2
Caloric restriction	Rat	Liver	↑ CYP3A

Note: CYP3A1 and CYP3A2 are expressed in rodents but not humans. Humans express CYP3A4 and CYP3A5. Substrate's binding affinity to CYP3A4/5 is different from that of CYP3A1/2.
   From ref. *78*.

4. CONCLUSION AND RECOMMENDATIONS

The area of dietary supplements is a growing topic of interest within the public and the medical community. Unfortunately, physicians, nurses, pharmacists, and other health care professionals, for the most part, were never formally trained in the use, efficacy, and monitoring of these agents. However, the public trusts that health care professionals are valuable sources of information on this subject. Indeed, this is true. There are a number of ways health care professionals can prepare themselves to treat patients who are using non-nutrient-containing dietary supplements and to help tailor therapy to avoid potential interactions. First, all patients should be screened routinely for dietary supplement use. This will not only enable clinicians to gather additional information about a patient's medication regimen, but will also heighten the public's awareness of the importance of reporting use of these products to health care professionals. Second, wherever herbals or supplements are mentioned on the medication history, clinicians should seek out information about that product from a reliable source. Third, practitioners should be aware of prescription agents with many known drug interactions and they should be wary when these agents are mentioned along with herbal products or supplements in the patient's medication history. If a known medicinal agent has many interactions it may be prudent to avoid its use with other agents whose interaction profiles are not currently well understood. And finally, health care professionals should explain to patients the concerns associated with the use of non-nutrient-containing dietary supplements. Data on these

products in the medical literature are just currently beginning to accumulate. However, for the most part, there still is a great deal of information, particularly in the field of non-nutrient-containing dietary supplements and drug interactions, which is currently not well understood. Explaining to patients the potential for dangerous interactions may prompt them to check with a healthcare professional before considering self-treatment with an herbal or other dietary supplement.

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12 Dietary Supplement Interaction With Nutrients

Mariana Markell

1. INTRODUCTION

The retail sales (in food stores, drug stores, mass market outlets) for herbal supplements in 2002 totaled more than $300 million out of pocket in the United States *(1)*. Sales are much greater in other markets (natural food stores, convenience stores, mail order, internet, etc.), although more difficult to estimate. This figure does not take into account expenditures for nutrient and other nonherbal dietary supplements, including minerals and "antioxidant" preparations, which account for many millions of dollars more. It is estimated that 30% of the population has used or is presently using herbal supplements *(2)*. No regulatory agency oversees the manufacture of herbs and dietary supplements, as the passage of the Dietary Supplement Health Education Act in 1994, excluded them from Food and Drug Administration (FDA) surveillance *(3)*. Thus, the true extent and prevalence of interaction of dietary supplements with nutrients is not truly known, and can only be surmised from anecdotal and historical reports, as well as few animal model studies.

2. POTENTIAL AREAS OF INTERACTION

Based on the observation that herbal and nonherbal supplements may have pharmaceutical actions, it is reasonable to assume that interactions with nutrients can occur through one of the following pathways (Table 1): alteration of absorption either through alteration of intestinal uptake/transport or alteration of gastric emptying, alteration of metabolism, including effects on the hepatic cytochrome P450 (CYP) or other enzyme systems (e.g., β-hydroxy-β-methylglutaryl [HMG]-CoA reductase) or interaction with peripheral uptake mechanisms (e.g., glucose transporter), and alteration of intestinal or renal elimination.

Perhaps the most worrisome of dietary supplement interactions with nutrients is that posed by herbals or other supplements that alter renal function, including those with diuretic action, of which there are many (Table 2). These supplements are especially problematic in patients with kidney or heart disease, for whom they are most commonly prescribed. They may potentiate hypokalemia, with the worst effects occurring in patients who are taking concomitant pharmacologic diuretic therapy *(4,5)*. Far fewer are the supple-

Table 1

Mechanisms by Which Dietary Supplements Could Interfere With Nutrients

Interference with absorption
    Alteration of gastric emptying
    Alteration of intestinal transport
Alteration of metabolism
    Interaction with cytochrome P450 enzymes
    Interaction with molecular targets (e.g., glucose transporter)
Interaction with metabolic enzymes (e.g., HMG-CoA reductase)
Interference with excretion
    Alteration of renal excretion
    Alteration of gastrointestinal transit time

Table 2

Common Herbs With Diuretic Actions

Buchu leaves (*Barosma betulina*)
Cleavers plant (*Galium aparine*)
Corn Silk (*Zea mays*)
Coffee bean (*Caffea arabica*)
Gravelroot root (*Eupatorium purpureum*)
Horsetail plant (*Equisetum spp*)
Juniper berries (*Juniperus spp*)
Parsley fruit (*Petroselinum sativum*)
Scotch broom (*Oxydendron arboreum*)
Tea leaves (*Camellia sinensis*)

From refs. *4,5*.

ments (predominantly derived from fruits) that may potentiate hyperkalemia in patients with kidney failure or aldosterone resistance, either intrinsic, as occurs with longstanding diabetic patients who develop hyporeninemic hypoaldosteronism, or in patients who are taking pharmacologic aldosterone antagonists (spironolactone) or angiotensin converting enzyme (ACE) inhibitors, or receptor blockers (ARBs).

Alteration of hepatic function has been reported with herbal products that utilize the CYP system for metabolism, especially the CYP3A fraction *(6,7)*. Although no specific alteration in nutrient levels has been reported, severe drug interactions can occur after ingestion, as increased synthesis of hepatic enzymes results in decreased levels of drugs including indinavir and cyclosporine *(8,9)*. There are also herbal supplements available (Table 3) that alter the action of hepatic synthetic enzymes, resulting in decreased serum cholesterol *(10)*.

Interference with the absorption of nutrients can occur through ingestion of supplements that either increase gut motility (decreased transit time) or create a barrier to absorption. Laxative herbs are many (Table 4). Classically, the irritant anthroquinones, or the other laxative herbs, that decrease transit time through the gut, could alter nutrient absorption or increase excretion. Hypokalemia has been reported following their ingestion *(4,5)*. Other supplements, including grapefruit juice, have reported activities on P-glyco-

Table 3

Common Herbal Products With Effects on Cholesterol/Lipid Metabolism

Gugulipid (*Commiphora mukul extracts*)
Garlic (*Allium sativum*)
"Red rice" statin (*Monascus purpureus*)

Table 4

Common Herbs With Laxative Effects

Aloe resin (*Aloes spp*)
Buckthorn fruit (*Rhamnus frangula*)
Cascara sagrada bark (*Rhamnus purshiana*)
Castor bean oil (*Rincus communis*)
Rhubarb root (*Rheum palmatum*)
Senna leaves and pods (*Cassia spp*)
Yellow dock root (*Rumex crispus*)

From refs. *4,5*.

protein and affect drug absorption. Theoretically, these substances could affect nutrient absorption as well *(11)*.

Herbs that are high in mucilage (water-soluble, hydrocolloidal fiber; Table 5), including the demulcents, can theoretically create a barrier to absorption of nutrients across the gut wall—with the greatest effect on absorption of glucose *(12)*. These herbs may also slow gastric emptying, resulting in altered nutrient absorption.

Finally, there are herbs and dietary supplements with miscellaneous actions. Hypoglycemia may be potentiated by supplements that alter insulin secretion, sensitivity of the insulin receptor to insulin, or that have insulin-like activity (*see* Table 6).

Probably most worrisome, is that as herbals and other supplements remain poorly regulated in the United States, untoward effects are often not reported, and effects on nutrient disposition and elimination are for the most part, unknown, especially in the patient who ingests multi-ingredient formulations.

3. SPECIFIC HERB/SUPPLEMENT–NUTRIENT INTERACTIONS

3.1. Effects on Potassium

Herbs are commonly prescribed for the purpose of diuresis, both in patients with kidney as well as heart disease *(13)*. As is true of the pharmacologic diuretics, potential for hypokalemia and hypomagnesemia exists, especially if abused. The mechanism by which diuretic action occurs has not been elucidated for most supplements. Interestingly, dandelion (*Taraxacum officianale*) root contains an inulin-like substance that may obligate an osmotic diuresis, while its leaves are high in potassium and could offset potassium wasting *(5)*. Hypokalemia can also be potentiated by licorice (*Glycerrhiza glabra root*) *(14)*, whose saponin component has aldosterone-like activity, resulting in renal potassium wasting through actions on the distal tubule, as well as sodium and fluid retention, and hypertension in susceptible people *(15)*.

Table 5

Common Herbs With Hydrocolloidal Activity

Aloe gel (*Aloe vera*)
Carageenan gum (*Gigartina mamillosa*)
Fenugreek seed (*Trigonella foenum-graecum*)
Flax seed or meal (*Linum usitatissimum*)
Guar gum seed endosperm (*Cyamopsis spp*)
Konjac powder—glucommanan from tubers (*Amorphophallus konjac*)

From refs. *4,5.*

Table 6

Common Herbs With Effects on Blood Glucose

Bitter melon fruit (*Momordica charantia*)
Fenugreek seeds (*Trigonella foenum-graecum*)
Garlic clove (*Allium sativum*)
Ginseng root (*Panax ginseng*)
Gymnema leaves (*Gymnema sylvestre*)

From refs. *4,5.*

Hypokalemia may also be exacerbated by herbs with laxative effects (Table 4), including Cascara sagrada (*Rhamnus purshiana*) bark or Senna (*Cassia spp*) leaves and pods, Aloe vera resin, and Yellow Dock root (*Rumex crispus*). The effect is presumably through decreased transit time through the bowel, although exact mechanisms are unknown.

In patients with hyporeninemic hypoaldosteronism (Type IV renal tubular acidosis), or those taking aldosterone-blocking drugs such as spironolactone or ACE inhibitors or ARBs—herbs or supplements that are high in potassium may potentiate hyperkalemia. Any product derived from fruit substances will have a high potassium load, including "Tibetan Noni" (Indian Mulberry, *Morinda citrifolia*), Dandelion leaf (see earlier), and Star Fruit (*Carambola spp*). The latter is especially worrisome in patients with renal failure as it has been associated with seizures and coma *(16)*. Additionally, the pickling process alters oxalate metabolism and has been reported to cause oxalate kidney stones *(17)*.

3.2. Effects on Gastrointestinal Absorption

Herbs that are high in mucilage (Table 3) contain hydrocolloidal fibers that increase viscosity of gut contents and theoretically delay gastric emptying *(12)* and may act as a barrier to absorption, especially of glucose *(18)*. These substances are classically used for "stabilization of blood glucose" or as demulcents to sooth irritated gastrointestinal mucosa.

3.3. Effects on Blood Glucose

In addition to the mucilaginous herbs just mentioned, there are substances that may affect blood glucose through different mechanisms (Table 6), including direct effects on peripheral glucose utilization via alteration of glucose transport *(19)* or insulin sensitivity *(20)* purported to underlie the hypoglycemic effects of the Philippine herb Banaba,

Langerstoemia speciosum L. There is evidence that Asian ginseng (*Panax ginseng*) may alter glucose utilization through enhancement of aerobic glycolysis through β-agonist activity and increased enzyme activity of the tricarboxylic acid cycle *(21)*, and Bitter melon (*Momordica charantia*) has components that are structurally similar to animal insulins *(22)*.

Gymnema sylvestre has the odd property of suppressing sweet taste, and thus avoidance of simple sugars may underlie its actions *(23)*, although there are data suggesting it causes release of insulin from pancreatic β-cells and may alter glucose tolerance by that mechanism *(24)*.

3.4. Effects on Lipid Metabolism

Several herbs or herbal products have documented effects on lipid metabolism. Garlic (*Allium sativum*) may affect cholesterol through inhibition of synthesis by sulfur-containing compounds *(25)*, and triglyceride metabolism through inhibition of fatty acid synthesis *(26)*.

Cholestin, a dietary supplement that is prepared by fermentation of rice with red yeast (*Monascus purpureus*), has clear inhibitory actions on HMG-CoA reductase, containing a compound monacolin K that is identical in structure to mevinolin (lovastatin) *(27)*. The product has similar toxicities to lovastatin, including a report of rhabdomyolysis occurring in a transplant recipient receiving cyclosporine *(28)*. Cholestin has been removed from the US market by the FDA *(29)*, but is available in other countries.

Guggulipid, an Ayruvedic preparation of extracts from the *Commiphora mukul* tree, contains stereoisomers *E-* and *Z*-guggulsterone that act as agonists for the bile acid receptor FXR, a regulator of cholesterol homeostasis. This mechanism may underlie the purported lipid-lowering effects of the supplement *(30)*.

4. CONCLUSION

Dietary supplements are largely unregulated in terms of required documentation of interactions at present, and are available without prescription to anyone who enters a health food store or pharmacy. Although generally benign in action, some supplements possess potent pharmacologic activity that can have profound effects on nutrient levels in the body, including potassium and glucose homeostasis, cholesterol and triglyceride metabolism, and undoubtedly, effects that have not yet been recognized. We need to remain aware of altered nutrient status and the potential for dietary supplements to be responsible. It behooves those of us who are concerned with nutrition, to stay abreast of the developments in supplement marketing and development, in order to advise our patients about the risks and benefits of supplement ingestion, and guide their choices in an informed manner.

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IV INFLUENCE OF PHARMACEUTICALS ON NUTRITIONAL STATUS, NUTRIENT DISPOSITION, AND EFFECT

13 Drug-Induced Changes to Nutritional Status

Jane M. Gervasio

1. INTRODUCTION

Drug-induced changes to nutritional status may be a direct or indirect consequence of the drug or chemical. Medications may affect the patient's nutritional status by altering body weight, altering taste perception (thereby decreasing intake), altering macronutrient metabolism, decreasing nutrient absorption, or depleting essential vitamins and minerals. Either by the drug's mechanism of action or by its adverse effects, patient's nutritional status may be affected. Recognizing and acknowledging drug-induced changes to nutritional status is imperative for optimal patient care.

2. DRUGS ASSOCIATED WITH WEIGHT GAIN

Treatment with medications for therapeutic purposes may result in an adverse effect of weight gain. Psychotropic medications are the most commonly reported group of medications associated with weight gain. This drug-induced weight gain can result in increased risk for diabetes, coronary artery disease, and other health-related problems *(1)*. Negative self-image from weight gain can further complicate the patient's success with psychotropic therapy *(2)*. Psychotropic medications associated with large weight gain include chlorpromazine, clozapine, olanzapine, valproate products, lithium, amitriptyline, imipramine, and mirtazapine, although many of the remaining antipsychotic and antidepressant drugs have been associated with some weight gain *(3)*.

Other medications, in addition to psychotropic medications, have been reported to increase body weight. More commonly associated drugs include alcohol, β-blockers, insulin, oral contraceptives, estrogen, and methylprogesterone *(4,5)*.

Reported adverse effects of testosterone, testosterone derivatives, and selective estrogen receptor modulators include weight gain. Subsequently, these drugs have been used to facilitate weight gain in the malnourished patient. Oxandrolone, a testosterone derivative, is Food and Drug Administration approved to promote weight gain in patients who have lost weight as a result of chronic infection, surgery, or severe trauma (Prod Info: Oxandrin® 1997). Smoked marijuana, oral dronabinol, and anabolic steroids have been

successfully used for the promotion of weight gain in patients with human immunodeficiency virus/acquired immunodeficiency virus syndrome (HIV/AIDS) *(6,7)*.

Drug-associated weight gain does not regress easily, particularly given the degree of adiposity in the weight gain. The extent of weight change depends on the specific drug, the dosage, and the duration of treatment *(3)*. The clinician must assess each patient's clinical presentation. Lower dosages or alternative medications within a therapeutic category may need to be instituted. For example, psychotropic medications such as fluoxetine, isocarboxazide, and topiramate are associated with weight loss and may be an alternative to other medications. Lower dose oral contraceptives and estrogen products may alleviate the problem of increased weight seen with this class of drugs *(8)*.

The clinician must also assess true weight gain from the medication before changing or initiating new treatment. Patients starting hormone replacement therapy associate weight gain with their medication when in fact it may solely be a result of their entrance into menopause *(9)*. Patients experiencing relief from symptoms of depression may eat more or overindulge. Patient education concerning body changes, proper diet, and exercise must be incorporated into the overall care of the patient.

3. DRUGS ASSOCIATED WITH WEIGHT LOSS

Drugs associated with weight loss are predominantly central nervous system stimulants. Although the stimulants' anorexic properties have been used for weight loss in obese patients, many times it is an unwanted adverse effect. Children receiving stimulant medications for attention deficit disorder may also have minor growth suppression as well as weight loss, but this does not appear to affect adult height or weight *(10)*. More common drug stimulants include amphetamine, caffeine, dextroamphetamine, methylphenidate, and theophylline.

Other medications that may exhibit an anorexic adverse effect include antihistamines, bethionol, dacarbazine, epirubicin, etoposide, fluoxetine, fluvoxamine, perhixiline, pimozide, sibutramine, temozolomide, trazodone, and zonisamide.

Alcohol intake in women and nicotine intake in both men and women are associated with lower body weight. The mechanism of action of alcohol or nicotine weight loss is unknown. Perkins and colleagues *(11)* showed a significant thermogenic effect with nicotine alone or in combination with alcohol in men but not women. Alcohol alone in either men or women and nicotine alone in women showed no thermogenic effect. Hence, it is speculated that in women, nicotine acts by suppressing appetite but more research is needed.

The clinician must ascertain whether patient weight loss is related to a medication or is indicative of another underlying condition. The advantages relative to the disadvantages in discontinuing a medication must be weighed against the patient's unwanted weight loss. Lower dosages or alternative medications may be necessary. Drug holidays in children receiving stimulants may be indicated *(12)*.

4. DRUGS ALTERING TASTE PERCEPTION

Medication-induced changes to an individual's perception of taste can result in decreased oral intake and weight loss *(13,14)*. Taste is mediated by chemosensory nerves that respond to stimulatory chemicals by direct receptor binding, opening ion channels, or second messenger systems using cyclic nucleotides and phosphorylated

inositol *(15,16)*. Medications disrupting these cellular processes may result in symptoms of ageusia (loss of taste), dysgeusia (distortion of taste), hypogeusia (decreased sense of taste), and phantogeusia (gustatory hallucination) (Table 1) *(15–18)*.

Dry mouth (xerostomia) is also associated with altering taste perception. Xerostomia results from the suppression of saliva production. Decreased saliva production alters the ion concentrations between the saliva and the plasma resulting in decreased taste sensation. Many drugs are associated with xerostomia, especially medications with anticholinergic properties. Medications often associated with xerostomia include amitriptyline, brompheniramine, bumetanide, cetirizine, cyclopentolate, cyproheptadine, didanosine, diphenhydramine, flecainide, flunitrazepam, granisetron, imipramine, isoniazid, loratadine, mesalamine, molindone, nizatidine, nomifensine, nortriptyline, ondansetron, olanzapine, orphenadrine, oxybutinin, pentoxyfylline, procainamide, propantheline, rimantadine, selegiline, sertraline, terfenadine, trazodone, and trimethobenzamide *(15)*.

If the offending medications cannot be discontinued, or the dosage decreased, supplemental therapy may be offered. Masking techniques include chewing sugarless gum or use of lozenges or breath mints to help alleviate dry mouth or altered taste. Artificial saliva spray and pilocarpine oral tablets have been used successfully for xerostomia. Davies and colleagues *(19)* reported statistically significant improvement in xerostomia symptoms with 5mg of pilocarpine three times a day over artificial saliva spray. Although both therapies improved dry mouth symptoms, many patients preferred the convenience of the saliva spray *(19)*.

Toothpaste containing betaine has been reported to reduce xerostomia in patients with chronic dry mouth. In a double-blind, crossover study, 60% of patients reported improvement from their symptoms of dry mouth after using toothpaste containing betaine. No changes were reported in saliva flow rates, oral mucosa, or mouth microflora *(20)*.

Conflicting reports have been shown using zinc supplementation for the treatment of taste disturbances *(18,21)*. Impaired taste sensation is a clinical manifestation of zinc deficiency. A variety of etiological factors have been attributed to zinc deficiency including drug therapy. If the patient is experiencing taste disturbances from zinc deficiency, administration of zinc sulfate may be beneficial.

The implementation of zinc therapy is not indicated for everyone. Souder et al. *(22)* reported 34% of patients with chemosensory disorders were treated with zinc, but only 6% of those patients experienced any relief of symptoms. Careful assessment of the underlying cause of the taste disturbance must be performed.

5. DRUGS ALTERING GASTROINTESTINAL FUNCTION

One of the primary functions of the gastrointestinal (GI) tract is to provide the body with a continual supply of water, electrolytes, and nutrients. The GI tract is composed of the following layers: the serosa, a longitudinal muscle layer, a circular muscle layer, the submucosa, and the mucosa. The innervation of the GI tract is supported by the intrinsic nervous system. The intrinsic nervous system controls most of the GI functions under the direction of the autonomic nervous system. Sympathetic and parasympathetic nervous signals from the brain to the GI tract strongly effect the degree of activity of the intrinsic nervous system. Acetylcholine and norepinephrine are the primary neurotransmitters for the parasympathetic and sympathetic system, respectively. Additional GI neurotransmitter receptors include cholinergic, histaminic, dopaminergic, opiate, serotonergic, and

Table 1
Drug-Induced Taste Disorders

Drug	Taste Defect	Drug	Taste Defect
Acemetacin	D	Bretylium	H-salt
Acetazolamide	D-acid	Bromocriptine	P
Acetylsulfosalicyclic	D	Bupropion	D
Adriamycin	D	Butorphanol	D
Albuterol	D	Cadmium	D-metallic
Alcohol		Calcifediol	D-metallic
Allopurinol	D-metallic	Calcitriol	D-metallic
Alprazolam	H	Calcitonin	D-metallic, P-salt
Ambifylline	D-bitter	Calcium Salts	D-metallic
Amethocaine	D-bitter/sweet	Captopril	A,D-bitter, P-metallic/salt/ sweet
Amezinium	D	Carbamazepine	A, H, P
Amiloride	A, D-salt, H	Carbenicillin	D
Amiodarone	D	Carbimazole	H
Amiloride	A, D-salt	Carboplatin	H
Amitriptyline	H	Carmustine	D-metallic
Amlodipine	D	Cefacetrile	D, H
Amonafide	D	Cefadroxil	D
Amphotericin B	H, P-metallic	Cefamandole	D
Amphetamine	D- bitter/sweet	Cefpirome	D
Ampicillin	H	Cefodizime	D
Amrinone	H	Cefpodoxime	D
Amydricaine	D-sweet	Ceftriazone	P-metallic
Anisotropin	A	Cephalexin	D
Antimony	D-bitter	Chlorhexidine	D, H- salt
Antithrombin III	D	Chlormezanone	A, H, P
Apomorphine	D-metallic	Chlorthalidone	D
Apraclonidine	D	Cholestyramine	D
Aspirin	D-bitter, H	Choline magnesium trisalicylate	A
Auranofin	H, D-metallic	Cilazapril	D
Azathioprine	H, P	Cimetidine	H, P
Azelastine	D-bitter, metallic	Ciprofloxacin	D
		Cisplatin	A,D, H
Aztreonam	D	Clarithromycin	H
Bacampicillin	H	Clomipramine	D
Baclofen	A, H, P	Clofibrate	H
Beclomethasone	A, H	Cocaine	D-sweet, H
Benoxaprofen	A	Colchicine	H
Benzocaine	D-sour	Corticosterones	H
Bepridil	D	Cyclobenzaprine	P
Biguanides	D-metallic, H	Dantrolene	D
Bismuth	D-metallic	Deferoxamine	D
Bleomycin	A, D, H	Desipramine	D

Table 1 (*continued*)

Drug	Taste Defect	Drug	Taste Defect
		Foscarnet	D
Dexamphetamine	D	Fosinopril	H
Diazepam	H	Furosemide	D-sweet, H, P-sweet
Diazoxide	A, D, H	Gallium	D-metallic
Diclofenac	D	Glipizide	D
Dicyclomine	A	Glycopyrrolate	A
Didanosine	D, H	Gold Salts	A, D-metallic, P
Diltiazem	A, D, H	Granisetron	D
Dimethyl Sulfoxide	D	Griseofulvin	D, H
Dinitrophenol	H	Guanfacine	D
Dinoprostone	D	Hydralazine	D
Dinitrophenol	D-salt	Hydrochlorothiazide	A, D
Dipyridamole	D-metallic, P-salt	Hydrocortisone	H
Disulfiram	D, P-metallic	Hyoscyamine	A
Dicyclomine	A	Ibuprofen	D, H
Doxazosin	D	Idoxuridine	D
Doxepin	H	Imipramine	H
Doxorubicin	D, H	Inamrinone	D, H
EDTA	D	Indomethacin	H
Enalapril	A, D-metallic, H, P-salt	Insulin	A, H
Ergocalciferol	P-metallic	Interferon-Alpha	D, P
Esmolol	D	Interferon- Gamma	D-metallic
Estazolam	D	Interleukin-2	H
Ethacrynic Acid	H	Iodine	D-metallic
Ethambutol	D-metallic, H, P-metallic	Isococaine	D-sweet
Ethchlorvynol	P	Isopropamide	A
Ethionamide	D-metallic	Isosorbide Nitrates	P
Etidronate	A, H	Isotretinoin	D, H
Etodolac	D	Ketoprofen	D, H
Etretinate	D	Ketoralac	D
Eucaine	D-sweet, H	Labetalol	D
Famotidine	D	Lead	D-metallic
Felbamate	D	Levamisole	D-metallic
Fenfluramine	D	Levodopa	D-bitter, H, P
Filgrastim	D	Lidocaine	D-sweet, H
Flecainide	D	Lincomycin	D, H
		Lisinopril	D, H
Flosequinan	D	Lithium	D-metallic
Flunisolide	A, D, H	Lomefloxacin	A
5-Fluorouracil	D-sweet, P	Lomustine	D
Fluoxetine	D	Loratadine	D
Fluphenazine	P	Losartan	A, D-salt/ sour/sweet
Flurazepam	D-metallic, bitter		
Flurbiprofen	D		

(continued)

Table 1
Drug-Induced Taste Disorders

Drug	Taste Defect	Drug	Taste Defect
Lovastatin	A	Pergolide	D
Mazindol	D	Perindopril	A, D-bitter
Mefenamic Acid	H	Phendimetrazine	D
		Phenformin	D-metallic
Mercury	D-metallic	Phenindione	D, H
Methimazole	A, H	Phentermine	D
Methocarbamol	D-metallic	Phenylbutazone	A, H, P
Methotrexate	H, D-metallic	Phenytoin	H
Methscopolamine	A	Piperacillin	H
Methyldopa	D-metallic, H, P-metallic	Pirbuterol	D, H
Methylthiouracil	H	Piroxicam	H
Metoclopramide	H	Pravastatin	D
Metolazone	P-metallic	Procainamide	P
Metronidazole	D-metallic, H, P-metallic	Procaine PCN	D-metallic, H
Mexiletine	D	Promethazine	H
Minocycline	D	Propafenone	D-metallic, bitter
Misoprostol	D	Propranolol	A, D, H
Monoctanion	D-metallic	Propylthiouracil	A, D, H
Moracizine	P	Protirelin	D-metallic
Nabumetone	D	Pseudoephedrine	D
Naproxen	D		
Nedocromil	D-bitter	Quinapril	D
Nickel	D-metallic	Rifabutin	A
Nicotine	D	Rimantadine	D, H
Nifedipine	A, D-metallic, H	Risperidone	P
Niridozole	D	Scopolamine	H
Nitroglycerin	A, D, H	Selegiline	D
Norfloxacin	D-bitter	Selenium	D-metallic
Nortriptyline	D	Sertraline	D
		Sodium Lauryl Sulfate	H
Nylidrin	D-metallic	Spironolactone	A, H
Ofloxacin	A, D	Stibogluconate	D-metallic
Omega Fatty Acids	D	Streptomycin	H
Omeprazole	D	Sucralfate	H
Opiates	A	Sulfasalazine	H, D-sweet, P-metallic
Oxaprozin	H, P	Sulindac	A, D-metallic, P-metallic
Oxazepam	H	Sumatriptan	D-bitter
Oxyfedrine	D, H	Tegafur	D-metallic
Paroxetine	D	Tellurium	D-metallic
Penicillamine	A, D-metallic/salt, H	Terbinafine	A, H
Pentamidine	D-metallic, H, P-metallic	Terfenadine	D
Pentazocine	D	Tetracycline	D-metallic

Table 1 (*continued*)

Drug	Taste Defect	Drug	Taste Defect
Thallium	D-metallic		
Thiamazole	A		
Tiopronin	A, D		
Tocainide	D-metallic		
Tolbutamide	D		
Tranylcypromine	D		
Trazodone	P		
Triamterene	H		
Triazolam	A, D		
Trichlormethiazide	H		
Tridihexethyl Chloride	A		
Trihexyphenidyl	H		
Trifluoperazine	P		
Trimipramine	P		
Venlafaxine	D, H		
Vincristine	H		
Vitamin D	D-metallic		
Zalcitabine	D		
Zidovudine	D		
Zinc Oxide	D-metallic		
Zolpidem	D		
Zopiclone	A, D-bitter		

D, dysgeusia; H, hypogeusia; A, aguesia; P, phantogeusia; EDTA, ethylenediaminetetraacetic acid.

benzodiazepine receptors. Any drug affecting these neurotransmitters, either centrally or locally, can affect GI tract function *(23,24)*. Ultimately, drugs altering the GI tract function of absorbing nutrients will affect nutritional status.

Prolonged or severe vomiting will alter the absorption of nutrients. Although vomiting is a reported side effect from numerous medications, it is usually not lingering. Tolerance to a medication or alternative therapy usually is rendered and nutritional complications are not a concern. Nutritional complications become a concern when vomiting is prolonged or severe, most notably from cytotoxic chemotherapy. Cytotoxic chemotherapy may be highly emetogenic. Chemotherapy agents associated with the most emetogenic potential include aldesleukin, altretamine, carboplatin, carmustine, cisplatin, cyclophosphamide, dacarbazine, dactinomycin, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, lomustine, mechlorethamine, mitoxantrone, pentostatin, and streptozocin *(23)*.

Medications that increase the motility of the GI tract or cause GI intolerance may result in abdominal pain, cramping, or diarrhea. Similar to vomiting, if these adverse effects are prolonged or severe, altered nutrient absorption may result. Patients experiencing abdominal pain and cramping from a medication may decrease nutrient intake simply resulting

from decreased appetite. Nutrient losses resulting from prolonged or severe diarrhea are owing to increased oral-cecal transit or decreased GI absorption time. Aspirin, nonsteroidal antiinflammatory agents, and iron are notorious for causing GI irritation. Medications associated with increasing motility include metoclopramide, erythromycin, and cisapride.

Patients may become tolerant of the offending medication. If adverse effects do not subside, alternative therapy may be instituted or the medication may be discontinued. Antidiarrheal medications may be introduced, but careful consideration must be given to potential contraindications. Resulting decreases in GI motility from antidiarrheal medications may cause constipation and bowel obstruction.

As previously mentioned, decreased GI motility may also result in inadequate delivery of nutrients. Decreased GI motility is associated with opiates and anticholinergic medications or medications with anticholinergic effects. Opioids increase the resting tone of smooth muscles in the GI tract, resulting in delayed gastric emptying and decreased peristaltic movement *(24)*. The effectiveness of opioids for pain relief is often limited by its side effect of GI dysfunction. Implementation of stool softeners or laxatives may be indicated. Novel selective peripheral opioid receptor antagonists are being investigated for their use in managing opioid-induced bowel dysfunction *(25,26)*.

Anticholinergic medications decrease GI motility by blocking the action of acetylcholine at the parasympathetic GI receptor sites. Several anticholinergic medications are currently available. Common anticholinergic medications include atropine, belladonna, benztropine, hyoscyamine, ipratropium, isopropamide, oxybutynin, scopolamine, and trihexyphenidyl. Commonly prescribed medications with anticholinergic effects include psychotropic agents such as amitriptyline, imipramine, olanzapine and zotepine, diphenhydramine, and procainamide. In patients with severe constipation or bowel obstruction, these medications should be discontinued and alternative therapy instituted.

6. DRUG-INDUCED METABOLIC EFFECTS

Alterations in metabolism affecting the nutritional status of a patient may be attributed to medications. Drug-induced alterations in glucose and lipid metabolism have been reported with several medications. Metabolic changes may range from transient to life threatening for the patient.

6.1. Hyperglycemia

Drug-induced hyperglycemia may result from fluctuations in a patient's metabolism. Drug-induced episodes of hyperglycemia may worsen glucose control in the diabetic patient as well as increase patient risk for developing hyperglycemia and subsequent diabetes. β-Blockers, especially in Type 2 diabetics, have been reported to cause hyperglycemia resulting from inhibition of insulin release *(27)*. Corticosteroids are associated with decreased peripheral utilization of glucose, promotion of gluconeogenesis, and accelerated synthesis of glucose. Hyperglycemia reported from the use of oral contraceptives is associated with decreased insulin receptor binding or a postreceptor defect in insulin actions *(28)*. Other commonly reported drugs implicated in the induction of hyperglycemia include alcohol, caffeine, growth hormone, nicotine, thiazide diuretics, protease inhibitors, atypical antipsychotics, calcium channel blockers, cyclosporine,

tacrolimus, morphine, phenytoin, sympathomimetic amines, thyroid products, and theophylline *(29–31)*.

6.2. Hypoglycemia

Not surprisingly, the most common causes of drug-induced hypoglycemia are insulin and sulfonylureas when used for treatment of hyperglycemia *(32)*. Although excessive alcohol intake induces glucose intolerance, alcoholic hypoglycemia is the better known alteration of carbohydrate metabolism *(33)*. The increased oxidation of ethanol results in reduced gluconeogenesis, hypoglycemia, and ketoacidosis.

Additional medications associated with hypoglycemia include anabolic steroids, aspirin, angiotensin converting enzyme inhibitors, calcium channel blockers, insulin-like growth factor-1 (IGF-1), salicylates, tetracycline, and warfarin *(30,32,34)*.

6.3. Lipid Changes

Drugs may adversely effect a patient's serum lipid profile. Anabolic agents, β-blockers, diuretics, progestins, combined oral contraceptives containing progestins, danazol, immunosuppressive agents, protease inhibitors, and enzyme-inducing anticonvulsants negatively affect serum lipid profiles. These drugs increase total cholesterol, low-density lipoprotein cholesterol and triglycerides by up to 40, 50, and 300% respectively *(35)*.

6.4. Protein Effects

Anabolic agents including growth hormone, anabolic steroids and IGF-1 effect protein synthesis. Growth hormone effect on protein metabolism includes increasing protein synthesis without affecting protein degradation *(36)*. IGF-1 promotes growth function as well as having insulin-like metabolic action including inhibition of lipolysis in adipose tissue and stimulation of glucose and amino acid transport into muscle *(37)*. Anabolic steroids have been shown to improve nitrogen retention and restore muscle mass in HIV/AIDS, trauma, and thermally injured patients *(38–41)*.

Corticosteroids, including inhaled corticosteroids, have been associated with a decreased rate of growth in children especially with high-dose, long-term treatment. Corticosteroids decrease the secretion of growth hormone as well as decrease the tissue's sensitivity to its effect *(42)*.

Alcohol may also induce protein loss by inhibiting intestinal protein absorption and urinary nitrogen excretion. Negative nitrogen balances have been reported in patients consuming alcohol and the catabolic effects continued for one week after the abstinence of alcohol *(33)*.

7. DRUG-INDUCED NUTRIENT DEPLETIONS

Changes in a patient's nutrient status may not be directly the result of the medication but a nutrient deficiency resulting from the medication. Multiple drugs, including alcohol and illicit drugs, have been reported to cause electrolyte, mineral, and vitamin deficiencies. Tables 2 and 3 *(17,43)* are a select list of drug-induced nutrient depletions. See additional chapters elsewhere in this volume for greater detail on interactions that impact on minerals and on folate status. Refer to Micromedex® Healthcare Series *(17)* and the

Table 2
Drug-Induced Mineral Depletions

Mineral/Electrolyte Deficiencies

Hypocalcemia

Alendronate	Edetate Disodium	Pentamidine
Amphotericin B	Estrogens	Phenobarbital
Antacids	Ethacrynic Acid	Phenytoin,
Bleomycin	Famotidine	Phosphates
Bumetanide	Fluocortolone	Polymyxin B
Carboplatin	Fluorouracil	Propylthiouracil
Cholestyramine	Foscarnet	Ranitidine
Cisplatin	Furosemide	Rituximab
Cimetidine	Gentamicin	Saline Laxatives
Citrate Salts	Hydroclorothiazide	Sargramostim
Codeine	Interferon	Sodium Polystyrene
Corticosteroids	Isoniazid	Sulfonate
Corticotropin	Lansoprazole	Sulfonamides
Cytarabine	Leucovorin	Terbutaline
Daunorubicin	Magnesium	Tetracyclines
Didanosine	Mineral Oil	Tobramycin
Digoxin	Nizatadine	Torsemide
Diethylstilbestrol	Pamidronate	Triamterene
Doxorubicin	Pentobarbital	Zoledronic Acid

Hypomagnesemia

Albuterol	Digoxin	Penicillamine
Amphotericin B	Docusate	Pentamidine
Bumetanide	Estrogen	Phosphates
Carboplatin	Ethacrynic Acid	Sargramostim
Chlorothiazide	Ethanol	Sulfonamides
Cholestyramine	Foscarnet	Tacrolimus
Cisplatin	Furosemide	Tetracylines
Corticosteroids	Gentamicin	Tobramycin
Cyclosporine	Hydrochlorothiazide	Zoledronic Acid
Dextrose	Oral Contraceptives	
Didanosine	Pamidronate	

Hypophosphatemia

Alendronate	Demeclocycline	Magnesium
Antacids	Dextrose	Pamidronate
Arginine	Digoxin	Sirolimus
Cefotetan	Ethanol	Tacrolimus
Cholestyramine	Felbamate	Zoledronic Acid
Cisplatin	Foscarnet	

Hypokalemia

Acetazolamide	Albuterol	Ammonium Chloride
Activated Charcoal	Amiloride	Amphotericin B

Table 2 (continued)

Mineral/Electrolyte Deficiencies

Hypokalemia

Aspirin	Doxorubicin	Penicillin G
Betamethasone	Ethacrynic Acid	Phosphates
Bisacodyl	Fluconazole	Piperacillin
Bumetanide	Fluoxetine	Polymyxin B
Carbenicillin	Foscarnet	Prednisolone
Carboplatin	Furosemide	Prednisone
Carmustine	Ganciclovir	Risperidone
Chlorothiazide	Gentamicin	Saline Laxatives
Chlorpropamide	Hydrochlorothiazide	Sargramostim
Chlorthalidone	Hydrocortisone	Sirolimus
Cisplatin	Isoflurane	Sodium Bicarbonate
Colchicine	Isosorbide Mononitrate	Sodium Lactate
Corticosteroids	Itraconazole	Sodium Polystyrene
Corticotropin	Levalbuterol	Sulfonate
Cortisone	Levodopa/Carbidopa	Sotalol
Cyanocobalamin	Lithium	Tacrolimus
Cytarabine	Methylprednisolone	Testosterone
Desirudin	Mezlocillin	Ticarcillin
Dexamethasone	Nafcillin	Tobramycin
Dextrose	Nifedipine	Torsemide
Didanosine	Ondansetron	Triamcinolone
Digoxin Immune Fab	Oxacillin	Vincristine
Dobutamine	Pamidronate	

Zinc Deficiency

Antivirals	Estrogen	Potassium-sparing
Captopril	Ethambutol	Diuretics
Corticosteroids	Folic Acid	Thiazides
Deferiprone	Hydrochlorothiazide	Valproic Acid
Edetate Calcium Disodium	Oral Contraceptives	

Iron Deficiency

Aspirin	Erythropoietins	Sulfonamides
Calcium	Ethanol	Tetracyclines
Cholestyramine	Indomethacin	
Deferoxamine	Neomycin	

Copper Deficiency

Antacids
Antivirals
Ethambutol
Zinc Salts

Selenium Deficiency

Valproic Acid

Table 3
Drug-Induced Vitamin Depletions

Vitamin Deficiencies

Folic Acid Deficiency

Aspirin	Indomethacin	Primidone
Carbamazepine	Methotrexate	Pyridoxine
Celecoxib	NSAIDS	Sulfasalazine
Cholestyramine	Oral Contraceptives	Valproic Acid
Corticosteroids	Phenytoin	
H2 Blockers	Potassium-sparing	
	Diuretics	

Vitamin A (Retinol) Deficiency

Cholestyramine	Mineral Oil
Ethanol	Neomycin

Vitamin B$_1$ (Thiamin) Deficiency

Aminoglycosides	Ethanol	Phenytoin
Cephalosporins	Fluoroquinolones	Sulfonamides
Digoxin	Loop Diuretics	Tetracyclines

Vitamin B$_2$ (Riboflavin) Deficiency

Aminoglycosides	Oral Contraceptives	Tetracyclines
Cephalosporins	Phenothiazines	
Fluoroquinolones	Sulfonamides	

Vitamin B$_3$ (Niacin) Deficiency

Aminoglycosides	Isoniazid	Valproic Acid
Cephalosporins	Sulfonamides	
Fluoroquinolones	Tetracyclines	

Vitamin B$_6$ (Pyridoxine) Deficiency

Aminoglycosides	Fluoroquinolones	Oral Contraceptives
Cephalosporins	Hydralazine	Sulfonamides
Estrogen	Isoniazid	Tetracyclines
Ethanol	Loop Diuretics	Theophylline

Vitamin B$_{12}$ (Cyanocobalamin) Deficiency

Aminoglycosides	Fluoroquinolones	Phenytoin
Antivirals	H2 Blockers	Proton Pump Inhibitors
Cephalosporins	Metformin	Sulfonamides
Cholestyramine	Neomycin	Tetracyclines
Colchicine	Oral Contraceptives	

Vitamin E Deficiency

Aspirin	Loop Diuretics
Corticosteroids	Oral Contraceptives

(continued)

Table 3 (continued)

Vitamin Deficiencies

Vitamin K Deficiency

Aminoglycosides	Cholestyramine	Sulfonamides
Barbiturates	Fluoroquinolones	Tetracyclines
Cefotetan	Mineral Oil	
Cefoperazone	Phenytoin	

Lexi-comp, Inc. Drug-Induced Nutrient Depletion Handbook *(43)* for extensive and updated drug-induced nutrient depletions.

8. CONCLUSION

Drugs and chemicals may alter the nutritional status of patients in a multitude of ways. Clinicians need to recognize which medications have the potential to disrupt a patient's nutritional status. Patients must be assessed to determine if a change in their nutritional status is related to a drug-induced complication. Drug dosages may need to be decreased, alternative medications incorporated, drug holidays administered, or the offending medication discontinued. Medications will continue to be identified as causes for changes in nutritional status. Further research must be conducted to identify new or alternative agents with fewer adverse effects or better resources to control these nutritional changes.

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14 Cardiac Drugs and Nutritional Status

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1. INTRODUCTION

Cardiac disease is the leading cause of mortality in America *(1)*. Treatment employs lifestyle changes and medical therapeutics as primary methods of combating cardiac disease. The pharmaceutical armamentarium designed to treat the various aspects and incarnations of cardiovascular disease is vast *(2,3)*. The use of potent and often multiple drug therapies necessitate vigilant treatment of the cardiac patient. Many of these drugs impact on nutritional status in both acute and chronic settings. Often, the impact is seen in adverse reactions and drug–nutrient interactions (DNIs) *(4,5)*. Acute reactions, such as nausea and abdominal pain, affecting food intake may adversely affect nutritional status, whereas specific DNIs may have diffuse effects on pharmacokinetics such as drug bioavailability or drug clearance. Carbohydrate, protein, and lipid metabolism may all be altered as a consequence of cardiac pharmacotherapy. Although many interactions have been identified, the clinical relevance of these interactions is not always evident, so the physician should remain aware of all consequences of prescribed regimens.

Complicating the treatment of heart disease are the associated conditions often seen in these patients. These conditions include diabetes, kidney disease, or obesity *(6)*. The patient with heart disease is often at greater risk for adverse outcomes to DNI because of these prevalent comorbidities and the required additional drug therapy. Heart disease is especially prevalent in the elderly, who are also predisposed to malnutrition and may be more sensitive to adverse DNIs *(7)*. Additionally, cardiac pharmacotherapy most often requires long-term use as well as multiple drug regimens and chronic, cumulative effects of drug therapy should be monitored along with acute effects.

The complex treatment of cardiovascular disease requires the physician to remain aware of all expected outcomes and possible interactions these medications may have with daily nutrition as well as dietary supplements. The emergence of alternative medicine including herbal remedies (i.e., dietary supplements) poses an additional and growing challenge to the clinician in balancing patient treatment, both traditional and nontraditional. The physician must work and communicate more than ever with his or her patient to prevent injury and to assure the optimum outcome of treatment.

2. ANTIHYPERTENSIVES

The strategies used in controlling hypertension rely on multiple pharmacologic agents and actions. Diuretics attempt to optimize volume status, whereas drugs such as the angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers attempt control of vascular tensions. The effect of these drugs on nutritional status as mediated by acute gastrointestinal (GI) effects such as nausea or in DNIs that affect bioavailabilty of specific antihypertensive agents should be considered in the management and continued treatment of the hypertensive patient. DNIs with antihypertensive agents are summarized in Table 1.

2.1. Diuretics

The mechanism of action of diuretics includes a decrease of extracellular volume and indirectly reduced vascular resistance. Together, the several classes of diuretics are the most commonly used antihypertensive agents in the United States. Their role is important in other subsets of cardiac patients, such as those with congestive heart failure or cardiomyopathy.

Benzothiadiazines ("thiazides") and related agents are the most commonly prescribed diuretic agents. Thiazides mediate their diuretic effect by inhibiting the reabsorption of sodium (Na) at the distal convoluted tubule. The loss of potassium (K) is promoted by the increased availability of Na for exchange with K at the distal segments of the nephron *(8)*. Long-term use of thiazides may produce episodes of protracted hypokalemia, necessitating increased intake of foods rich in potassium or even K supplementation. Thiazides may adversely affect other electrolyte levels as well. Hypochloremia, hypomagnesemia, and hypercalcemia are untoward effects that are promoted by the use of thiazide diuretics. The supplementation of K and chloride (Cl) should be considered if the levels of these minerals become depleted. The avoidance of excessive amounts of calcium-containing foods or supplements should be considered as well. Thiazide diuretics are also known to decrease glucose tolerance. In an incompletely understood mechanism, hyperglycemia may be produced through reduced insulin release and altered glucose metabolism *(4)*. Thiazide diuretics may also increase the levels of plasma low-density (LDL), total cholesterol, and the LDL/high-density lipoprotein (HDL) ratio. The use of thiazides may necessitate the decreased cholesterol intake if not already undertaken by the hypertensive patient.

Loop diuretics act by preventing Na–K–Cl cotransport in the ascending loop of Henle. Their influence on nutritional status is mediated by their effects on electrolyte excretion and increased need for supplementation of K and magnesium (Mg). Unlike the thiazides, loop diuretics promote excretion of calcium (Ca) and their use may require increased intake of foods containing calcium or supplementation. Loop diuretics also have a similar effect on cholesterol levels and less commonly on glucose tolerance. The two most commonly used loop diuretics, furosemide and bumetanide, have shown differing responses when taken with food. Although bumetanide has shown no appreciable reduction in absorption in relation to food, furosemide has repeatedly been shown to be affected by food intake *(9,10)*. The bioavailability of furosemide is reduced 16–45% when taken with food. The clinical significance may be negligible in relation to the effect, however, it should be considered in those patients who exhibit furosemide resistance.

Table 1
Antihypertensive Drug Interactions

Drug	Gastrointestinal Effects	Macronutrient/ Metabolic Effects	Micronutrient Effects	Other
Diuretics				
Thiazide diuretics		$\downarrow K^+$, $\downarrow Na^+$, $\downarrow Mg^{2+}$, $\downarrow Cl^-$, $\uparrow Ca^{2+}$	$\downarrow$glucose tolerance, $\uparrow$LDL, $\uparrow$cholesterol	
Loop diuretics		$\downarrow K^+$, $\downarrow Na^+$, $\downarrow Mg^{2+}$, $\downarrow Ca^{2+}$		$\downarrow$bioavailability with meals
Potassium-sparing diuretics		$\uparrow\uparrow K^+$		
Carbonic anhydrase inhibitors			Metabolic acidosis	$\uparrow$bioavailability with meals
β-blockers	P-gp inhibition (may decrease GI absorption)	$\uparrow K^+$	Hypoglycemia, $\downarrow$free fatty acids	
ACE inhibitors	Dysgeusia	$\uparrow K^+$		
Calcium channel blockers				
Dihydropyridines (e.g., nifedipinie)				$\uparrow$bioavailability with grapefruit juice
Nondihydro-pyridines (e.g., verapamil)	Inhibits P-gp			$\uparrow$efficacy of drug with xanthines
Vasodilators				
Hydralazine			$\downarrow$B6	
Diazoxide			Hyperglycemia	
Nitroprusside			Hypothyroidism (rare)	
α-receptor blockers	Abdominal pain, nausea, peptic ulcer exacerbation			

Potassium-sparing diuretics such as spironolactone, when used alone, increase the risk for hyperkalemia. In patients prone to hyperkalemia, avoidance of potassium supplements or excessive intake of potassium-rich foods such as bananas, beans, and citrus fruits should be advised, particularly in the presence of renal dysfunction *(11)*. Adverse effects of K^+-sparing diuretics include diarrhea, gastritis, and peptic ulcers. They are contraindicated in peptic ulcer disease and production of these effects may adversely affect nutritional status. Triamterene has been implicated in folate deficits.

Carbonic anhydrase inhibitors are also employed as diuretics. The prototype and most well known of them being acetazolamide. Their action at the proximal convoluted tubule inhibits the reabsorption of Na HCO_3 and promotes the excretion of HCO_3^-. This method of diuresis also promotes the excretion of Na^+ and K^+ ions and patients must be observed for hyponatremia or hypokalemia and hypochloremia to a lesser degree. A metabolic acidosis may also be promoted as the buffer, HCO_3^-, is being lost in the urine. The question of whether diuretics increase losses of thiamin in addition to electrolytes has not been adequately answered.

Overall, diuretic therapies provide a valuable tool in the fluid and volume balance of cardiovascular patients. However, fluid and electrolyte balance must be carefully monitored in these patients to avoid adverse outcomes.

2.2. β-*Blockers*

The β-adrenergic receptor antagonists or β-blockers have long been candidates for first-line treatment in the management of a wide variety of hypertensive patients. Their therapeutic effect in ischemic heart disease, congestive heart failure, and certain arrhythmias maintains their wide distribution and use.

β-blockers can impact on several aspects of patient nutrition and metabolism. Metabolic effects of β-blockers are mediated through carbohydrate and lipid interactions. Catecholamines stimulate glycogenolysis and glucose release into the bloodstream in response to hypoglycemia and stress. This effect is blunted by β-blockade and hypoglycemia may be exacerbated. This adverse effect is more commonly seen with nonselective β-blockers such as propranolol and labetalol and less so with $β_1$-selective blockers such as metoprolol and esmolol. Caution should be used when prescribing these drugs to poorly controlled diabetics. The use of selective $β_1$-antagonists may be preferred in such patients where beta blockade is indicated. Other selective $β_1$-antagonists include esmolol, pindolol, and acebutolol.

Lipid metabolism is also affected by the use of β-blockers. β-adrenergic receptors stimulate the release of free fatty acids (FFA), which serve as an important energy source for active muscle. β-blockade may inhibit this release and deprive the muscle of a vital source of energy *(12)*. Paradoxically, nonselective β-blockers are also noted to produce a rise in plasma triglycerides and a decrease in HDLs. The overall effect of these actions has not been fully characterized. Again, the use of $β_1$-selective antagonists may mediate the adverse effects of β-blockade on lipid metabolism.

β-Blockers have a well-characterized effect on potassium levels. Exercise induces release of K^+ from muscle into the circulation. Epinephrine promotes the uptake of K^+ back into skeletal muscle, which serves to buffer any likely hyperkalemia. β-blockade blunts this buffering effect and may promote hyperkalemia *(13)*. The proper development and strengthening of muscle requires increased intracellular potassium, which may be adversely affected by nonselective β-antagonism.

Carvedilol is a newer generation nonselective β-receptor antagonist as well as an $α_1$-receptor antagonist. Carvedilol has adverse effects including nausea, vomiting, and diarrhea or constipation. Along with propranolol, and the calcium channel blocker verapamil, carvedilol has been implicated in the inhibition of the P-glycoprotein (P-gp) transport system *(14)*. This system acts to inhibit the absorption of drugs and nutrients

from the GI, hepatic and renal systems. Inhibition of this system may alter absorption and metabolism of various substrates, but requires further investigation.

2.3. ACE Inhibitors

Angiotensin II is one of the most potent vasoconstrictors used by the body. The systemic hypertension produced by this vasoconstriction can be reduced by inhibiting the conversion of the relatively inactive angiotensin I to the potent angiotensin II by ACE.

ACE inihibitors can have adverse effects on the electrolyte balance of patients using them. A common side effect is hyperkalemia. Although the effect is normally mild in persons with normal renal function, care should be used in those with decreased renal function and in those who are taking medications that have potassium-retaining properties such as the K^+-sparing diuretics or those on K^+ supplementation. Again, dietary intake may need to be adjusted for those patients prescribed this class of antihypertensive medication.

ACE inhibitors have also been implicated in the loss of both protein and glucose in the urine. The long-term effect of these losses is not well characterized.

Dysgeusia or alteration of taste has also been noted to occur in patients using ACE inhibitors. This is most commonly seen with captopril. Dysgeusia may adversely affect food intake and should be watched for in these patients.

Newer classes of drugs related to the ACE inhibitors are the angiotensin II receptor antagonists such as losartan and valsartan. These are purported to have similar therapeutic effects as the ACE inhibitors, but with diminished side effects. Their bearing on nutritional status should be considered as similar to ACE inhibitors with similar precautions until better defined by further study.

2.4. Calcium Channel Blockers

Calcium channel blockers inhibit the elevation of calcium in the vascular smooth muscle required for contraction. By blocking this rise, the calcium channel blockers produce arteriolar relaxation and decrease in vascular resistance. As a group, the calcium channel blockers are known to cause nausea and constipation. Minor elevations of liver function tests have been reported. These elevations may indicate interactions affecting presystemic metabolism. The effect of food ingestion and bioavailability of nifedipine has been well studied and the mode of delivery of nifedipine correlated with meals may significantly alter the clinical effects. Sustained release formulations have their bioavailability and hypotensive effects significantly increased by food ingestion (15) but modified release and controlled release formulations do not seem to be pharmacodynamically altered by meals (16,17).

Nifedipine and other dihydropyridines have increased oral bioavailability when ingested with grapefruit juice evidenced by hypotension and tachycardia (18,19). This effect is not seen in the other classes of calcium channel blockers such as diltiazem and verapamil (20,21). Avoidance of grapefruit juice or alternatives to the dihydropyridines should be considered in those patients using calcium channel blockers.

Verapamil, a phenylalkylamine, has also been reported to have similar effects on the P-gp system as described for carvedilol and may affect the absorption of various sub-

strates in the digestive tract *(22)*. Multiple drug–drug interactions and DNIs have also been reported for verapamil. Alterations in drug levels of digoxin and caffeine are among those documented.

2.5. Vasodilators

Arterial dilators mediate their antihypertensive effects by direct relaxation of vascular smooth muscle. Hydralazine is a member of this class of drugs, which is known to induce a deficiency of vitamin B_6 (pyridoxine). Hydralazine complexes with pyridoxine to form a hydrazone and depletes the circulating pyridoxine. The manifestation of this deficiency is seen as a polyneuropathy. This may be corrected with supplementation of pyridoxine and is rarely seen with intakes below 200 mg per day of hydralazine. Conversely, deficiency may be more likely in a patient receiving other vitamin B_6 antagonists or with a poor baseline pyridoxine status. The bioavailability of hydralazine has been shown to be affected by food intake and first-pass metabolism *(23)*. Most recent studies have shown a decreased bioavailability of hydralazine and blunted antihypertensive effect when taken with food *(24)*. The variant effects of hydralazine may be temporized by consistent intake of the drug in relation to meals *(5)*.

Diazoxide is an arterial vasodilator with side effects disturbing glucose tolerance. Hyperglycemia is induced by the inhibition of insulin release by the pancreas. Rare side effects that may affect nutrient intake include alterations in taste and smell and increased salivation.

Nitroprusside relaxes both arterial and venous smooth muscle via its metabolite nitric oxide. Nitroprusside may also be converted into the toxins cyanide and thiocyanate. Excessive production of thiocyanate may induce hypothyroidism by inhibiting iodine uptake by the thyroid gland, and may alter vitamin B_{12} status as well. Although nitroprusside is rarely used for more than 24 to 48 h, iodine supplementation may be considered in those requiring prolonged treatment.

2.6. Centrally Acting Agents

Methyldopa is a prodrug that exerts its antihypertensive effect via an active metabolite. Through brain receptors, methyldopa exerts a sympatholytic effect and lowers vascular resistance. Hepatotoxicity may be seen with its use and nutrient metabolism may be altered by hepatic dysfunction. Hepatotoxicity should be suspected in those with fever and hepatitis-like presentation. A minor side effect that may alter dietary habits is the production of dry mouth.

Clonidine and other α_2-adrenergic agonists such as guanabenz and guanfacine may have minor effect on dietary habits due to similar side effects of dry mouth, xerostomia, and parotid gland swelling although specific DNIs are not well defined.

2.7. Peripheral α-Receptor Antagonists

Phentolamine exerts its antihypertensive effect by blockade of peripheral α-adrenergic receptors causing an overall relaxation of vascular smooth muscle and decrease in peripheral resistance. Stimulation of the GI tract may result in abdominal pain, nausea,

Table 2
Antihyperlipidemic Drug Interactions

Drug	Macronutrient/ Metabolic Effects	Micronutrient Effects	Other
HMG-CoA reductase inhibitors	Increased bioavailability with grapefruit juice		
Fibric acid derivatives			↑transaminases ↑homocysteine Hepatotoxicity
Niacin	Flushing especially with coffee/tea	↓B_6	Hyperglycemia Insulin resistance Hyperuricemia ↑homocysteine
Cholestyramine		↓vitamin A,D, E,K	↑homocysteine

and exacerbation of peptic ulcers. These may lead to an overall decrease in dietary intake or altered feeding.

Prazosin and related selective α_1-adrenergic antagonists are widely used in the treatment of hypertension. Their overall effect on nutritional status and DNIs are not well characterized.

3. ANTIHYPERLIPIDEMICS

The control of hyperlipidemia in the context of cardiovascular disease has proved to be an invaluable mode of therapy. Their mode of action is intimately related to GI function and absorption and requires close scrutiny of dietary intake and supplements *(25)*. A number of DNIs have been described with this group of drugs (Table 2).

3.1. HMG-CoA Inhibitors

The β-hydroxy-β-methylglutaryl (HMG)-CoA reductase inhibitors otherwise known as statins (e.g., simvastatin and pravastatin) are considered the most effective and best-tolerated agents used for treatment of hyperlipidemia. These drugs inhibit an early step in the biosynthesis of cholesterol, thereby reducing plasma levels. The decreased plasma cholesterol levels leads to a decreased rate of atherosclerotic plaque formation. Higher doses of the more potent statins may also reduce triglyceride levels along with cholesterol levels. Some DNIs involving the statins are well documented. The presystemic metabolism of simvastatin, lovastatin, and atorvastatin is altered when taken with grapefruit juice *(20)*. Ingestion of grapefruit juice inhibits the cytochrome P450 (CYP)3A4 enzyme in the GI mucosa and liver and enhances the oral absorption of these three statins. Pravastatin however is not appreciably metabolized by the CYP enzymes and does not appear to be similarly affected.

3.2. Bile Acid Sequestrants

Cholestyramine and colestipol are highly positively charged resins and are used as hypolipidemic agents through their binding of negatively charged bile acids. They are not absorbed in the gut because of their large size and are eliminated in the stool. Their principal DNI involves presystemic binding of the fat soluble vitamins A, D, E, and K. By elimination of the bile acids required for absorption of fats, they may induce a deficiency of the fat-soluble vitamins that may require supplementation or altering therapy. A newer agent, colesevelam, appears to not interfere with the absorption of these vitamins and may be a better alternative. Long-term use of cholestyramine may also lead to folic acid depletion. An important effect of these lipid-lowering agents is their effect on plasma levels of homocysteine. This thiol-containing amino acid is an established risk factor for vascular disease and hypercoagulable conditions *(26)*. Bile acid sequestrants have proven to elevate levels of homocysteine, which may undermine the cardiovascular benefits provided by these drugs. The effect is also seen in niacin but not in HMG-CoA reductase inhibitors *(26–28)*. The clinical significance of this relationship requires further serious study, but may describe an advantage of the HMG-CoA reductase inhibitors over the other lipid-lowering agents.

3.3. Niacin

Niacin or nicotinic acid is a water-soluble vitamin (B_3) that acts on multiple levels of lipoprotein metabolism. Niacin reduces transport of FFAs to the liver and decreases liver triglyceride synthesis. It also has a beneficial effect on the HDL/LDL ratio of dyslipidemic patients. Adverse effects include flushing and dyspepsia. The flushing is exacerbated by ingestion of coffee or tea and these should be avoided. The dyspepsia may interfere with normal dietary intake of meals and is less likely to occur if niacin is taken on a full stomach. The most serious side effect is hepatotoxicity, which may also cause a hyperglycemia. The toxic effect is most often seen in over-the-counter preparations of 2 g or more of sustained release niacin. Diabetics are cautioned against niacin because of its induction of insulin resistance. Severe hyperglycemia may result and may necessitate a switch to insulin therapy for those on oral hypoglycemics. Niacin also has a hyperuricemic effect and may reactivate gout.

3.4. Fibric Acid Derivatives

Gemfibrozil is a fibric acid derivative that is commonly used to treat hypertriglyceridemia and type III hyperlipoproteinemia. Adverse effects include elevation of transaminases and alterations in renal function. DNIs may involve altered clearance of nutrients but these interactions are not well defined.

4. DRUGS USED IN THE TREATMENT OF HEART FAILURE

The treatment of heart failure requires multiple modalities of pharmacologic intervention the primary mainstays of treatment include ACE inhibitors and β-adrenergic receptor antagonists. Other classes of drugs commonly used in the treatment of heart failure include cardiac glycosides, diuretics, and calcium channel blockers, which are discussed in other sections of this chapter.

4.1. Cardiac Glycosides

The cardiac glycosides digoxin and digitoxin work by inhibition of the Na–K–ATPase. The inhibition of the enzyme resident in the cell membrane of cardiac cells exerts an inotropic and antiarrhythmic action. They are also recognized to have a modulatory effect on the sympathetic nervous system. Currently, digoxin is the only widely used member of the cardiac glycosides. Digoxin is noted to cause significant anorexia and nausea. Digoxin levels have been shown to be affected by intake of various foods and herbs. St. Johns wort, a popular herbal remedy, may affect hepatic or GI transport proteins resulting in decreased levels of digoxin *(30)*. Digoxin levels are also affected in those with high fiber or bran-containing diets. Concurrent ingestion may decrease absorption of digoxin and decrease pharmacologic effect.

4.2. Inotropic/Pressor Agents

Dopamine and the related dobutamine have inotropic effects mediated through multiple receptors present in renal, mesenteric, coronary, and myocardial tissues. The GI effects are attributable to the sympathomimetic properties of the drugs. Nausea, vomiting, and GI distress are common side effects.

Epinephrine, by virtue of its role as a primary messenger of the sympathetic system, often induces effects on the GI system. Nausea, vomiting, and epigastric pain are commonly seen in its use. Epinephrine also has significant metabolic effects. Lactate, glucose, and glucagon levels are significantly elevated, whereas insulin release is inhibited by epinephrine. FFA concentrations are elevated in the plasma by stimulation of β receptors on adipocytes. Epinephrine has an overall calorigenic action and may increase oxygen consumption 20 to 30% at usual doses. Norepinephrine appears to have less effect on these metabolic mechanisms. These effects may be seen in relatively larger doses as compared to epinephrine.

5. DRUGS USED IN ISCHEMIC HEART DISEASE

The treatment of ischemic heart disease centers on promoting oxygen delivery to the deprived myocardium and improvement of the primary symptoms of angina pectoris.

5.1. Nitrates

Organic nitrates serve to promote coronary blood flow and redistribution by dilation of coronary vessels. Nitroglycerin, isosorbide-5-mononitrate, and isosorbide dinitrate comprise the organic nitrates. All smooth muscle is affected by the nitrates, including the esophagus and the GI tract. Nitrates all share the common side effects of abdominal pain, nausea, and vomiting.

5.2. Antithrombotics/Antiplatelets

DNIs have been described for a number of antiplatelet and antithrombotic drugs (Table 3). Aspirin and the salicylates have been proven to decrease mortality in patients suffering myocardial ischemia. Use of aspirin as an antiplatelet agent provides a significant tool in the acute and chronic management of these patients. The interactions of aspirin with the GI, hepatic, and renal systems are well documented and may have significant impact on the nutritional status of those patients prescribed its use. GI effects include epigastric distress, nausea, and vomiting. The inhibition of prostaglandins in

Table 3
Antithrombotic/Antiplatelet Drug Interactions

Drug	Gastrointestinal Effects	Macronutrient/ Metabolic Effects	Important DNIs and Effect
Aspirin/ Salicylates	GI bleed, dyspepsia	Metabolic acidosis, salt retention, hyperglycemia, glycosuria, uricosuria, ↓plasma FFA	Vitamin C is gastroprotective
Warfarin		Inhibit cytochrome P450	Danshen, Devil's claw, Dong quai, Papain, Vitamin E increased warfarin efficacy
			Coenzyme Q (Ubiquinone), Ginseng, Green tea, Vitamin K decreased warfarin efficacy
Heparin	Hepatotoxicity		
Clopidogrel	Nausea, vomiting		

gastric mucosa also leads to decrease in the protective lining of the stomach. Aspirin-induced gastric bleeding, when acute, may lead to critical blood loss, and if chronic, may lead to an iron deficiency anemia. Recent studies have shown a gastroprotective effect from vitamin C that may be a beneficial complementary therapy for those on prolonged aspirin therapy *(31)*.

Hepatic injury may be caused by salicylates usually after prolonged use. Symptoms may include right upper quadrant pain and elevations in liver enzymes, and the metabolism of hepatically cleared nutrients may be affected. Salicylates have also been implicated in Reye's syndrome. Renal effects may induce retention of salt and water, and decreased function. Salicylate ingestion with other analgesic mixtures has been shown to produce papillary necrosis and interstitial nephritis. Dietary intake of salts and fluids may need to be adjusted in those on aspirin therapy especially in the context of renal insufficiency.

Salicylates also have been implicated in metabolic alterations that could have significant effect on overall nutritional status. Salicylates may produce an initial respiratory alkalosis then shift to a metabolic acidosis with multiple effects. Large doses may affect carbohydrate metabolism and induce hyperglycemia and glycosuria as well as deplete liver and muscle glycogen. Nitrogen metabolism is also affected by the use of salicylates. A negative nitrogen balance produced by toxic doses and catabolic states may be the result. Salicylates also reduce lipogenesis by disturbing the incorporation of acetate into fatty acids. Other effects include inhibition of lipolysis in adipose tissue. The overall effect is the increased uptake and utilization of FFA in muscle and liver, and a lowering of the plasma FFA levels.

Table 4
Substances With Reported Effect on Warfarin Therapy

Possible increase in warfarin efficacy	Danshen, Devil's claw, Dong quai, Papain, vitamin E
Possible decrease in warfarin efficacy	Coenzyme Q (Ubiquinone), ginseng, green tea, vitamin K

Heparin is a naturally occurring glycosaminoglycan found in mast cells and is one of the most widely used antithrombotic agents in medicine. Heparin is only used parenterally and has no associated GI symptoms. However, heparin may induce a chemical hepatitis with elevation of liver enzymes and altered metabolism of hepatic substrates. A miscellaneous effect of heparin is the clearing of lipemic plasma. Heparin releases lipoprotein lipase into the plasma, which effects a breakdown of triglycerides into more absorbable glycerol and FFA. Effectively decreasing plasma levels of lipids and a rebound hyperlipidemia may occur upon discontinuation of heparin.

Warfarin is an orally available anticoagulant widely used in the inpatient and ambulatory setting. Warfarin inhibits the action of vitamin K-dependent coagulation factors. The ingestion or deficiency of vitamin K-rich foods alters the effectiveness of warfarin as a therapy. Those patients with a decreased oral intake and altered intestinal flora (a minor source of systemic vitamin K) may be prone to bleeding complications. Vitamin E has also been implicated in the potentiation of warfarin anticoagulation by inhibiting a required step in the oxidation of vitamin K. Warfarin has also been well studied for its interactions with other dietary supplements and alternative medicines *(32)*. Warfarin is hepatically metabolized through the CYP enzyme system. Alterations of metabolism may occur in foods metabolized by this particular enzyme. These studies primarily grew out of observed and unexpected elevations or decrements of International Normalized Ratio (INR), an important coagulation parameter, in patients on warfarin. An elevated INR indicates decreased clotting ability. Many commonly ingested foods, vitamins, as well as alternative medicines, have been implicated in the modulation of warfarin's anticoagulant efficacy (Table 4).

Ticlopidine and clopidogrel are antiplatelet agents often used in the therapy of unstable angina and coronary artery disease. The most common side effects are nausea, vomiting, and diarrhea.

Glycoprotein IIb/IIIa inhibitors are a newer class of antiplatelet drugs used in ischemic cardiac disease. GI and nutritional effects are not commonly reported, although not well evaluated.

6. ANTIARRHYTHMICS

Antiarrhythmics are commonly classified into four groups according to predominant mechanism of action. Class I are Na-channel blockers; Class II are β-blockers; Class III prolong action potential (usually by K channel blockade); Class IV are calcium channel blockers. Other drugs are also used for arrhythmias and do not fit into these four classes. Individual drugs may mediate more than one effect, but are usually classed by the predominant antiarrhythmic action. Many of the antiarrhythmics have adverse effects related to anorexia, nausea, diarrhea, or constipation. The presence of any of these may have

Table 5
Antiarrhythmic Drug Interactions

Antiarrhythmic	Gastrointestinal (GI) Tract Effects	Drug–Nutrient Interaction
Adenosine		Xanthines may decrease efficacy
Amiodarone	Nausea, inhibits cytochrome P450	Grapefruit juice may increase bioavailability
Quinidine	Diarrhea (resultant hypokalemia)	Taking with meals may decrease adverse effects
Bretylium	Nausea, GI distress	
Disopyramide	Anticholinergic effects—dry mouth, constipation, GI distress	
Mexilitine	Drug-induced hepatitis	
Procainamide	Nausea, anorexia, bitter taste, diarrhea	
Propafenone	Inhibits cytochrome P450	
Sotalol	Nausea, diarrhea, constipation	

detrimental effects on the nutritional status of patients undergoing therapy and should be monitored by the patient and physician.

Adenosine is a nucleoside used for the acute termination of supraventricular tachycardia and does not fit into one of the four classifications. The drug has a half-life of seconds and most adverse effects are short lived. The principal DNI of adenosine involves caffeine-containing products. Methylxanthines such as theophylline and caffeine bind to adenosine receptors and those ingesting caffeine-containing drinks may require increased doses of adenosine to achieve desired effect.

Amiodarone, a class III drug, is eliminated very slowly and its effects tend to be longer lasting. Nausea occasionally occurs in therapy and the effect may be avoided by decreasing the daily dose during the loading phase. Amiodarone affects the hepatic metabolism at CYP3A4 and may impair the metabolism of nutrients processed by this enzyme. Like some of the statins and calcium channel blockers, caution should be used when taking amiodarone with grapefruit juice (20). Although not common, hypothyroidism associated with this drug may lead to weight gain.

Quinidine is one of the oldest known antiarrhythmics and is commonly described as a class I drug, although it may have properties similar to the other classes of antiarrhythmics. The most common side effect of therapy is diarrhea. Up to 50% of patients may experience diarrhea usually during the first few days of therapy. Diarrhea-induced hypokalemia may even potentiate torsade de pointes. Hepatitis is a rare side effect that may be seen in quinidine use as well. Taking quinidine with meals has been shown to slow the absorption rate but not the bioavailability of quinidine. Taking quinidine with meals appears to inhibit the adverse effects and should be recommended.

7. ALTERNATIVE MEDICINE

An increasing group of alternative therapies, predominantly the dietary supplements, have emerged as a modality in the fight against cardiac disease. Vitamin therapy has long been proposed by many as having beneficial health effects and cardioprotective proper-

ties. Strong evidence is being gathered for other supplements as alternatives or complements to traditional pharmacologic treatments of heart disease. Fish oils, garlic, and coenzyme Q are just some of the therapies being investigated for their possible therapeutic role in cardiovascular disease *(33,34)*. The effects of these drugs may be seen in multiple aspects of cardiac disease as seen in the interactions with warfarin and the statins. A concerted effort must be made by practicing physicians to educate themselves and their patients on the implications of their use and possible interactions.

8. CONCLUSION AND FUTURE DIRECTIONS

More resources are now available to both patient and physician than ever before. Pertinent information has become more readily accessible through the internet through multiple organizations both public (e.g., the National Institutes of Health web site) and private. Medical institutions and societies are more able to disseminate important data and findings through internet sites to professionals and the public. Both patient and caregiver are able to tap these resources to gain and maintain a better understanding of impact of current treatment and possible alternatives. The successful management of cardiovascular disease requires a coordinated effort between physician and patient. Optimal care and treatment will be achieved when all clinicians and caregivers remain vigilant to all possible impacts of prescribed treatment. A holistic approach should be taken when prescribing any of the available pharmacotherapies. Nutritional status should be optimized by anticipating added needs such as vitamin or mineral replacement and avoiding possible adverse DNIs. The patient as well should remain conscious of all the effects that may be attributable to their prescribed regimens. The patient should be educated and encouraged to take an active role in the maintenance and monitoring of the progress of his or her treatment. Communication between physician and patient is vital for success in the treatment of cardiac disease.

A focused effort to evaluate the nutritional implications of common medications used in caring for patients with cardiac disease is needed. This should involve not only drug–food interactions and bioavailability, but also influences on food intake, macronutrient metabolism, and micronutrient storage and excretion.

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15 Drug–Nutrient Interactions Involving Folate

Leslie Schechter and Patricia Worthington

1. INTRODUCTION

The importance of maintaining optimal folate status throughout all phases of the life cycle has grown increasingly apparent in recent years. Studies have produced convincing evidence linking folate deficiency to health risks that extend well beyond the classic association with macrocytic anemia. The strongest evidence exists for the relationship between folate deficiency and neural tube birth defects *(1)*. Research also indicates that inadequate folate levels may increase risks for other types of birth defects, early miscarriage, atherosclerotic cardiovascular disease, some types of cancer, and neurological and neuropsychiatric disorders *(2,3)*. Among the many factors that influence folate status, drug–nutrient interactions (DNIs) stand out as a significant, and largely avoidable, cause of folate deficiency *(4)*.

2. BASIC REVIEW OF FOLATE

2.1. Description

Folate and folic acid are synonyms for the water-soluble B-complex vitamin, B_9. Folate consists of a group of structurally similar compounds known as pteroylglutamates that occur naturally in food, whereas folic acid refers to a stable, synthetic form of folate (pteroylglutamic acid) that is used in dietary supplements and fortified foods *(5)*. Folate coenzymes participate in a variety of key metabolic pathways that involve the transfer of one-carbon units, giving this nutrient an essential role in amino acid metabolism and DNA synthesis. Folate also acts in conjunction with vitamin B_{12} as an essential cofactor in the remethylation cycle that converts homocysteine to methionine *(2,6)*. For this reason, a deficiency of either folate or vitamin B_{12} can lead to hyperhomocysteinemia, which has been identified as an independent risk factor for cardiovascular disease *(7,8)*.

Folate is naturally present in a wide range of foods including fresh green leafy vegetables (e.g., spinach and turnip greens), yeast, dry beans and peas, and citrus fruits. However, modern methods of cooking, processing, and distributing food can substantially reduce the amount of the dietary folate available. Population surveys have histori-

cally revealed a high incidence of suboptimal folate levels among otherwise well-nourished individuals, making folate deficiency the most common vitamin deficiency found in developed nations *(2,9)*. To address the problem of widespread folate deficiency, the Food and Drug Administration has mandated that food manufacturers fortify breakfast cereals and other grain products such as bread, pasta, and rice, with folic acid, an action that has led to substantial improvements in the folate status of the US population *(10,11)*.

2.2. Risk Factors for Folate Deficiency

Although low consumption of dietary folate ranks as the leading cause of folate deficiency, inadequate levels can develop through a variety of mechanisms. Conditions that impair absorption or utilization, elevate nutrient requirements, or increase excretion of folate can also lead to a deficiency state. The risk for folate deficiency is especially high during periods of rapid growth or hypermetabolic activity *(5)*. Suboptimal folate status is often found in pregnant women, chronic alcoholics, the elderly, and individuals with sickle cell disease. Table 1 provides additional information concerning risk factors for folate deficiency *(2,5)*.

2.3. Identifying Folate Deficiency

Laboratory tests used to assess folate status include serum folate levels, erythrocyte folate concentrations, and serum homocysteine concentrations. Serum folate levels fluctuate with changes in dietary folate intake, serving primarily as an indication of current folate balance. Because low serum folate levels do not discriminate between a transient deficit in folate intake and a chronic state of tissue depletion, this laboratory test alone is a not a reliable indicator of folate status. Erythrocyte folate concentrations, on the other hand, do reflect tissue supplies of the vitamin. However, this value does not detect recent changes in folate status and may miss a developing deficiency *(5)*. Finally, plasma homocysteine levels, which increase as folate stores become depleted, can serve as an early, indirect measure of folate status *(2,9)*. Elevated homocysteine levels that occur in conjunction with low erythrocyte folate levels strongly suggest the presence of a subclinical folate deficiency. However, vitamin B_{12} deficiency must also be excluded as an additional cause of elevated homocysteine levels *(12)*.

Folate deficiency develops slowly, over a period of several months to years *(12)*. Four stages of folate deficiency have been described, in which metabolic abnormalities occur before clinical signs of deficiency appear. The initial stage of folate deficiency involves negative folate balance characterized by low serum folate levels, while erythrocyte folate concentrations remain within the normal range. In stage 2, erythrocyte folate concentrations fall below 160 ng/mL, indicating a condition of folate depletion. Stage 3 is marked by a further drop in erythrocyte folate (below 120 ng/mL), elevated homocysteine levels, and evidence of metabolic dysfunction. In the final stage, clinical folate deficiency becomes apparent *(5)*.

The clinical picture of folate deficiency bears many similarities to vitamin B_{12} deficiency, although folate deficiency does not cause the neurological damage associated with vitamin B_{12} deficiency. Patients with folate deficiency typically present with nonspecific, often subtle complaints such as diarrhea, anorexia, and weight loss. Additional symptoms include cheilosis, glossitis, forgetfulness, irritability, and behavioral disorders *(3,5)*. Megaloblastic anemia with elevated mean corpuscular volume (MCV) is charac-

Table 1
Risk Factors for Folate Deficiency

Poor Eating Habits: Low intake of folate-rich foods, preference for cooked or processed foods over raw vegetables and fresh fruit.

Elevated Requirements: Periods of rapid growth including pregnancy, and infancy; lactation, sickle cell disease; tumor growth, hypermetabolic states.

Malabsorption: Celiac disease, inflammatory bowel disease, short bowel syndrome, drug effects.

Impaired Utilization: Chronic alcoholism, smoking, liver disease, drug effects, age-related changes, B_{12} deficiency, congenital enzyme deficiency

Increased Excretion: Renal dialysis, biliary diversion, B_{12} deficiency

From refs. *2,5.*

teristic of the fourth, most advanced phase of folate deficiency. Because some metabolic activities require both cobalamin and folate, a B_{12} deficiency can lead to a functional folate deficiency.

2.4. Folate Requirements

The Recommended Dietary Allowances for folate appear in Table 2 *(9)*. These values are expressed as Dietary Folate Equivalents (DFE) to account for differences in bioavailability between naturally occurring dietary folate, and synthetic folic acid *(9)*. Overall, the bioavailability of folic acid is substantially greater than for natural folate, although data on bioavailability is quite limited. Naturally occurring dietary folate has a bioavailability of approx 50%. Synthetic folic acid is nearly 100% bioavailable when taken on an empty stomach, but adding folic acid to food reduces the bioavalability by approx 15%. Despite these differences in bioavailability, both the natural and synthetic forms of folate perform identically after entering the bloodstream *(3)*.

According to the calculation for DFEs, one DFE is equal to 1 μg of naturally occurring dietary folate. If folic acid is taken on an empty stomach, 1 μg folic acid is equivalent to 2 μg DFE. However, when folic acid is taken with meals or in fortified food, 1 μg folic acid equals 1.7 μg DFE *(9,13)*. Thus, 200 μg of synthetic folic acid taken on an empty stomach would provide 100% of the 400 μg of DFE recommended for adults. Of particular importance are the current guidelines for the prevention of neural tube defects. All fertile women, regardless of age, should receive 400 μg of synthetic folic acid from fortified foods or as a supplement in addition to natural dietary folate. This level of supplementation would provide approx 1000 μg of DFE *(9,13)*.

2.5. Safety of Folic Acid Supplementation

Folic acid toxicity is rare. Studies have demonstrated the safety of folic acid supplementation at daily doses of 15 mg over a period of 5 yr *(14)*. Yet, because high doses of folic acid can mask the hematological signs of vitamin B_{12} deficiency, the upper limit for folic acid consumption has been set at 1 mg/d. This amount of folic acid is considered unlikely to mask vitamin B_{12} deficiency. High doses of folic acid can prevent macrocytic anemia, but will not prevent the potentially irreversible neurological damage associated

Table 2
Recommended Dietary Allowances (RDA) for Folate

Age	RDA (µg/day, Dietary Folate Equivalents)
Infants (months)	
0–6	65
7–12	80
Children (years)	
1–3	150
4–8	200
9–13	300
14–18	400
Adults	
>18	400
Pregnancy	600
Lactation	500

From ref. 9.

with vitamin B_{12} deficiency. This upper limit does not apply to situations in which higher doses of folic acid are used therapeutically under medical supervision (9). Guidelines for patients with conditions that increase folate demands, including those receiving drugs with antifolate properties, typically recommend folic acid supplementation in the range of 1 mg to 5 mg daily. However, the potential exists for patients to exceed the 1 mg/d limit with a combination of fortified food and vitamin supplementation, underscoring the importance of monitoring vitamin B_{12} status (15).

2.6. Folate Metabolism

Both dietary folate and folic acid are ingested in a chemically inactive polyglutamate form. Before absorption, folate polyglutamates must first undergo deconjugation by folate conjugases, found in saliva and in the small intestine, to form monoglutamate folate. Absorption of monoglutamate folate then takes place in the proximal small intestine, primarily in the duodenum and jejunum (2). Monogluamates undergo reduction by the enzyme dihydrofolate reductase to form a biochemically active tetrahydrofolate (THF) form of the vitamin, which then enters the portal circulation. The dominant THF is 5-methylenetetrahydrofolate; however, fully reduced THFs can exist in several active derivatives (5,6). One of these fully reduced folate derivatives, 5-formyl tetrahydrofolic acid or folinic acid, is used therapeutically in cases where dihydrofolate reductase activity is blocked by antifolate drugs (5,6).

Much of the folate in the portal circulation is taken up by the liver, the primary storage site for the vitamin. Some free folate is present in plasma, but approx 60% is bound to proteins such as albumin or transferrin. Folate excretion occurs primarily in urine and in bile, although enterohepatic circulation appears to play a role in maintaining serum folate levels (2,5).

3. DRUG–FOLATE INTERACTIONS

A well-known association exists between long-term use of certain drugs and the development of megaloblastic anemia resulting from folate depletion. In some instances, the antifolate properties of the drug represent the intended mechanism of action; in other cases, the interaction is an unwanted side effect of the drug. Until recently, drugs that depleted folate stores were thought to pose a hazard only to individuals in high-risk categories. However, DNIs involving folate have received increased scrutiny with the recognition that even subclinical folate deficiency can have serious and far-reaching health consequences. Specifically, studies that have shown an association between the use of antifolate drugs and elevated homocysteine levels have raised concerns regarding the safety of long-term use of these agents in patients at increased risk for cardiovascular disease *(16,17)*. Other studies indicate that homocysteine levels may play a role in predicting the potential for toxicity with certain antifolate drugs *(18)*. Furthermore, evidence linking folate depletion to a broad range of congenital defects in infants of women who took dihyrdofolate reductase inhibitors during pregnancy requires that the clinical significance of these DNIs be reassessed *(19)*.

Folate antagonists can disrupt folate activity through a variety of mechanisms. For example, drugs can impair intestinal absorption, block the release of folate from cells, enhance liver metabolism of the vitamin, or alter protein binding of folate in the circulation *(20)*. A number of folate antagonists act by inhibiting the enzyme dihydrofolate reductase, thus blocking the conversion of dietary folate to the active THF derivative. Dihydrofolate reductase inhibition depletes the pool of THFs, which in turn, limits the availability of substrates for other folate-dependent enzymes. A better understanding of the numerous metabolic processes that depend on folate has led to the development of a new class of antineoplastic agents that target specific folate-dependent enzymes such as thymidylate synthetase and glycinamide ribonucleotide transformylase, both of which play a critical role in cell proliferation *(21)*. Administering folic acid or the reduced derivative, folinic acid, during treatment with antifolate drugs has the potential to alter both the therapeutic or toxic effects associated with the drug *(21)*.

4. LIMITATIONS OF THE DATA AND FURTHER RESEARCH NEEDS

Overall, information concerning DNIs that impact folate status is incomplete. An important limitation to the available data concerning drug–folate interactions is that much of the early research relied on the development of megaloblastic anemia as the clinical endpoint for defining a DNI. Additionally, relatively few studies have explored the clinical impact of antifolate drugs on homocysteine levels. This issue requires longitudinal trials that track the influence of antifolate drugs on homocysteine levels and long-term health risks, including the incidence of birth defects.

Theoretically, the improved folate status of the US population may lower the risk for drug-related folate deficiency by reducing the number of individuals who begin anitfolate drug therapy with marginal folate stores. However, data supporting this premise are not yet available. Many questions remain unanswered concerning the need for folic acid supplementation in patients receiving folate antagonists. Further studies that compare folic acid to folinic acid supplementation will help clarify the indications for both agents. Of great concern is the potential for folic acid supplementation to alter the therapeutic

activity of drugs. However, few guidelines are available regarding the optimal dosing regimen for folic acid supplementation or the need to adjust the dose of antifolate drugs. This issue requires further investigation that correlates vitamin status and drug levels with therapeutic efficacy and drug side effects. Additionally, studies must address the extent and frequency of monitoring that is appropriate for patients receiving antifolate drugs. In the years to come, research is likely to produce drug-specific recommendations for the management of potential DNIs involving folate. Ultimately, the objective for all research related to drugs that impact folate status is to delineate evidence-based clinical practice guidelines for maintaining optimal folate status without compromising therapeutic goals.

5. RECOMMENDATIONS

Despite the lack of evidence-based recommendations, basic measures designed to improve clinical outcomes related to the use of antifolate drugs are appropriate. For example, all fertile women should receive folic acid supplementation as recommended by the Institute of Medicine *(9)* and the Centers for Disease Control *(1)*. Additionally, documentation of vitamin B_{12} status should be routine for all patients who are initiating folic acid supplementation. A comprehensive approach for addressing DNIs that involve folate should include strategies for monitoring patients at risk for folate–drug interactions, patient education, and appropriate intervention.

Monitoring for patients receiving drugs with antifolate properties aims to ensure that therapeutic goals are met without compromising folate status. Current information makes clear that monitoring must not depend on the development of macrocytic anemia as the sole criteria for identifying a deficiency state. To accurately evaluate folate status, monitoring must include homocysteine levels and erythrocyte folate concentrations. Although homocysteine levels provide an early indication of declining folate stores, individual variation occurs in response to folate depletion and supplementation, suggesting that repeat testing may be necessary to ensure the validity of the marker *(22)*. Preliminary studies involving the newer antineoplastic antifolate agents suggest that homocysteine levels (performed in conjunction with markers for vitamin B_{12} deficiency) are strongly correlated with the development of drug-induced toxicity *(21)*. At a minimum, baseline folate status should be evaluated when drug therapy is initiated, whenever the drug dose is changed, and at regular intervals in stable patients. No consensus exists regarding the appropriate interval for routine monitoring in stable individuals, however.

Increasingly, guidelines recommend supplementation with folic acid for patients receiving antifolate drug therapy. Considerable variation exists in the dose of folic acid suggested, however. As noted earlier, pharmacologic dosing regimens range from 1 to 5 mg per day, although evidence from studies of some antifolate drugs suggests that lower doses of folic acid may be appropriate *(21)*. The ability to use lower doses of folic acid would reduce the potential to obscure evidence of vitamin B_{12} deficiency. However, further studies are needed to determine the optimal level of folic acid supplementation for patients undergoing treatment with antifolate drugs.

For patients receiving folic acid supplementation in conjunction with antifolate drug therapy, monitoring the therapeutic efficacy of the drug takes on great importance. Depending on the drug in question, monitoring may include regular measurement of

- Your healthcare provider has prescribed_____,
  which is a drug that can lower your body's stores of folic acid.

- Folic acid is a vitamin that prevents a certain type of anemia. Besides this, folic acid
  can also help prevent some birth defects and may lower the risk for heart disease
  and some kinds of cancer.

- Eat a healthy diet that contains lots of fruits and vegetables. Fruit and green, leafy
  vegetables are good natural sources of folic acid. Some foods have folic acid added
  to them. Look for "enriched" grain products such as flour, cereal, bread, pasta, and
  rice.

- Many breakfast cereals are high in folic acid. Check the label on the box, many
  contain 100% of the folic acid you need (100% of the Daily Value or DV). Eating
  one bowl of cereal each day can be a convenient way to get the folic acid you need.

- All women who are capable of becoming pregnant should take 400 µg of folic acid
  in a vitamin supplement or in a separate pill. When taken one month before
  conception and continued throughout the first 12 weeks of pregnancy, folic acid
  reduces the risk of certain birth defects.

- Folic acid can lower the effect of some medications. If you do not already routinely
  take a vitamin supplement, be sure to talk to your health care provider before you
  begin taking a vitamin that contains folic acid to see if your medication dose should
  be adjusted.

- Tell your healthcare provider about all medications and nutritional supplements you
  take, including over-the counter products and herbal supplements.

Fig. 1. Sample of patient handout explaining drug–nutrient interactions.

drug levels, assessing for clinical evidence of efficacy, or observing for toxic side effects. For example, studies indicating that folic acid supplementation may induce a rapid drop in serum phenytoin levels demands that phenytoin levels be monitored closely in the early phase of folic acid supplementation until a new steady state is established *(23,24)*. On the other hand, disease activity and evidence of toxicity guide decisions regarding the need to adjust the dose of methotrexate in patients being treated for rheumatoid arthritis or psoriasis *(25,26)*. Table 3 provides more information regarding interactions between folic acid and specific drugs *(27–67)*.

Finally, patient education plays a fundamental role in the management of DNIs that impact folate status. Patients require information regarding the harmful effects of folate deficiency as well as the ability of folate consumption to alter drug activity. Awareness of the potential for an interaction can help patients avoid circumstances that could lead to unfavorable outcomes. A simple handout can be used to provide patients with the facts they need concerning DNIs involving folate (*see* Fig. 1 for an example).

Table 3
Recommendations for Managing Potential Drug–Folate Interactions

Drug	Proposed Mechanism	Recommendations/Precautions
Antiepileptics		Folic acid supplementation is especially important for women with epilepsy who are capable of becoming pregnant. Practice guidelines recommend doses ranging from 400 µg/d *(27,28)* to 4 mg/d *(29,30)*. More recent authors suggest 1mg/d for all patients with controlled epilepsy, including pregnant women *(31–33)*. Further research is needed to confirm the safety and efficacy of this level of folic acid supplementation.
Phenytoin	An interdependent reaction exists between phenytoin and folate. Phenytoin may deplete folate by (a) raising intestinal pH, causing folate malabsorption, (b) inhibiting intestinal conjugases, (c) impairing folate transport or (d) inducing hepatic microsomal enzymes. Folate serves as a cofactor for phenytoin metabolism, potentially lowering phenytoin levels in patients receiving folic acid *(23,24)*.	When possible, initiate phenytoin and folate supplementation (1mg/d) together after documenting normal vitamin B_{12} status *(23,24)*. Further study is needed to determine the efficacy of lower doses (400 µg/d) *(23,34)*. When initiating folic acid supplementation in patients stabilized on phenytoin therapy, monitor phenytoin levels closely for the first 10 to 15 d of folic acid therapy, until a new steady state is achieved. Greatest declines occur in patients with high phenytoin levels at the start of folic acid supplementation. Increases in phenytoin dose may be required *(23,24)*.
Valproic acid	Inhibits glutamate formyl transferase, altering the distribution of folate derivatives. May inhibit the synthesis of homocysteine to methionine *(31,32)*.	Conflicting data exists concerning the effect of valproic acid on folate status. Further research is needed.

(continued)

Table 3 (continued)

Drug	Proposed Mechanism	Recommendations/Precautions
Phenobarbital Primidone Carbamazapine	Induction of hepatic microsomal enzymes, accelerating folate degradation *(31,33,35)*.	Studies have demonstrated lower serum folate concentrations with prolonged use. The clinical significance of the drug–nutrient interaction is not clear.
Antimetabolites		
Methotrexate High-dose antineoplastic therapy	Dihydrofolate reductase inhibitor	Folinic acid is used for rescue therapy following high-dose methotrexate administration. Dosing guidelines for folinic acid are based on serum methotrexate levels. Excessive amounts of folinic acid may impair the antineoplastic effects of methotrexate *(36)*.
Low-dose therapy for rheumatoid arthritis and psoriasis		Methotrexate treatment leads to increased levels of homocysteine that respond favorably to folic acid supplementation *(37–39)*. Both folic acid and folinic acid reduce methotrexate toxicity *(26,40,41)*. Dosing guidelines for folic acid recommend 1 mg/d folic acid or 2.5 mg to 5 mg/wk for folinic acid *(42–44)*. The timing of folinic acid supplementation with respect to methotrexate administration may be important with folinic acid but not with folic acid *(45)*. Folic acid is significantly less expensive than folinic acid *(26,40,43)*.
Fluorouracil (5-FU) Capcitabine	The presence of excessive reduced folates increases trapping of 5-FU anabolites within cells, possibly delaying elimination *(46,47)*.	Coadministration of folinic acid with fluorouracil or capcitabine may improve therapeutic efficacy in certain cancers, but fluorouracil toxicity may be enhanced *(46,47)*. Monitor for signs of fluorouracil toxicity.

(continued)

Table 3 (continued)

Drug	Proposed Mechanism	Recommendations/Precautions
Antimicrobial Agents		
Pyrimethamine	Dihydrofolate reductase inhibitor	Folinic acid (10–20 mg/d) may be used to reduce toxicity during treatment for toxoplasmosis without affecting pyrimethamine efficacy *(48)*. In leukemic patients being treated for toxoplasmosis, folinic acid may worsen leukemia or induce a relapse *(49)*. Folic acid should not be used during pyrimethamine treatment for toxoplasmosis because a pharmacodynamic antagonism results, impairing the antiparasitic effects of pyrimethamine *(36,50)*. Either folic acid or folinic acid can be used in conjunction with pyrimethamine during treatment of malaria *(51)*.
Trimethoprim	Dihydrofolate reductase inhibitor	Studies suggest that trimethoprim use during early pregnancy increases risk of congenital defects. Folic acid supplementation appears to reduce the risk of birth defects associated with trimethoprim *(19)*. Long-term use of trimethoprim may increase homocysteine levels, raising concern regarding the safety of long-term use for patients with high cardiac risk *(16)*. However, the role of folic acid supplementation has not been adequately studied in this patient population. Use of folinic acid in conjunction with trimethoprim-sulfamethoxazole for treatment of pneumocystitis carinii has been linked to an increased risk for therapeutic failure and death *(52)*.

Table 3 (continued)

Drug	Proposed Mechanism	Recommendations/Precautions
Psychotropic drugs		
Lithium Fluoxetine	Suboptimal folate status may impair synthesis of 5-hydroxy-tryptamine and noradrenaline. A deficiency of one or both of these monoamines is thought to play a role in the pathogenesis of depression *(53)*.	Provide a daily supplement of 300-400 μg of folic acid for patients on long term lithium therapy *(54)*. Women receiving 500 μg of folic acid with fluoxetine demonstrated improved antidepressant action *(55)*. Further study is required to determine if folic acid supplementation at higher doses will have a similar effect in men receiving fluoxetine *(55)*.
Diuretics		
Loop diuretics Thiazide diuretics	Long-term diuretic use increases elimination of folate and has been linked to elevated homocysteine levels *(56)*; triamterene inhibits dihydrofolate reductase *(57)*.	Supplementation with folic acid may be beneficial, particularly in patients with other risk factors for folate deficiency. Further research is needed to determine clinical significance.
Miscellaneous		
Pancreatin	Pancreatic extract impairs folate absorption by forming an insoluble complex with folic acid *(58)*.	Folate status should be monitored for patients receiving treatment for pancreatic insufficiency. Folic acid supplementation may be indicated.
Sulfasalazine	Competitively inhibits jejunal folate conjugase enzyme; also raises require-ments through chronic hemolysis *(59,60)*.	Administer folic acid supplements; monitor for hematologic and hepatic toxicity *(61)*. Pregnant women are advised to take 2 mg of supplemental folic acid daily *(62)*. In some cases, folinic acid appears more effective in restoring folate stores than folic acid *(63,64)*.
Cholestyramine Colestipol	Binds folic acid, increasing elimination of the vitamin *(65,66)*.	Administer folic acid supplements 1 h before or 4–6 h after cholestyramine/colestipol dose *(67)*.

6. CONCLUSION

DNIs between therapeutic drugs and folate can impact both drug levels and vitamin status. Clinicians have long recognized the potential for DNIs to impact folate status but the full clinical significance of these interactions has only recently begun to emerge. A tremendous need exists for research aimed at developing recommendations for the management of DNIs involving folate. Areas that require further study include measures to promote optimal folate status without compromising therapeutic goals, appropriate dosing regimens for folic acid supplementation, monitoring guidelines, and the long-term health risks associated with drug-induced alterations in folate status including hyperhomocysteinemia.

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16 Effects of Antiepileptics on Nutritional Status

Mary J. Berg

1. INTRODUCTION

This chapter examines the effects of antiepileptic drugs (AEDs) on selected vitamins and minerals, including folic acid, vitamin D, calcium, and vitamin K. Where known, gender analysis is included. It will be noted in relationship to the AEDs if nutritional status is important for one gender. However, the major emphasis is on the impact of AEDs on folate status.

The drug–nutrient interaction (DNI) between folic acid and specific AEDs is an old clinical problem. However, the prevention of this dual and interdependent interaction between this B vitamin and the AEDs is not a standard of practice despite the research that began in the 1960s. Traditional AEDs such as phenytoin, carbamazepine, valproic acid, phenobarbital, and primidone lower endogenous folate *(1–6)* as shown in Fig. 1. To date, there is no information on the newer AEDs, except with the possibility of lamotrigine, which may have antifolate properties *(7)*.

2. FOLIC ACID

2.1. Phenytoin–Folic Acid Interaction

Phenytoin is the major AED with the most available basic and applied literature on this dual and interdependent DNI. As discussed here, this interaction clinically is a "double-edge sword."

2.1.1. PHENYTOIN DECREASES ENDOGENOUS FOLATE

Initially, phenytoin lowers endogenous folate once a patient diagnosed with epilepsy starts this AED. Decrease in this vitamin, as measured by serum folate, has ranged from 27 to 91% in studies *(2)*. This lowering occurs 6–24 mo after initiation of phenytoin treatment. However, this time period was based on clinic visits in those early international studies (primarily in Great Britain) rather than on protocols designed for a designated time period. It should be noted that this large range in the decrease of serum folate was prior to the 1998 US fortification of grains with folic acid (140 µg per 100 g) *(8)*. There is only mandated fortification of folic acid in Hungary and none in the rest of Europe or Great Britain.

Folic Acid

Dihydrofolate

Tetrahydrofolate

VPA inhibits GFT

5-formaltetrahydrofolate

5,10-methylenetetrahydrofolate

Cysteine

PHT inhibits MTHFR   MTHFR   B6

Homocysteine

5-methyltetrahydrofolate   B12
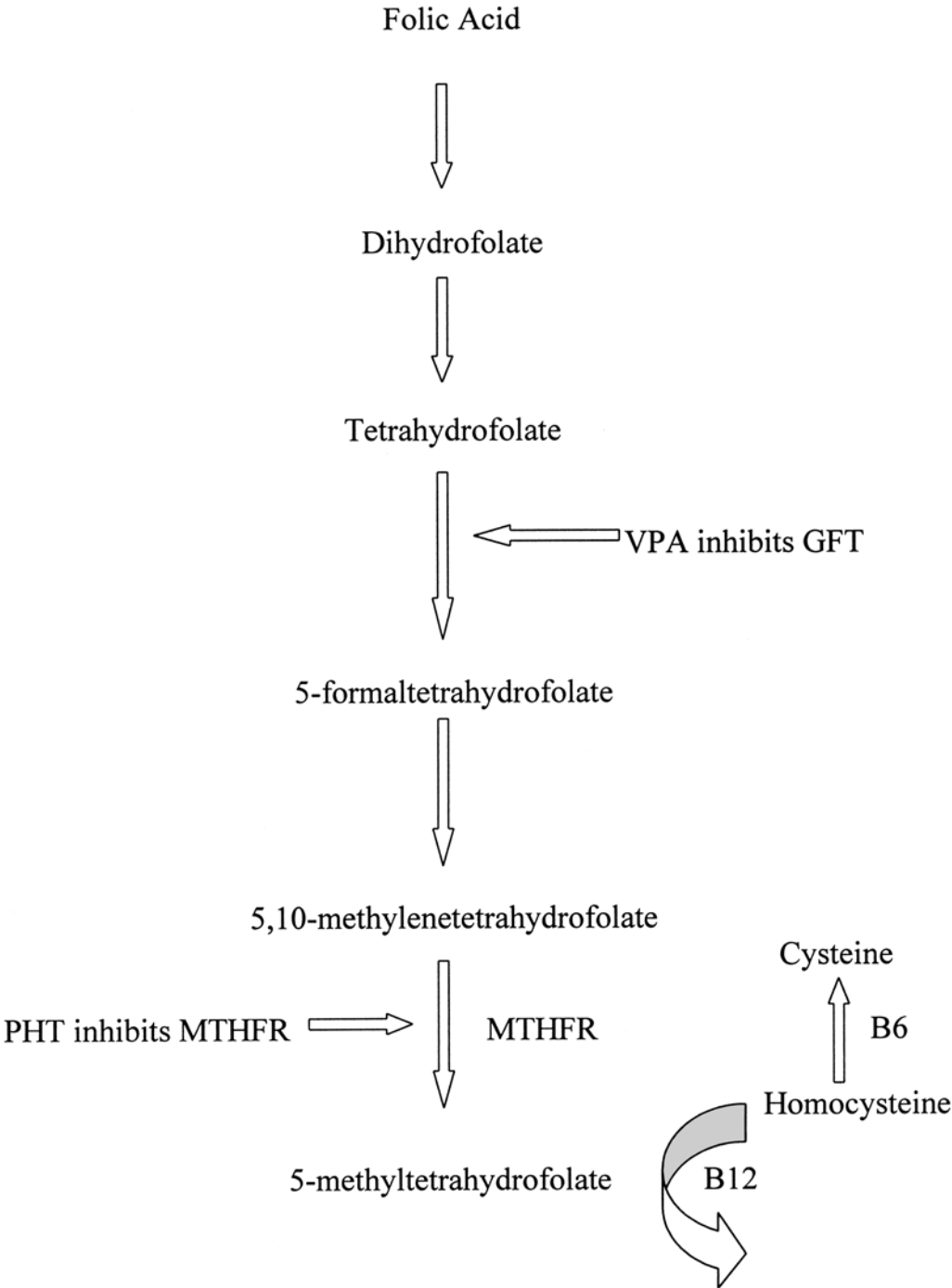
Fig. 1. Metabolic scheme of folic acid and its interrelationship to the antiepileptic drugs vitamins B_6 and B_{12} and homocysteine.

Several studies have been done in healthy volunteers to mimic naïve patients starting phenytoin. One demonstrated that male volunteers age 18–35 yr with an average ($\pm$ standard deviation) total serum phenytoin concentration of 8.4 $\pm$ 2.7 µg/mL decreased serum folate by an average of 42.15 $\pm$ 21.44% in a mean of 24.1 $\pm$ 5.6 d *(9)*. This study further examined therapeutic and subtherapeutic total serum phenytoin concentrations and their effects on serum folate. This study confirmed previous investigations that stated the higher the total serum phenytoin concentration the greater the decrease in serum folate *(10–12)*. A second study in healthy female volunteers age 18–40 yr confirmed that the serum folate decreased by a similar average of 40.7 $\pm$ 14.2% with a mean total serum phenytoin concentration of 10.9 $\pm$ 4.9 µg/mL *(13)*. This was the only human study, where healthy volunteers or patients with epilepsy had their dietary folate recorded using daily food records throughout the study period. Folate intake for that age group of female volunteers was less than recommended. There appeared to be no gender differences in the decrease in serum folate when phenytoin was initiated in these two healthy volunteer studies. The previous clinical studies had aggregate data when both male and female patients with epilepsy were included. Therefore, no gender analysis of the effect of phenytoin on serum folate was possible.

Progression to megaloblastic anemia occurs in less than 1% of those patients with epilepsy taking phenytoin *(14)*. Despite such a low percentage, an early study in this area showed that 38% of 45 nonanemic patients demonstrated early evidence of megaloblastic changes *(15)*. Clinically, the serum folate is not routinely monitored in patients taking phenytoin or any of the other AEDs. Instead, the mean corpuscular volume (MCV) is measured when the annual complete blood count is drawn along with the liver function tests. When the MCV exceeds 93 fL, serum folate, red blood cell (RBC) folate, and serum B_{12} are measured. Both the serum folate and RBC folate are decreased, whereas serum B_{12} is usually in the normal range. Phenytoin also lowers RBC folate as well as cerebrospinal fluid (CSF) folate in the same direction as the serum folate *(16)*. It should also be noted that even with subnormal serum folate, there may not be evidence of megaloblastic changes in the marrow *(17)*.

2.1.2. Folic Acid Supplementation Changes the Phenytoin Concentration

The second part of this dual and interdependent DNI occurs when the patient taking phenytoin is started on folic acid to correct the folate deficiency. The amount of this vitamin in the studies and case reports varied, from 1 to 30 mg/d, not the 400 µg that is routinely found in nonprescription multivitamin products *(4,19–28)*. When folic acid supplementation was added to phenytoin therapy, the phenytoin concentrations decreased from 4 to 50%. Several patients either became preictal or experienced seizures because they did not have the necessary threshold for the phenytoin concentration to control their epilepsy. The addition of the vitamin supplement increased the serum folate whether in folate-deficient patients taking phenytoin or in healthy volunteers. The dose of 1 mg/d increased the serum folate back to the baseline in healthy volunteers whereas a higher dose of 5 mg increased the serum folate to a higher value, but by less than a factor of 5, suggesting a nonlinearity process in some aspect of the pharmacokinetics of folic acid supplementation *(9)*.

The case reports allowed for more in-depth study of the folate-deficient patient with epilepsy. They showed that when folic acid intake was increased through supplementa-

tion, serum folate increased and total serum phenytoin concentrations decreased. There was a situation where the serum folate returned to the normal range, but the total serum phenytoin concentration had to be increased in order to have better seizure control. This was accomplished by decreasing the dose of supplemental folic acid. Therefore, this situation showed that the converse was true *(28)*. This opposite situation of decreasing folic acid is an example that is not used routinely in clinical practice, but dramatically demonstrates this interrelationship.

Therefore, the previous sections demonstrate the double-edge sword nature of this dual and interdependent DNI, which has been studied primarily with the AED, phenytoin.

2.2. Mechanisms for Phenytoin Decreasing Folic Acid

Four mechanisms of action have been hypothesized for the decrease in folate status by phenytoin. They include (a) malabsorption of dietary folate owing to an increased intraluminal pH that is caused by phenytoin; (b) inhibition of intestinal conjugases that split (hydrolyze) the dietary polyglutamate form to the absorbable monoglutamate form; (c) impaired folate transport into tissues by phenytoin; and (d) depletion of folate in the metabolism of phenytoin with the assumption that folate is a cofactor in the metabolism of phenytoin *(29)*.

Folic acid is only 60% bound to plasma proteins and therefore, it is believed that there is no displacement of folic acid by phenytoin to cause a lowered folate *(30,31)*.

2.2.1. "pH Theory"

The first hypothesis is called the "pH theory" *(32)*. The pH theory is based upon the idea that only the nonionized form of folic acid is absorbed. The primary site for the absorption of folic acid is the proximal small intestine *(33,34)*. The maximum absorption of folic acid occurs at pH 6.3. With the administration of phenytoin, the pH of the proximal intestine increases, thereby causing more folate to exist in the nonabsorbable ionized form. With an increase of pH 0.1, there was a 12% decrease in folate absorption *(35)*. There were several studies that indicated no change in the intraluminal pH when phenytoin was taken by both healthy volunteers and patients with epilepsy *(36,37)*. However, there was a significant decrease in absorption of folic acid that could not be explained by the pH theory *(21)*. Therefore, there is controversy with this hypothesis.

2.2.2. Interference With Intestinal Conjugases

The second hypothesis is that phenytoin interferes with the intestinal conjugases that split the dietary form of folic acid, which is the polyglutamate form, to the absorbable monoglutamate. Several studies have shown that phenytoin, even in a subtherapeutic dose of 100 mg, decreased the absorption of conjugated folate, whereas there was no decrease in folic acid absorption when phenytoin was administered with the unconjugated crystalline form that is found in multivitamin preparations *(38)*. This was confirmed by another investigation *(39)*. However, several studies did not verify this theory *(40–42)*.

2.2.3. Inhibition of Folate Uptake in Tissue

The third hypotheis is that of phenytoin inhibiting tissue uptake of folate. This is extremely controversial. Animal and in vitro experiments have shown that phenytoin had no affect or an extremely weak affect on the uptake of 5-methyltetrahydrofolate into the CSF or RBC *(43,44)*. However, several healthy volunteer studies showed the opposite *(45,46)*.

2.2.4. Folate As a "Cofactor" in Phenytoin Metabolism

The fourth hypothesis, that folic acid is used in the metabolism of phenytoin, has the least controversy. In the late 1960s and early 1970s, the measurement for increased hepatic activity was the measurement of D-glucaric acid in the urine *(47)*. There was a noted increase in glucaric acid excretion when phenytoin was taken and a decrease in serum and RBC folate. It was concluded that folic acid was a cofactor in phenytoin metabolism *(48)* as shown in Fig. 2. Following is a separate section delineating the effect of folic acid on the pharmacokinetics of phenytoin.

2.3. Folate Depletion: Interdependence
Between Phenytoin Pharmacokinetics and Endogenous Folate

The development of folate deficiency by phenytoin was determined primarily by the measurement of serum folate. RBC folates were measured in a few studies, but the majority of the clinical literature reported only serum. Historically, it should be remembered that this work was started in the mid- to late-1960s, with most studies being done through the mid-1990s and the standard of practice was to measure primarily serum. RBC folate began to be examined, not in relationship to phenytoin or the other AEDs, but to the risk of neural tube defects (NTDs) in the mid-1990s. RBC folate is considered a better biological marker and not affected by immediate intakes of food *(49)*.

The following studies examined the folate depletion caused by phenytoin, based primarily on serum folate concentration,. The effects of different doses of folic acid ranging from 1 to 30 mg on the pharmacokinetics of phenytoin were also examined.

The following points are examined regarding the effect of folate depletion by phenytoin: (a) total serum phenytoin concentrations; (b) metabolites of phenytoin in the urine; (c) the effects on percent binding of phenytoin; (d) changes in the Michaelis-Menten constant, Km, but not V_{max}, the capacity of the liver; and (e) possible differences between men and women in regard to the DNI (i.e., gender analysis). A subsequent section examines the effect of folic acid supplementation on the pharmacokinetics of phenytoin.

It is essential to examine both folate and phenytoin pharmacokinetics together because there is an interdependence between the two. The pharmacokinetics of phenytoin cannot be considered without knowing the nutritional status of folate.

2.3.1. Folate Depletion: "Pseudo-Steady-State" of Phenytoin Pharmacokinetics

The literature of the mid-1980s applied the term "pseudo-steady-state" to phenytoin pharmacokinetics *(50)*. This term implied that a person was at steady-state or equilibrium with phenytoin, but in reality was not. Total serum phenytoin concentrations are usually monitored clinically every month when a dosage change occurs. This AED exhibits Michaelis-Menten pharmacokinetics (frequently referred to as dose-dependent or nonlinear kinetics) and the calculations predict that steady-state should occur in less than 1 mo. However, it has been shown that phenytoin does not reach steady-state as described by Eq. 1 *(13,51,52)* for the time to reach 90% of steady-state:

$$t_{90\%} = \frac{0.9 \, Css \, Vd}{R - V_{max}} - \frac{Km \, V_{max} \, Vd}{\left(R - V_{max}\right)^2} \ln\left(1 - 0.9\right) \tag{1}$$

Phenytoin Metabolism

Phenytoin

Vmax, Km   Folic Acid
                 (co-factor)

Epoxide

p-HPPH   m-HPPH   dihydrodiol

3-O-Methyl catechol
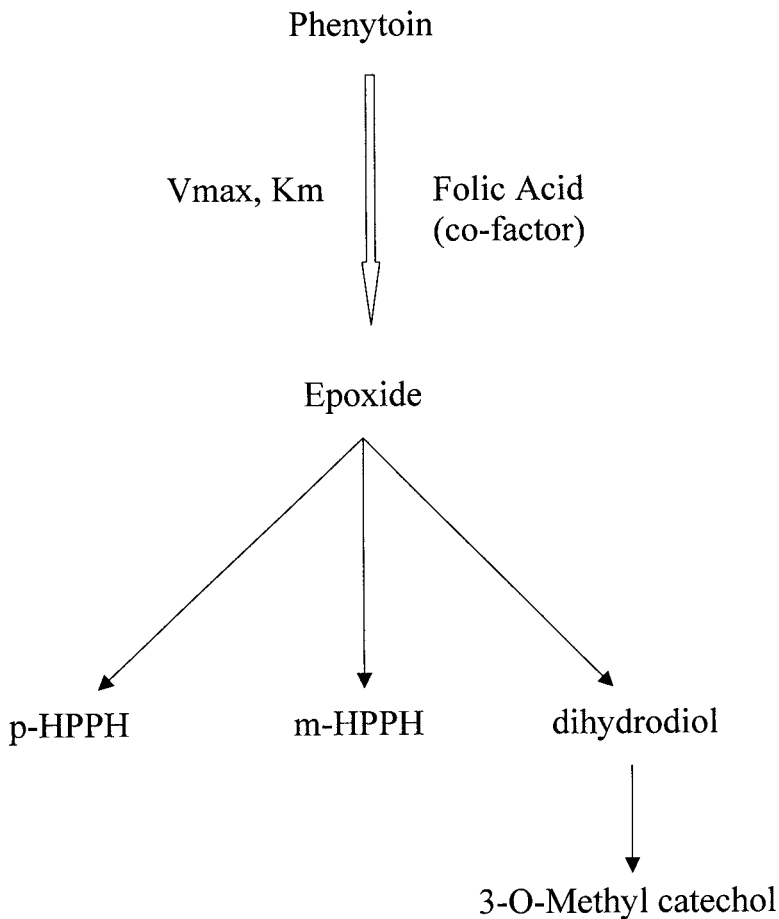
Fig. 2. Metabolism of phenytoin indicating that folic acid is a cofactor in the metabolism of this antiepileptic drug.

It has been shown that serum phenytoin concentrations obtained on two consecutive days, 1 wk after initiation of phenytoin, were within 10% of each other. Normally, one would consider that the individual was at steady-state. However, when the results were repeated 1 wk later on two consecutive days, the phenytoin concentrations were higher still—indicating that the previous values did not represent steady-state. This pattern continued to the third week. During this same 21-d period, the serum folate was decreasing. The implication for this higher phenytoin concentration over the 3 wk was that less endogenous folate was available as a cofactor for the metabolism of phenytoin. However, because it was being depleted by the presence of this AED, less endogenous folate was available to metabolize phenytoin. That would explain the increasing concentration of total serum phenytoin over that time period. These concentrations may have appeared as steady-state, but in reality, they were "pseudo-steady-state." Therefore, the

total serum phenytoin concentration at steady-state is dependent on when the cofactor, the endogenous folate, reaches its own equilibrium, which may be at a point of deficiency *(13)*.

There is an inverse relationship where the serum folate concentration is a mirror image of the total serum phenytoin concentration *(13)*. Folate is hypothesized as a cofactor for phenytoin metabolism and, in the absence of folic acid supplementation, the endogenous folate must re-establish a new equilibrium or steady-state when a patient or healthy volunteer takes phenytoin. Therefore, when routine clinical monitoring is done on a monthly basis, the patient is usually at equilibrium with both serum folate and total serum phenytoin concentrations, even though this point is not addressed in discussions of phenytoin monitoring at times when a dosage adjustment is made. One month follow-up clinic visits have been the standard of practice for dosage adjustments of AEDs in neurology without regard to the folate nutritional status.

Phenytoin is a drug that exhibits nonlinear pharmacokinetics known as Michaelis-Menten or dose-dependent *(52)*. Michaelis-Menten pharmacokinetics assumes that there is no perturbation of the system. However, folate depletion is a perturbation that is not taken into account when Eq. 1 is used to calculate the time it takes the patient to reach 90% of steady-state. In a healthy volunteer study, the time to steady-state for phenytoin took longer than calculated by at least three to four times because steady-state should have occurred at approx 1 wk *(13)*. In a male volunteer study *(51)*, the observed total serum phenytoin concentration was higher than the predicted. This could mean that endogenous folate was being depleted and less was available as a cofactor for drug clearance. Therefore, the total serum phenytoin concentration would be higher and it was. This is an excellent example of how the metabolism of a drug is also dependent on the endogenous status of a nutrient.

2.4. Folic Acid Supplementation

The effect of folic acid supplementation from 1 to 30 mg on the pharmacokinetics of phenytoin is examined in this section. The international studies used the higher doses of at least 5 mg. There were no studies that examined 400 µg of folic acid.

2.4.1. TOTAL SERUM PHENYTOIN CONCENTRATIONS AND PHENYTOIN URINARY EXCRETION

There are limited studies on the effect of folic acid supplementation on the total serum phenytoin concentrations. These have included both patients who were folate deficient while on phenytoin therapy and healthy volunteers, both taking oral doses of folic acid from 1 to 30 mg/d for a time period between 10 d and 6 mo. The decrease in total serum phenytoin concentration with supplementation ranged from 4.1 to 50% *(4,18–28)*.

When folic acid supplementation was initiated at the same time that phenytoin was started, steady-state was reached sooner *(13)*. It was close to the predicted $t_{90\%}$ value which is based on no perturbation of the system—an assumption of Michaelis-Menten kinetics.

2.4.2. PHENYTOIN URINARY METABOLITES

The effect of folic acid supplementation on the urinary excretion of phenytoin and its metabolites is limited and confusing. The latter point is due to the fact that few studies were extended to a time period where both serum folate and phenytoin were at steady-

state. Only in a small study and a case report were the folate deficient patients studied for at least 1 yr *(24,25)*. These two reports showed that oral folic acid supplementation of 1 mg/d increased the percentages of phenytoin metabolites in the urine back to the percentages usually reported for 5-(ρ-hydroxyphenyl)-5-phenylhydantoin (ρ-HPPH) and 5-(3,4-dihydroxy-1,5-cyclohexadienlyl)-5-phenylhydantoin (DHD) *(53–56)*. This data supports the concept that folic acid supplementation restores the impaired ability of the oxidative metabolism of phenytoin.

2.4.3. FOLIC ACID SUPPLEMENTATION: PLASMA-PROTEIN BINDING OF PHENYTOIN TO ALBUMIN

Because folic acid is only 60% nonspecifically bound to plasma proteins, it would be assumed that the binding of phenytoin, which is at least 90% bound to albumin, would not be altered. This has been confirmed in a small study of folate-deficient patients with epilepsy where folic acid did not change the binding of phenytoin *(24,25)*. A healthy volunteer study confirmed that no change in binding in the therapeutic range of phenytoin occurred whether 1 or 5 mg of folic acid was taken orally and there was no circadian rhythm effect on the binding of phenytoin (unpublished data).

2.4.4. FOLIC ACID SUPPLEMENTATION: MICHAELIS-MENTEN PHARMACOKINETICS OF PHENYTOIN

There have been four studies/case reports in folate-deficient patients taking phenytoin where the Michaelis-Menten constant (Km) and the V_{max} have been examined (24,25,27,28). Km is an inverse affinity constant between the enzyme and the drug as shown in Fig. 2, and V_{max}, describes the metabolic capacity of the liver. Km is expressed in terms of concentration and is the concentration at $\frac{1}{2}$ V_{max}. Km is considered the concentration below which phenytoin exhibits linear pharmacokinetics and above which, nonlinear at the therapeutic concentration for this AED. V_{max} is the dose of phenytoin that would saturate all the liver enzymes. Obviously, that would be toxic. In a computer simulation for total serum phenytoin concentration, it was shown that Km had a greater affect on total serum phenytoin concentration (57). There was no mention of the folate status in that study.

The patient studies showed that the decrease in total serum phenytoin concentration was dependent on the Km at the time of the folate deficiency *(24,25)*. The lower the Km, the greater the decrease in total serum phenytoin concentration when supplementation of 1 mg folic acid was added. With this addition of folic acid, the Km decreased further indicating increased affinity between the enzyme and drug *(24,25,27,28)*. This indicated increased metabolism of phenytoin. The V_{max} remained the same with or without folic acid supplementation. Therefore, the capacity of the liver did not change.

2.5. Gender Analysis

There is no information on the gender analysis of folic acid. Only two studies have analyzed the effect of sex on the decrease of endogenous serum folate when therapeutic doses of phenytoin were administered *(9,13)*. These were done in Caucasians. However, none of the DNI studies have been done since the introduction of pharmacogenetics. It is known that CYP2C9 and CYP2C19 metabolize phenytoin and there is no gender difference in the Caucasian group. However, there are ethnic differences, which may also mean gender differences within the particular ethnic group. Therefore, the DNI of folic

acid–phenytoin may be different among ethnic groups and between the genders within an ethnic group. And the amounts of folic acid and phenytoin may not be the same in those groups. Study length may need to vary by group as well.

2.6. Other Traditional AEDs and Their Lowering of Endogenous Folate

As seen in Figs. 1 and 2, there are implications or knowledge about the lowering of folic acid by the other AEDs *(58)*. In Fig. 2, phenytoin is metabolized to an epoxide. Carbamazepine is metabolized through the arene oxide pathway to form an epoxide metabolite similar to phenytoin *(59)*. Long-term therapy with phenobarbital, primidone, and phenytoin has shown decreased serum folate concentrations *(11,12,60)*. Phenobarbital is hydroxylated, as is phenytoin, and this may explain the decrease in endogenous folate. Primidone is metabolized to phenobarbital and phenylethylmalonic acid. Again, hydroxylation may be the cause for lowering folate *(61)*. Valproic acid inhibits glutamate formyltransferase, the same enzyme responsible for converting tetrahydrofolate to 5-CHO-tetrahydrofolate (Fig. 2) *(5,6)*.

2.7. Implications for Homocysteine

Because the traditional AEDs lower endogenous folate, the implication can be extended as to the affect on serum homocysteine as shown in Fig. 1. With decreased folate, homocysteine would be increased. This would have an affect on peripheral vascular disease, stroke, myocardial infarction, coronary artery disease, and congenital birth defects such as NTDs *(62)*. Perhaps in the future, the status of homocysteine will be routinely monitored in patients taking AEDs that lower the folate status because the implication is that folate-lowering drugs may cause iatrogenic diseases.

2.8. Future Research Needs and Recommendations

This DNI between AEDs and folic acid can be studied in both healthy volunteers and patients with epilepsy.

1. Healthy volunteers of diverse ethnic groups can be used to study different doses of folic acid supplementation on the pharmacokinetics of phenytoin. The studies mentioned in this chapter have all used pharmacological doses of 1–30 mg. The dose of 400 µg found in multivitamins should be studied and compared to the prescription dose of 1 mg folic acid. These studies should also include an evaluation of dietary folate intake, especially given the recent fortification of grains in the United States. It was not discussed in this chapter, but folic acid is also related to vitamins B_6 and B_{12} as shown in Fig. 1 and the status of those should also be noted.
2. Patients newly diagnosed with epilepsy and started on phenytoin should also be started on folic acid supplementation. Baseline serum and RBC folate should be obtained and dietary intake of folic acid should be recorded, again given the fortification of grains. This type of study would require working with the National Institutes of Health. The science is available to perform a large multicenter study with different ethnic groups. This type of research must go beyond the neurologist and include the nutritionist and the pharmacist with the inclusion of dietary supplemental intake and pharmacokinetics, including pharmacogenetics.
3. Assess the pharmacokinetic and pharmacodynamic outcome of folic acid and phenytoin concomitant therapy.

2.9. Summary and Recommendations

2.9.1. SUMMARY OF DUAL AND INTERDEPENDENT DNI (FOLIC ACID–PHENYTOIN)

The following statements can be made about the dual and interdependent DNI between folic acid and phenytoin. It should be emphasized that folic acid, whether it is decreased or increased through supplementation, does affect the Michaelis-Menten pharmacokinetics of phenytoin, the most commonly used of the traditional AEDs.

1. Serum folate starts to decrease immediately upon initiation of phenytoin therapy.
2. Only when serum folate is at steady-state is the total serum phenytoin at steady-state.
3. Total serum phenytoin concentration is higher than predicted because there is depletion of folic acid as a cofactor and therefore, less folic acid available for the metabolism of phenytoin.
4. Folic acid is a cofactor in the metabolism of phenytoin, which can be implicated from the lowering of the Km value (i.e., a greater affinity of the enzyme for phenytoin), which translates into a faster metabolism of phenytoin. It was also represented by an increase in the urinary phenytoin metabolites.
5. V_{max}, the capacity of the liver, for phenytoin is not affected by folic acid supplementation.
6. Folic acid supplementation does not affect the plasma protein binding of phenytoin.
7. Concomitant use of 1 mg folic acid and typical therapeutic doses of phenytoin when phenytoin is started results in no change in the serum folate and total serum phenytoin concentration reaches steady-state faster. This time to steady-state with phenytoin is consistent with the Michaelis-Menten calculation, which assumes no perturbation of the system. The use of this drug–vitamin combination may someday be a routine standard of practice just as the combination of isoniazid (for tuberculosis) and pyridoxine (vitamin B_6) is.
8. There appears to be a higher intake of folate (supplements and food) in women of childbearing years taking AEDs for epilepsy. However, there appears to be a saturation of folate intake based on RBC folate. Therefore, perhaps less folate supplementation may be needed than what is currently recommended.

2.9.2. RECOMMENDATIONS

There are currently no general recommendations to increase folic acid for patients with epilepsy taking antifolate medications, such as phenytoin, The only recommendation is for women in childbearing years with epilepsy to take from 0.4 to 5 mg/d of folic acid *(63)*. This range was not based on folate intake and resultant serum/RBC folate levels. In a recent study, there may be saturation of the amount of daily folate intake, based on both food and supplemental folate, and the resultant RBC folate in pregnant women with epilepsy followed up to 6 mo postpartum. The amount of folic acid supplementation in women taking AEDs may be less than the upper end of the recommended range *(64)*.

In a 1977 master's thesis *(65)*, Michaelis-Menten pharmacokinetics was demonstrated for serum folate. No RBC folate was measured during that time. Saturation of liver occurs *(66)*, but there is an implication for saturation of other tissues, such as RBCs. Today, the biological marker, RBC folate, best measures folate status.

Folic acid is a water-soluble vitamin and there is a misconception that what is not used by the body is excreted and the patient is always safe. With Michaelis-Menten kinetics of folic acid, it means less is metabolized as the dose is increased. When a 500 µg dose is taken, little unmetabolized folic acid is recovered in the urine *(67)*. When a 4 mg dose

is taken, 25% is recovered as urinary folate. Folic acid, not the circulating folate in the form of 5-methylenetetrahydrofolate, inhibits dihydropteridine reductase (DHPR), which leads to lower concentrations of dopamine, norepinephrine, and serotonin in the central nervous system *(68)*. This is of concern because it is known that inherited DHPR deficiency can result in neurologic damage and death.

3. AEDS AND THEIR EFFECTS ON VITAMIN D

3.1. Effect of AEDs on Bone Health

AEDs can alter bone health through several mechanisms: (a) induction of vitamin D metabolism; and (b) decrease of calcium absorption by two mechanisms: direct effect of AED on calcium absorption, less vitamin D available for calcium absorption *(69–71)*. Women taking AEDs are at greater risk than men, given their smaller bone mass. Women taking AEDs are at a greater risk for osteopenia, osteomalacia, and fractures. Therefore, women on AEDs should take calcium along with vitamin D to increase the absorption of calcium. There are no specific recommendations made for increasing the amounts of the minerals and vitamins at this time. Obviously, where possible, women with epilepsy taking AEDs should maintain physical activity (e.g., walking).

Both men and women taking AEDs have decreased bone health because they have a higher incidence of hypocalcemia and reduced levels of vitamin D. The majority of the AEDs, whether traditional or new, induce liver metabolism and induction of vitamin D metabolism would be key in these patients.

The effect of AEDs on bone health has been known, but little research has been done in this area.

3.2. Research on the Effect of AEDs on Bone Health

It is key to define the effects of the AEDs on the bone health of both men and women. This is important in these patients because they may require more calcium and vitamin D than individuals not taking AEDs. The daily amounts of both this mineral and vitamins are needed for patients with epilepsy taking AEDs.

4. EFFECT OF AEDs ON VITAMIN K

AEDs, such as phenytoin, carbamazepine, primidone, and phenobarbital, have been associated with an increased risk of fetal hemorrhage. This occurs because the AED can cross the placenta and enter the fetal liver, thereby decreasing vitamin K and decreasing production of vitamin K-dependent clotting factors. Bleeding occurs within the first 2 d after delivery in the baby *(72,73)*.

The American Academy of Neurology recommends that vitamin K supplementation be provided as vitamin K_1 at 10 mg/d during the last month of pregnancy *(74)*. Or at the time of birth, the neonate is administered vitamin K.

5. CONCLUSION

Even though the AEDs have been used in clinical practice starting in the early 20th century, the majority of the traditional drugs, phenytoin, carbamazepine, valproic acid, primidone appeared over a 40-yr span between 1938 and 1978. The decade of the brain

(the 1990s) brought the new AEDs that are primarily used as add-on therapy to the traditional AEDs, with the exception of gabapentin and lamotrigine. However, it is the older AEDs that are more commonly used, with phenytoin being the most widely used AED in the world. It is evident that these "old drugs" do affect the nutritional status. There is a group of folate-depleting AEDs with phenytoin having the most information of the group. This work was started in the 1960s, but it was obvious by the literature that not many studies were done to thoroughly examine this dual and interdependent DNI or realized the interrelationship between the pharmacokinetics of both the vitamin and the drug. It is a unique relationship because the drug affects the vitamin and vice versa. It is probably very difficult to get this point across when discussing this DNI because health care individuals are trained to think of an interaction going in one direction, not both. However, it is obvious that further research in this area is necessary, especially because lower folate status leads to elevated homocysteine, which is implicated in several diseases, including heart disease for both men and women. Not only is gender analysis important in this area, but also ethnic analysis because there are differences in the pharmacogenetics of AEDs. Perhaps someday, folic acid supplementation will be started and given concomitantly with those AEDs lowering folate, just as pyridoxine (another B vitamin) is given with isoniazid.

The effect of AEDs on bone health have been known for a long time and yet, there are no recommendations for specific calcium and vitamin dosing.

The effect of AEDs on vitamin K appears to be followed rather closely in pregnant women with epilepsy because these patients are considered high risk. Therefore, the woman, along with the neonate, appears to receive excellent care.

The fact that AEDs affect the nutritional health of patients is important to study because this type of work requires a preventive type of approach in order to avert clinical problems. Federally funded grants now need to address AEDs, especially in the area of the folic acid–phenytoin dual and interdependent DNI.

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17 Drug–Nutrient Interactions That Impact Mineral Status

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1. INTRODUCTION

Concurrent administration of medications and nutrients can bring about interactions that change the absorption or metabolism of the medication or nutrient *(1,2)*. There are many more dietary supplements and drugs that are now taken simultaneously and some interact with each other *(3)*. Certain drugs may exhibit decreased absorption or activity as a result of chelation and adsorption. Mineral status may be altered because of decreased absorption, increased excretion, or an altered mineral metabolism (Fig. 1). The results of such interactions may be clinically insignificant or severe. This chapter discusses mineral bioavailability and absorption and reviews mineral requirements, their sources, deficiency, and toxicity signs, and normal levels in the serum (Tables 1 and 2). Drugs that will affect mineral status (Table 3) in contrast to those minerals expected to interfere with drug absorption or activity (Table 4) are reviewed. The tables in this chapter have been designed to provide a simple and practical guide for practitioners.

1.1. Overview of Mineral Absorption and Bioavailability

Absorptive efficiency for many minerals is governed by homeostatic feedback regulation. When the body is in a depleted state, the intestine upregulates absorption of the nutrient. At a biochemical level, this regulation can be expressed by the control of intraluminal binding ligands, cell-surface receptors, intracellular carrier proteins, intracellular storage proteins, or the energetics of the transmembrane transport.

The bioavailability of minerals is defined as the efficiency with which a natural or manufactured source of an element delivers the element to storage, or supplies it to metabolically active tissue or to a protein. To assess for bioavailability, the following must be determined: (a) whether the intake is below or above the physiologic requirement, (b) tissue mineral contents, if possible, as dependent variables, (c) range of linearity

Effect of medication on nutrient absorption

1. Drug complexes with mineral preventing the absorption of nutrient and/or drug (i.e., antibiotics chelate with cations such as Ca, Mg, Fe, Zn).

2. Drug alters vitamin absorption that indirectly affects mineral (i.e., mineral oil decreases vitamin D absorption, thereby decreasing Ca absorption).

3. Drug alters gastric acidity (i.e., long term use of antacids may decrease absorption of iron).

4. Drug damages mucosal surface (i.e., antineoplastic drugs may induce mucosal damage and decrease nutrient absorption.

Effect of medication on mineral utilization

1. Drug causes molecular modifications, (i.e., mitomycin C inhibits Zn/Cu superoxide dismutase transcription).

2. Drug changes the metabolism of nutrients resulting in higher requirements (i.e., phenobarbital may increase the metabolism of Vitamin D thereby decreasing Ca absorption).

Effect of medication on nutrient excretion

1. Drug increases urinary loss of minerals (i.e., loop diuretics increase excretion of Na, K, Cl, Mg and Ca).

2. Drug decreases urinary excretion (i.e., thiazides decrease urinary Ca excretion)

Fig. 1. Effect of medications on mineral kinetics. Ca, calcium; Mg, magnesium; Fe, iron; Zn, zinc; Na, sodium; K, potassium; Cl, chlorine; Cu, copper.

between mineral dose and response, and (d) the results of a slope ratio analysis. In general, mineral bioavailability decreases because of many drugs, decreases with age, and in the presence of malnutrition, is associated with poorer integrity of the small intestine. Therefore, older individuals who are often taking numerous medications and who are eating more poorly than younger people are at greater risk of mineral deficiencies.

The chemical form of a mineral is an important factor in its absorption and bioavailability. Although few studies have been done comparing absorption differences among mineral supplements, there is evidence that the form in which minerals are ingested affects absorption *(4)*. For example, the particle size, surface area, and solubility of a substance affect its dissolution rate *(5,6)*. Other manufacturing variables that may affect the release characteristics of minerals in a tablet include tablet compression force and the type and amount of coating materials.

The composition of foods and beverages determines the chemical form of a mineral component. In many solid foods, elements are not free, but firmly bound in the food matrix. They can be in covalent association with a protein, as in metalloenzymes, or in electrochemical chelation arrangements to a nonspecific binder. Chelated forms of minerals may interact with other minerals or drugs to reduce absorbability. Food fortification may affect mineral absorption *(8)*. The recommended Food and Drug Administration (FDA) meal used in food–drug interaction studies is a high-fat, high-calorie meal with minimal micronutrient content. With changing patterns in food preferences, fortification and dietary supplementation, revision of current regulatory guidelines should take into account potential new nutrient–drug interactions.

Factors that enhance mineral absorption include the form of the mineral ingested, maintenance of chemical stability, presence of a specific transporter, small particle size, solubility, ascorbic acid, and low intestinal motility. Although certain fibers inhibit absorption of minerals, soluble fibers such as nondigestible oligosaccharides (prebiotics) such as oligofructose and inulin or lactulose, stimulate absorption and retention of several minerals, particularly magnesium, calcium, and iron *(9)*. The mechanism underlying these positive effects is most likely related to increased solubility of these minerals in the cecum and the colon as a consequence of increased microbial fermentation and lower luminal pH. Clinical trials show evidence that prebiotics will enhance calcium absorption *(10,11)*. However, not all studies show positive effects *(12)*.

Factors that inhibit absorption of minerals include oxalic acid, phytic acid *(13)*, fiber *(14)*, sodium, tannins *(15)*, caffeine, protein, fat, antacids, rapid transit time, malabsorption syndromes, precipitation by alkalinization, other minerals *(16)*, hormones and nutritional status *(17)*. In addition, excess mineral excretion can occur as a result of diarrhea, a common side effect of antibiotics, which may be caused by the elimination of beneficial bacteria normally found in the colon. In this case, yogurt-containing probiotic microorganisms can protect against other antibiotic-induced diarrhea.

Finally, genetics may also influence the absorption of minerals *(18)*. This is likely to be an important mechanism for individual absorptive responses to a specific drug, but currently there is limited information about how genes influence mineral and/or drug absorption and metabolism. A goal should be to identify pharmacogenomic biomarkers that stratify individuals based on a likely response to a particular medication, both positive and negative responses, efficacy, and development of side effect or toxicity *(19)*.

Table 1
Clinical and Serum Assessment of Macromineral and Trace Mineral Status

Mineral Food Sources and Adult RDA or AI/d	Symptoms		Normal Serum Levels and Diseases Altering Status
	Deficiency	Toxicology	
Sodium			
Salt, soy sauce, processed foods AI: 1.2–1.5 g	Muscle cramps, mental fatigue, anorexia, weight loss, poor growth, nausea	Hypertension in salt-sensitive individuals ↑ Renal disease, dehydration	135–148 mmol/L (or mEq/L) ↓ Renal disease diarrhea, profuse sweating, excess ADH, overhydration, CHF, cirrhosis
Potassium			
Meats, milk, vegetables, fruits, grains, legumes estimated minimum AI: 4.7 g	Muscular weakness, paralysis, confusion, possible death, cardiac arrhythmias, paralysis, weight loss	Muscular weakness, vomiting	3.5–5.3 mmol/L (or mEq/L) ↓ GI loss (vomiting, diarrhea), urine loss (Cushing's Disease, drug-induced), alkalosis, sweating, dehydration ↑Acidosis, renal disease, hypoaldosteronism
Calcium			
Dairy products, small fish with bones, broccoli, kale, tofu, Ca-enriched products AI: 1–1.2 g/d	Stunted growth, osteoporosis, rickets, osteomalacia, tetany, parathyroid hyperplasia	Constipation	2.2–2.6 mmol/L (8.5–10.5 mg/dL) Free ionized 4.4–5.4 mg/dL Tight regulation of serum levels ↓Hypoparathyroidism, diseases (liver, renal, critical illness) ↑ Hyperparathyroidism, excess vitamin D, renal failure, immobilization
Phosphorus			
Animal protein (all meats) RDA: 700 mg/d	Rare Neurological, skeletal, hematological, renal manifestations, rickets, osteomalacia, anorexia	Occurs with low Ca intake→secondary hyperparathyroidism Results in reduced growth or bone loss	0.7–1.4 mmol/L (2.3-4.3 mg/dL) ↓ Alkalosis, GI, malnutrition recovery, renal disease ↑ Renal, malignancy, sarcoidosis, immobilization Mg deficiency, bone malignancy, Cushing's Disease

Table 1 (continued)

Mineral Food Sources and Adult RDA or AI/d	Symptoms		Normal Serum Levels and Diseases Altering Status
	Deficiency	Toxicology	
Magnesium			
Nuts, legumes, grains, seafood, dark green vegetables, chocolate RDA: 420 mg/d (M), 320 mg/d (F)	Weakness, confusion, hypertension, tingling, muscle weakness, poor growth, convulsions neurological signs	Diarrhea (as with large doses of Epson salts), hypotension, hypothermia	0.7–1.0 mmol/L (1.8-2.3 mg/dL) ↓ Surgery, alcoholism, malabsorption, some renal diseases, diabetes, acidosis ↑ Sepsis, cardiac arrest, burns
Iron			
Meats, fish, shellfish, eggs, legumes, leafy green vegetables, enriched cereal/bread RDA: 8 mg/d (18 mg for women <50 yr)	Anemia, weakness, pallor, reduced ability to concentrate, lowered cold tolerance	Infections, liver injury, possible heart attack, acidosis, bloody stools, shock, colorectal cancer	80–150 μg/dL (14–24 μmol/L) ↓ Renal disease, malnutrition, ↑ Hemochromotosis
Copper			
Liver, shellfish, water grains, nuts, seeds RDA: 900 mg/d	Rarely occurs, bone abnormalities, anemia, neutro- and leukopenia	Vomiting, diarrhea, liver and renal damage	85–150 μg/dL (13–24 μmol/L) ↓ Diarrhea, malnutrition Menke's disease (kinky hair) ↑ Wilson's disease
Zinc			
Meats, fish, shellfish, grains, vegetables RDA: 11 mg/d (M) 8 mg/d (F)	Anorexia, growth and sexual retardation, anemia, poor taste, smell and wound healing; hair, nails, skin changes	Nausea, vomiting, diarrhea, dizziness, atherosclerosis, renal failure	60–130 μg/dL (9–20 μmol/L) ↓ Liver disease, stress, malnutrition, infection, burns, ↑ Industrial exposure

RDA, Recommened Dietary Allowance; AI, adequate intake; ADH, antidiuretic hormone; CHF, congestive heart failure; GI, gastrointestinal; Ca, calcium; Mg, magnesium; M, male; F, female.

Table 2
Clinical Assessment of Ultratrace Minerals

| Mineral/Food Sources | Symptoms | |
	Deficiency	Toxicity
Chromium		
Meat, unrefined foods, Brewer's yeast, beer RDA: 20–35 µg/d	Diabetes-like condition; reduced glucose control	Rare
Selenium		
Seafood, organ meats, meat, grains, certain vegetables RDA: 55 µg/d	Higher risk for heart disease, cardiomyopathy, increased red blood cell fragility, poor growth, muscle pain	Nausea, abdominal pain, nail and hair changes, nerve damage
Fluorine (fluoride)		
Drinking water, tea, seafood, toothpaste AI: 4 mg/d (M); 3 mg/d (F)	Dental caries, osteoporosis	Fluorosis (pitting and discoloration of teeth; skeletal osteosclerosis), nausea, diarrhea, itching, vomiting
Iodine (I)		
Iodized salt, seafood, plants grown in high I soil, and animals fed high I plants RDA: 150 µg/d	Goiter, cretinism, myxedema, increased blood lipids, liver gluconeogenesis, retention of sodium and water	Decreased thyroid activity, goiter-like enlargement
Manganese		
Most foods AI: 1.8-2.3 mg/d	None reported in humans, possibly impaired growth, skeletal abnormalities, impaired central nervous system, defects in lipid and carbohydrate metabolism	Rare; nervous system disorders
Molybdenum		
Legumes, grains, dark green leafy vegetables, organ meats RDA: 45 µg/d	Rare; induces increased uric acid and xanthine excretion, mental disturbances, coma, hypermethioninemia	None reported

RDA, recommended dietary allowance; M, male; F, female; AI, adequate intake.

2. MACROMINERALS

The macrominerals are discussed with respect to absorption and bioavailability, assessment of status, and drug interactions. Status is typically measured in the serum (and sometimes in the urine). In general, hair mineral testing has been found to be an unreliable and crude estimate of mineral status because of contamination from the environment (i.e., shampoos and emissions) *(20)*. Remarkable progress is being made in understanding the molecular basis of disorders of human mineral metabolism, but this topic is tangential to our focus and therefore is not discussed.

2.1. Sodium

Sodium is the most abundant (93%) of the cations in the blood. Its primary location is on the surface of bone crystals, and the rest is in the extracellular fluid, nerves, and muscles. Ingested sodium is almost completely absorbed in the intestine, with only 5% unabsorbed and excreted in the feces. Intestinal absorption may occur via the sodium/ glucose cotransport system (distributed throughout the small intestine), the sodium chloride cotransport system (located in the small intestine and proximal colon), and a colon-located electrogenic sodium absorption mechanism. A basolateral sodium pump maintains the inward gradient necessary for sodium absorption in all the described processes. With this very high absorption capacity, more than necessary will enter the system and excess sodium absorbed is excreted by the kidneys, a process that is controlled by aldosterone. Low sodium concentrations signal the release of the hormone and this promotes renal sodium reabsorption. Sodium is also lost through the sweat, however the amount excreted is variable (i.e., exercise, temperature conditions, etc.). Normal serum concentrations of sodium range between 135 and 148 mmol/L (Table 1) and are measured routinely in the laboratory to determine electrolyte balance.

2.1.1. DRUG INTERACTIONS

Excess use of sodium bicarbonate to relieve acid indigestion may cause hypernatremia, and consumption of a high sodium diet, especially in the elderly with heart disease, may pose an elevated risk for metabolic derangements *(21–23)* (Table 3). Sodium retention may also occur with other drugs, such as nonsteroidal anti-inflammatory drugs (NSAIDs) *(24)*, estrogens, *(25)* and corticosteroids *(26)*.

Increased excretion of sodium occurs with diuretic use and angiotensin-converting enzyme inhibitors (ACEIs) (Table 3). Dietary sodium restriction improves the antihypertensive action of diuretics and other blood pressure-lowering drugs. In patients taking lithium, both sodium and potassium excretion are increased *(27)*. In individuals who form kidney stones, hypercalciuria may be associated with a high sodium intake *(28)*, and sodium restriction alone or with thiazide diuretics helps to reduce urinary calcium *(29,30)*. Although immunosuppressive agents, such as cyclosporine, may not alter sodium levels in the body, subtle renal injury induced by cyclosporine could lead to salt sensitivity *(31)*. There can also be negative consequences of sodium restriction, especially in cases where the mechanisms to conserve sodium are impaired. Sodium restriction in combination with ACEIs can precipitate acute renal failure, and sodium repletion improves renal function *(32)*.

Table 3
Potential Mineral Interactions As a Result of Medications or Ethanol

Mineral	Malabsorption	Risk of Tissue and/or Serum Mineral Depletion	Increased Risk of Mineral Retention
Sodium	colchicine laxative overuse	hydrochlorothiazide, loop diuretics (bumetanide ethacrynic acid, furosemide) ACEIs (captopril, enalapril, quinapril), lithium	antacids with sodium bicarbonate, NSAIDs (ibuprofen, celecoxib, etodolac, indomethacin), estrogens, corticosteroids
Potassium	colchicine laxatives (mineral oil, bisacodyl, docusate, senna) neomycin	thiazide and loop diuretics amphotericin B bronchodilators (terbutaline, albuterol) aminoglycosides (gentamicin, tobramycin), felodipine, corticosteroids chemotherapy (cisplatin), digoxin, haloperidol, laxatives, thioridazine, ipecac abuse, licorice, lithium, aspirin, ethanol	potassium-sparing diuretics (triamterene, amiloride, spironolactone) β-blockers (atenolol, betaxolol, labetolol, metoprolol, propranolol), ACEIs, losartan, heparin, NSAIDs, haloperidol sulfamethoxazole
Calcium	bile acid sequestrants (cholestyramine, colestipol), primidone, corticosteroids (prednisone) diphosphates, methotrexate antibiotics (neomycin, cycloserine, erythromycin, minocycline), glutathimide, sulfonamides (trimethoprim, sulfamethoxazole), mineral oil, orlistat[¶], anticonvulsants (phenobarbital, phenytoin)	loop diuretics triamterene aminoglycosides corticosteroids felodipine, Al-hydroxide albuterol, indomethacin cisplatin, felodipine isoniazid thyroid hormones	calcium acetate NSAID (diclofenac[⊥]) estrogens[⊥] hydrochlorothiazide[⊥] oral contraceptives[⊥] sucralfate

(continued)

Table 3 (continued)

Mineral	Malabsorption	Risk of Tissue and/or Serum Mineral Depletion	Increased Risk of Mineral Retention
Phosphorus	mineral oil	antacids (aluminum- or magnesium hydroxide and calcium carbonate) albuterol phosphate binders cisplatin, indomethacin	
Magnesium	antibiotics sulfonamides	thiazide and loop diuretics, nitrofurantoin albuterol, amphotericin B, corticosteroids, cisplatin, digoxin, felodipine, aminoglycosides, sotalol[¶], cyclosporine, quinidine pentamidine, foscarnet isoniazid, metformin, ethanol, oral contraceptives	laxative overuse (epson salts, aluminum magnesia), potassium-sparing diuretics[¶], estrogens[¶] medroxyprogesterone[¶] mixed amphetamines
Iron	magnesium hydroxide-containing antacids cholestyramine H₂-blockers (cimetidine famotidine, ranitidine), tetracyclines, neomycin, penicillamine, haloperidol, zinc salts	aspirin, NSAIDs haloperidol deferoxamine, stanozolol	oral contraceptives
Copper	zinc salts H₂-blockers	penicillamine zidovudine valproic acid[¶]	oral contraceptives
Zinc	cholestyramine	thiazide and loop diuretics, penicillamine, tetracycline zidovudine, ACEIs corticosteroids, aspirin, ethanol, oral contraceptives valproic acid[¶]	zinc lozenge overuse estrogens[¶] medroxyprogesterone[¶]

[⊥]may help maintain a positive calcium (and bone) balance.

[¶]evidence is considered preliminary; clinical significance remains questionable.

ACEIs, angiotension-converting enzyme inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs.

Examples are given in parentheses; physician should check mineral levels, and supplementation can be advised.

Because antibiotics are usually given for 2 wk, deficiency of minerals is not usually a problem.

Table 4
Minerals That Interfere With Drug Absorption or Activity

	Ca	Mg	Fe	Cu	Zn
Antibiotics					
ofloxacin	✔	✔	✔		✔
azithromycin		✔			
ciprofloxacin	✔	✔	✔	✔	✔
doxycycline	✔	✔	✔		✔
levofloxacin		✔	✔		
nitrofurantoin		✔			
tetracyclines	✔	✔	✔		✔
minocycline	✔	✔	✔		✔
Zidovudine					✔ +
Bisphosphonates	✔	✔	✔		✔
β-blocker (nadalol, sotalol)	✔				
Carbidopa, levodopa			✔		
Chlorhexidine			✔		✔ +
Famotidine		✔			
Fentanyl		✔ +			
Glipizide		✔			
H$_2$-blockers (cimetidine)		✔	✔		
Hydroxychloroquine		✔			
Methyldopa		✔			
NSAIDs (etodolac, oxaprozin, ibuprofen)				✔ +	
Penicillamine			✔		✔
NSAID (COX-2) - rofecoxib	✔				
Sulfasalazine			✔		
Warfarin		✔	✔		✔

✔ : Reduces absorption or activity.

✔ +: Increase activity of drug.

There are many drug interactions and not every drug within a class is listed.

Ca, calcium; Mg, magnesium; Fe, iron; Cu, copper; Zn, zinc; NSAID, nonsteroidal anti-inflammatory drugs; COX-2, cycloxygenase-2.

2.2. Potassium

Potassium is the major intracellular fluid cation. It plays a crucial role in muscle contractility (smooth, skeletal, and cardiac) and in the excitability of nerve tissue. In addition, it is relevant in the maintenance of electrolyte and pH balance. As opposed to the case of sodium, intestinal absorption of potassium is not so well understood. The cation is largely (90%) absorbed, and it has been suggested that the colon is the main site. Among the proposed mechanisms are a potassium/proton adenosine triphosphatase pump, apical membrane, and potassium channels. Potassium balance is regulated in the kidney, with aldosterone promoting its excretion.

Elevated serum potassium concentrations (hyperkalemia) may result in severe cardiac arrhythmias and cardiac arrest. However, this situation is not likely to occur by dietary means in an individual with normal circulation and renal function, because there is a delicate control of potassium concentrations. Hypokalemia, on the other hand, may occur with severe vomiting and diarrhea, and is associated with muscular weakness, nervous irritability, and mental disorientation. Normal serum potassium is 3.5 to 5.3 mmol/L, commonly assayed to identify renal disease and monitor electrolyte balance (Table 1).

2.2.1. Drug Interactions

Common drugs that cause potassium deficiency include thiazide and loop-type diuretics, and laxatives (Table 3). Long-term treatment with diuretics may lead to total body potassium and magnesium deficiencies, which are not detectable using the standard methods of serum analysis and may occur despite potassium supplements *(33)*. Increased serum potassium levels have been reported with use of β-blocking drugs in conjunction with potassium-sparing diuretics *(34)*. Hyperkalemia may also occur with drugs like ACEIs, salt substitutes, NSAIDs, and heparin, among others, and this may be exacerbated by the presence of diabetes mellitus, renal insufficiency, hypoaldosteronism, and older age.

2.3. Calcium

Calcium is the most abundant divalent cation in the human body, averaging about 1.5% of total body weight. Approximately 99% of the body's calcium is in bones and teeth, and the remaining 1% is in both the intracellular and extracellular fluids. Normal serum calcium concentrations range from 2.2 to 2.6 mmol/L (8.5 to 10.5 mg/dL) in adults (Table 1). Because total serum calcium concentrations are tightly regulated, its measurement tells little about calcium status. Serum-*ionized* calcium better reflects alterations in calcium metabolism.

About 30% of dietary calcium is absorbed in the intestine via two main transport processes. In the duodenum and proximal jejunum, a saturable, energy-dependent process occurs, which is regulated by calcitriol (1,25-dihydroxyvitamin D) and involves a calcium-binding protein that transports the cation through the cell *(35)*. The other process occurs throughout the small intestine and is nonsaturable and does not require energy. In this process, calcium is absorbed between the cells (rather than through them). The large intestine contributes to approx 4% of dietary calcium absorption. Calcium is absorbed in its ionized form; therefore it must be released from the insoluble salts in which it usually comes in food and dietary supplements. Although most calcium salts are dissolved in the acidic pH of the stomach, absorption is not guaranteed because calcium may form insoluble complexes with other dietary components within the more alkaline pH found in the small intestine, limiting its bioavailability. One of these components is fiber. Additionally magnesium and calcium compete for intestinal absorption when an excess of either is present in the intestinal tract.

Excessive oxalate consumption in situations where calcium or magnesium is unavailable (e.g., with consumption of aluminum hydroxide gels that bind these minerals) may lead to formation of kidney stones and interstitial renal failure. In addition, kidney stones have been associated with excessive dietary salt and protein rather than excessive calcium intake *(28)*.

2.3.1. DRUG INTERACTIONS

Furosemide, ethacrynic acid, triamterene, and other oral diuretics produce significant hypercalciuria. Furosemide has been utilized to control symptoms of hypercalcemia and has been observed to increase parathyroid hormone levels as it increases urinary calcium excretion *(36,37)* and this has been associated with renal calcification *(38)*. Thiazide diuretics like chlorothiazide and hydrochlorothiazide, on the other hand, cause renal calcium retention by stimulating calcium transport across the epithelial cells of the distal tubule, and can cause hypercalcemia, although this side effect may only be transient. However, thiazide users do have a greater bone mineral content than age- and sex-matched nonusers *(39)*. It has been suggested that thiazide drugs might have a therapeutic role in the management of osteoporosis *(40)*.

Indirectly, calcium status may be affected by long-term intake of anticonvulsant drugs (Table 3). These medications, particularly phenobarbital and phenytoin, may induce vitamin D deficiency *(41)*, which in turn is expected to impair intestinal calcium absorption. More recently, it has been reported that epileptic patients under treatment have low bone mass in the absence of vitamin D deficiency *(42)*. Vitamin D deficiency, and therefore decreased calcium absorption, can also occur with medications that impair fat absorption such as anti-obesity medications (e.g., orlistat) and hypolipidemic agents (e.g., cholestyramine). Gentamicin has been associated with hypocalcemia (low calcium levels) in humans *(43)*. Nevertheless, excess oral calcium supplementation may reduce gentamicin-induced kidney damage *(44)*. Prednisone and other glucocorticoids cause calcium malabsorption and increased renal excretion that may lead to bone loss and secondary hyperparathyroidism *(45)*.

2.4. Phosphorus

Phosphorus is second only to calcium in abundance among the inorganic elements in the human body. Approximately 85% of phosphorus is in the skeleton and the remainder is associated with organic substances of soft tissue. Approximately 55 to 70% of dietary phosphorus is absorbed with normal dietary intakes, and this may increase to 90% when intake is low or in infants and children. Phosphorus absorption occurs in its inorganic form throughout the small intestine, by a saturable, carrier-mediated active transport system or a linear, concentration-dependent, diffusion process. Maintenance of phosphorus balance is achieved mainly through renal excretion. Magnesium, aluminum, and calcium impair phosphorus absorption. In adults, plasma inorganic phosphate ranges between 0.7 and 1.4 mmol/L (2.3 and 4.3 mg/dL) (Table 1), however, this varies largely with dietary phosphate, age, growth, time of day, hormones, and renal function. Because of the widespread availability of phosphorus in food, deficiencies are rare and therefore status assessment is not a major consideration. In addition, evaluation of serum phosphorus concentrations lack sensitivity and specificity and may be affected by several confounding factors unrelated to phosphorus status.

2.4.1. DRUG INTERACTIONS

Aluminum hydroxide combines with phosphates in the intestine and aluminum phosphates thus formed are then excreted in the feces. The prolonged use of antacids containing nonabsorbable aluminum and magnesium hydroxide may result in hypophosphatemia

(47) (Table 3). Phosphate depletion with the use of antacids has been described to cause bone demineralization and osteomalacia and rickets, and symptoms of malaise and bone pain associated with hypophosphatemia and hypercalciuria *(48,49)*. These antacids have been used to correct hyperphosphatemia associated with chronic renal failure. Calcium acetate and calcium carbonate are used as phosphate-binding agents in people on hemodialysis with hyperphosphatemia. Sucralfate is another aluminum-containing medication capable of reducing serum phosphate concentrations.

2.5. Magnesium

Magnesium is the second most abundant intracellular cation, after potassium. A total of 21 to 28g of magnesium are distributed between bone (60%) and extracellular fluids and soft tissues (40%). Magnesium absorption occurs throughout the entire small intestine. Absorption in the ileum appears to be saturable. Typical ingested amounts via the diet are absorbed by a saturable, carrier-mediated facilitative transport system, with an efficiency of approx 30 to 60%, that increases when magnesium status is poor and/or intake is low. Magnesium absorption is influenced by a variety of dietary factors (phytate, fiber, fatty acids).

Even though the homeostatic mechanisms are unclear, concentrations of magnesium are maintained by the kidney and small intestine. Under conditions of magnesium deprivation, both organs increase retention of the mineral. Intestinal absorption, renal excretion, and transmembranous cation flux rather than hormonal regulation seem to be involved. Vitamin D increases magnesium absorption, but it is less relevant than its role regulating calcium absorption. If magnesium depletion continues, the bone store contributes by exchanging part of its content with extracellular fluid. Serum magnesium can be normal in the presence of intracellular depletion of the mineral, but low serum levels usually indicate significant magnesium deficiency *(50)*.

Magnesium status is difficult to assess because only about 1% of total body magnesium is located extracellularly, and because it is homeostatically regulated, normal serum levels, 0.7-1 mmol/L (1.8 to 2.3 mg/dL) (Table 1) may occur in presence of intracellular deficit. Magnesium status may be assessed by renal magnesium excretion after an intravenous magnesium load, where deficiency is revealed by a decreased excretion over two 24-h periods following the magnesium load.

2.5.1. DRUG INTERACTIONS

Magnesium and potassium deficiency may coexist with some diuretic drug therapies. Many drugs such as loop and thiazide diuretics, aminoglycosides, cisplatin, pentamidine, and foscarnet can cause increased urinary loss of magnesium and subsequent deficiency *(50,51)* (Table 3). Magnesium deficiency is also seen with other drugs (*see* Table 3), but this may be the result of inadequate intake rather than ethanol-induced alterations in magnesium bioavailability *(52)*. Excessive ethanol consumption may lead to decreased magnesium levels *(53)*, by inhibiting intestinal absorption or by increasing the rate of excretion *(52,54)*.

High serum magnesium may occur in response to drugs (Table 3). A case was reported where repetitive doses of the antacid aluminum magnesia for epigastric pain following bone marrow transplantation lead to hypermagnesemia with hypotension, hypothermia,

and coma *(55)*. It is noted that magnesium imbalance may not only be owing to the antacid therapy but that the posttransplant status with poor nutritional intake and other concomitant problems may have prompted this imbalance. In a randomized trial with eight healthy people, 850 mg magnesium hydroxide increased glipizide absorption and activity *(56)* (Table 4). In theory, such changes could be therapeutic or detrimental under varying circumstances. Therefore, people taking glipizide should consult with their doctor before taking magnesium supplements.

3. TRACE AND ULTRATRACE MINERALS

Trace minerals are those that occur in microgram quantities per gram of tissue and are required in the diet in milligrams per day. The trace minerals include copper, iron, and zinc. Ultratrace minerals are typically required in the diet in amounts of micrograms per day and include arsenic, boron, cadmium, chromium, cobalt, fluorine, iodine, lead, lithium, manganese, molybdenum, nickel, silicon, selenium, and vanadium. Some of the ultratrace minerals have been studied more than others and are considered essential in the diet (chromium, manganese, molybdenum, selenium, fluorine, iodine), whereas the function of others are less clear and toxicity is a greater concern. In this chapter, we discuss iron, copper, zinc, chromium, selenium, fluoride and iodine, and Table 1 and 2 includes information about these minerals as well as manganese and molybdenum.

3.1. Iron

The most common form of anemia is iron-deficiency anemia, resulting from an inadequate iron supply for erythropoiesis *(57)*. The number of red cells in the blood stream are related to iron levels, and the red cell's function of carrying oxygen depend on its hemoglobin content. Body iron is found primarily in hemoglobin, which is the most abundant and easily sampled of the heme proteins *(58)*. Iron is found mainly in a trivalent form as ferric oxide or hydroxide or its polymers. Iron absorption is very limited unless these salts can be solubilized and ionized by the intestinal contents to ferrous salts. The amount of iron absorbed from food can vary from 1 to more than 50%. Iron absorption depends on the constituents of the diet, on the type of iron compound present, and on the body's physiological need for iron, which is regulated by the intestinal mucosa. Under conditions of iron depletion, which exist for many women and children, the intestinal mucosa increases iron uptake efficiency, especially that of the nonheme iron *(59)*. If the body is iron replete, the percentage of iron absorbed will be low. Iron overload is thus prevented by this mechanism.

The availability of iron from food depends on its source (Table 1). For example, Asian diets contain a soybean inhibitor that adversely affects iron absorption *(60)*. Tannins, phytates, certain fibers (not cellulose), carbonates, phosphates, zinc, manganese, and low-protein diets also negatively impact iron absorption. In contrast, ascorbic acid, fructose, citric acid, stearic acid, high-protein foods, lysine, histidine, cysteine, methionine, and natural chelates (i.e., heme), all enhance the apparent absorption of iron. In addition, iron overload can result from a genetic disorder, hemochromatosis, which is associated with increased absorption of iron *(61)*. Iron stores are best evaluated with serum ferritin concentration *(62)*, but are also assessed with serum transferrin, red blood cell (RBC) count, hemoglobin and by RBC size and color *(63)*.

3.1.1. Drug Interactions

Drugs that interact with iron include the dopa drugs (methyldopa, levodopa, carbidopa), ciprofloxacin, penicillamine, thyroxine, and captopril that form stable complexes with iron *(64)* (Table 3). Aspirin use has been associated with lower serum ferritin in subjects with inflammation, infection, or liver disease *(65)*. The relations between aspirin, inflammation, and serum ferritin may confound associations between elevated serum ferritin, as an indicator of iron stores, and heart disease risk *(65)*. In addition, high pH induced by antacids may form iron aggregates and convert iron to its ferric form, decreasing absorption *(66)*. Aluminum hydroxide gels bind iron, also decreasing its absorption; however, certain antacids may not reduce the efficacy of iron absorption.

3.2. Copper

Copper is absorbed by the stomach to the small intestine and is typically in the range of 30–40%. The absorption of copper varies inversely with copper intake, and can be as low as 12% absorption with very high copper intakes to a theoretical maximum absorptive capacity of 67% *(67)*. In developed societies, these extremes in absorption would be rare. Copper absorption is believed to be equally distributed along the small intestine and occur through a rate-limiting active transport and diffusion component. The enterohepatic circulation is important for copper balance. Approximately 50% of the copper reaching the small intestine reappears in the bile and is lost in the stool. After absorption, copper is primarily bound to albumin and transported to the liver. Once copper reaches the liver, it is distributed throughout the body primarily by the copper binder, cerruloplasmin, with smaller amounts bound to albumin and other minor copper binders.

Copper salts including chloride, acetate, sulfate, and carbonate are highly bioavailable, with the exception of copper oxide. In general, the macronutrients and foods that will increase copper intestinal absorption include protein and polybasic amino acids, whereas a decrease in copper absorption has been shown with hemicellulose, fructose, long-chain fatty acids, and a vegetarian diet *(68,69)*. Copper absorption and bioavailability is reduced in the presence of divalent cations including zinc, iron, tin, and molybdenum. Copper and these minerals are antagonistic, following classical pharmacologic responses *(70)*. Age is an important determinant of copper absorption. A steady increase in serum copper levels has been reported from childhood to old age *(71)*, but this increase is not likely the result of an increased copper absorption *(68)*. Copper status is measured in the serum with normal adult levels ranging from 85 to 150 µg/dL (13–24 µmol/L).

3.2.1. Drug Interactions

Copper absorption is blocked by zinc salts *(72)*. Penicillamine, zidovudine, and valproic acid have been shown to deplete serum copper levels (Table 3) *(72)*. Copper supplementation may enhance the anti-inflammatory effects of NSAIDs while reducing their ulcerogenic effects *(73)*.

3.3. Zinc

The low pH of the stomach results in the release of bound zinc into its free form but none is absorbed in the stomach. In man, zinc absorption occurs from the duodenum to the ileum, with the greatest absorptive capacity in the jejunum. Zinc is typically absorbed

at a rate of 15–30%. At high zinc intakes, zinc absorption is inhibited and is owing to the production of intestinal cell metallothionein, a zinc-binding protein. Zinc salts are regularly used for the treatment of Wilson's disease, an inherited disease of copper accumulation and toxicity in brain and liver. Zinc's mechanism of action in blocking copper absorption is the result of metallothionein. Although metallothionein also block zinc absorption, it is believed that copper has a higher affinity for metallothionein than zinc. After absorption, copper and zinc are bound to albumin in the serum and transported to the liver. Zinc is repackaged and released into circulation bound to α2-macroglobulin. In circulation, zinc is bound to albumin (57%), α2macroglobulin (40%), and 3% to low-molecular-weight ligands such as amino acids. Zinc uptake into cells is carrier mediated and energy independent, but the specific mechanisms are not known *(74)*. In tissues, zinc is often bound to metalloenzymes involved in the degradation of the extracellular matrix and possibly involved in the process of tumor growth *(75)*.

Zinc is normally consumed in the form of organic complexes with protein and its content correlates with protein level. It is well known that the bioavailability of zinc from plant sources is poor compared to animal origins. Dietary supplements are typically in the form of zinc sulfate, acetate, or gluconate, which are better absorbed than zinc phosphate, citrate, carbonate, or oxide. Fiber and phytates (found in grains, cereals, and vegetables) will decrease zinc bioavailability. Other metals will also interfere with zinc absorption, such as aluminum salts (widely used as an antacid), phosphorus, and tin. Zinc will interfere with calcium, copper and selenium bioavailability *(76)*. Serum zinc levels do not normally change in most healthy people except under conditions of extreme deficiency (Table 1). Urinary zinc levels can be confounded because of contamination and disease states that increase its excretion *(77)*. A zinc tolerance test requires the subject to ingest 200 mg zinc sulfate after an overnight fast with blood draws at 2, 4, and 6 h after ingestion.

3.3.1. Drug Interactions

Cholestyramine reduces plasma cholesterol because of its ability to sequester intestinal bile acids. Metabolic alterations, including diminished intestinal absorption of vitamin D have been reported with long-term use of cholestyramine and may negatively affect magnesium balance, as well as calcium, iron, and zinc balance *(78)*. Zinc status is also altered by many other drugs, including aspirin, diuretics, and corticosteriods (Table 3). Zinc interferes with the gastrointestinal absorption of tetracycline in humans, among other antibiotics (Table 4). There is some evidence that zinc supplementation enhances the response to interferon therapy in patients with chronic hepatitis C *(79)* as well as other drugs (Table 4).

3.4. Chromium

Dietary chromium primarily exists as trivalent chromium [chromium (III)] in the food supply *(80)*. Chromium salts differ substantially in solubility and determine the absorption and utilization of chromium. It is widely available in a variety of foods, the adequate intake levels for chromium are between 20 and 35 μg/d for adults (Table 2). Chromium is needed for optimal action of insulin at target tissues. Chromium, in a form called chromium picolinate, has been studied for its potential role in altering body composition with inconclusive results, thus far. One clinical trial in type 2 diabetics found, however, that chromium picolinate helps to normalize glycosylated hemoglobin, blood glucose,

and serum cholesterol levels *(81)*. Importantly, a recent meta-analysis shows that there is no effect of chromium on glucose or insulin concentrations in nondiabetic subjects *(82)*. The data for persons with diabetes are inconclusive *(82)*.

3.4.1. DRUG INTERACTIONS

Chromium tablets taken together with a hypoglycemic drug require monitoring, because supplements can reduce the need for insulin, sulfonylureas, and metformin. Therefore, hypoglycemia can result if a patient's drug dosage is not adjusted *(83)*. The administration of 16,16-dimethyl prostaglandin E2 may decrease chromium absorption *(84)*. Preliminary data suggests that corticosteroid treatment increases chromium loss *(85)*. Finally, there is also preliminary evidence that chromium enhances mood in people taking sertraline *(86)* that is typically used for depression.

3.5. Selenium

Selenium is a relatively newly discovered mineral with both essential and toxic properties, and a narrow intake between the two. Selenium and vitamin E are both instrumental in the detoxification of peroxides and free radicals. The absorptive efficiency of selenium is high. However, the source of the mineral can have an effect on its absorption. Selenium is transported from the gut on the very low- and low-density lipoproteins (LDLs). Normal blood values for adults range from 55 to 72 µg/L. People with disorders that are manifested by increased oxidative stress to the red cell, i.e., β-thalassemia, diabetes, and/or smoking tend to have slightly lower blood selenium levels. Toxicity is rare unless the individual has excess intake or is exposed to environmental sources of selenium. Selenium deficiency is rare in the United States. This is not the case in China (Keshan disease) and other parts of the world where food choice is restricted to locally grown items from soils deficient in selenium. Both selenium and iodine deficiency are associated with impaired thyroid function that in turn results in poor growth, reduced mental capacity, and decreased longevity. Selenium deficiency has been demonstrated in premature infants *(87)* and in persons using long-term selenium-free enteral or parenteral solutions *(88)*.

3.5.1. DRUG INTERACTIONS

Clozapine is a neuroleptic used to control symptoms of schizophrenia when other treatments are ineffective. One controlled study showed that taking clozapine could decrease blood levels of selenium *(89)*. More research is needed to determine whether people taking clozapine require selenium supplementation. Valproic acid used to control (prevent) seizures in people with epilepsy is thought to decrease selenium levels *(90)*, yet a recent study in epileptic children shows no alterations of serum selenium with valproic acid *(91)*. Oral corticosteroids have been found to increase urinary loss of selenium *(92)*, but its clinical importance is not clear.

Selenium may reduce drug- or nutrient-induced oxidative stress *(93)*. In one study, administration of a selenium product, Seleno-Kappacarrageenan, reduced the kidney damage and white blood cell-lowering effects of cisplatin *(94)*. Others found that selenium supplementation prevents cisplatin resistance in patients with ovarian tumors *(95)*. The amount of selenium used in these studies may be toxic and should only be used under the supervision of a physician. Simvastatin and niacin have been shown to lower LDL

cholesterol and raise high-density lipoprotein (HDL) cholesterol yet may be less effective in raising HDL cholesterol when taken with antioxidants (including selenium) *(96)*.

3.6. Fluoride

Fluoride is the ionic form of the element fluorine. Fifty percent of fluoride is absorbed within 30 min after ingestion. Without simultaneous ingestion of calcium and other cations that may form insoluble compounds with fluoride, 80% may be absorbed *(97)*. Body fluid and tissue levels of fluoride concentrations are proportional to long-term intakes rather than homeostatic regulation. Fluoride is largely (~99%) bound to calcified tissues in the body. About 50% of absorbed fluoride is eliminated by the kidneys in the urine, whereas in young children only 20% may be excreted while the rest is retained for the developing bone and teeth *(98,99)*. Fluoride deficiency has been prevented with water fluoridation, mineral supplementation, and topical fluoride products. In general, fluoride has a high bioavailability from water and toothpaste but if consumed with other divalent or trivalent cations, absorption may be reduced up to 25% *(100)*. However, fluoride ingestion from toothpaste may result in intakes equaling those ingested from food sources in young children, thus possibly reaching recommended upper limits *(101,102)*. The primary adverse effect of chronic excess fluoride intake is enamel *(103)* and skeletal fluorosis. Enamel fluorosis that is due to high fluoride intakes before teeth erupt (before 8 yr of age) is only considered a cosmetic concern. The teeth are brownish in color with surface irregularities, and in mild cases may be more resistant to dental caries. In skeletal fluorosis, early signs may be an increased bone mass, stiffness, or pain in joints leading to osteosclerosis, muscle wasting, neurological defects *(97)* and osteoarthritis *(104)*.

3.6.1. DRUG INTERACTIONS

Fluoride (in the form of monoflurophosphate) taken in combination with estrogens, produces a beneficial synergistic effect on bone mass *(105)*. In addition, sodium benzoate and many compounds in tea, such as tannin, catechin, and caffeine in combination with fluoride may reduce dental caries but these studies need to be confirmed in human trials *(106)*. Aluminum hydroxide can cause decrease fluoride absorption *(107)*.

3.7. Iodine

Dietary iodide is rapidly and completely absorbed in the stomach and intestinal tract, with minor amounts appearing in the feces *(108)* ultimately. Several substances, called goitrogens, have been identified as capable of interfering with iodide metabolism and inhibiting thyroid hormogenesis. Some examples of such compounds are halide ions (bromide and astatide), thyocyanate, perrhenate, pertechnetate, and perchlorate. Nutritional assessment of iodide is accomplished with physical examination (i.e., presence of goiter), quantification of urinary iodide excretion, and determination of serum thyroxine. Radioactive iodide uptake by the thyroid gland may be measured. A high and quick overall iodide uptake suggests iodide deficiency.

3.7.1. DRUG INTERACTIONS

The anti-arrhythmic, amiodarone, induces thyrotoxicosis partly because of its rich iodine content *(109)*. These patients may have altered thyroid hormone profile without thyroid dysfunction, hypothyroidism, or thyrotoxicosis *(110)*. Interestingly, although considered generally very safe, cases of thyroid dysfunction have been reported with

long-term treatment with the antiseptic povidone-iodine. Careful monitoring of thyroid dysfunction is recommended in patients treated with long-term povidone-iodine *(111)*. Lithium, used to treat psychiatric disorders, inhibits thyroid hormone release from the gland. Lithium blocks the release of iodine and thyroid hormones from the thyroid, thus enhancing the effectiveness of radioiodine therapy *(112)*.

3.8. Other Minerals

A number of other minerals have been shown to be essential, such as manganese and molybdenum that are included in Table 2. Information about drug interactions for manganese and molybdenum are limited, but there is evidence that redox-active drugs, such as antibiotics, enhances manganese-superoxide dismutase activity *(113)*. Arsenic, a known poison, has been shown to be essential to chickens, rats, pigs, and goats, but its function in humans is unclear. It is thought to have a role in bone metabolism. Animals with arsenic deficiency display depressed growth, myocardial degeneration, and premature death. Boron is essential for rats, but its biological function is unknown. Silicon has been found essential to chickens and rats and seems to be involved in bone formation. Skeletal abnormalities typify silicon deficiency in these species. Lithium is a mineral that may be present in some supplements and is used to treat mood disorders (see section on Iodine). Taking celecoxib, ibuprofen, indomethacin, together with lithium can result in significant increases in lithium blood levels *(114)*. Because major changes in lithium blood levels can produce unwanted side effects or interfere with its efficacy, NSAIDs should be used with caution, and people taking lithium-containing drugs or supplements should consult their health care practitioner about having their lithium blood levels checked regularly.

Mercury is toxic and exposure causes cutaneous and neurological symptoms. In 1997, the FDA Modernization Act identified food and drug products that contain intentionally introduced mercury compounds. Although drug products under FDA oversight containing mercury have been removed from the market, some nondrug products (e.g., herbals, homeopathic remedies, etc.) may contain mercury. In 1999, the American Academy of Pediatrics and the US Public Health Service alerted clinicians and the public about thimerosal, a mercury-containing preservative used in some vaccines for children *(115,116)*. Mercury in dental fillings has also been implicated as potentially causing long-term toxic effects *(117)*. Chelating agents (i.e., dimercaprol) should be used for a symptomatic patient.

4. OTHER SUBSTANCES AFFECTING MINERAL STATUS

4.1. Ethanol

Excess alcohol consumption has been associated with malnutrition in general and studies have found alterations in several minerals. Higher hair zinc and copper values were found in 43 male alcoholics than in 39 controls *(118)*. Lower selenium status is found in heavy alcohol drinkers *(119)*, and is associated with impaired liver function in cirrhotic alcoholics, which may be corrected by selenium supplementation *(120)*. Alcoholics also commonly present magnesium deficiency, and short-term oral magnesium therapy has been observed to improve liver cell function, muscle strength, and electrolyte status (serum sodium, calcium, phosphorus, potassium, and magnesium) in these patients

(121). Moderate ethanol consumption increases both magnesium and calcium excretion *(122)*. Lower serum vitamin D metabolites and calcium levels below the reference limits have been observed in alcoholics without differences in serum parathyroid hormone, phosphorus, or magnesium *(123)*.

4.2. Caffeine

Caffeine is found in coffee, tea, soft drinks, chocolate, guaraná (*Paullinia cupana*), nonprescription drug products, and supplement products containing caffeine. Excess caffeine consumption is a concern in calcium nutrition because it not only increases urinary excretion but also impairs intestinal calcium absorption, both leading to a negative net calcium balance. It has been calculated that for each 6 fl oz serving of coffee (~100 mg caffeine), calcium balance is more negative by 4.6 mg/d. It has been observed that the harmful effects of caffeine on bone mass do not occur unless the person is drinking more than three cups of coffee per day with a calcium intake less than 800 mg/d *(124)*. Adding milk to coffee may be an easy way to offset this imbalance *(125)*. Ciprofloxacin may decrease the elimination of caffeine from the body, causing increased caffeine blood levels and unwanted actions *(126)*.

4.3. Nicotine

There are few studies on the effect of cigarette smoking on mineral or other nutrient status in general, even though impaired nutrient status may contribute to the development of smoking-related diseases. Many oxidants and pro-oxidants contained in tobacco smoke are capable of producing free radicals and enhance lipid peroxidation in biological membranes. Therefore, nutrients involved in cellular antioxidant processes would be affected, such as vitamin C, β-carotene and vitamin E, and vitamins of the B complex. Regarding mineral nutrition, cadmium, which is present in tobacco, decreases the bioavailability of selenium and acts antagonistically to zinc, a cofactor for the antioxidant enzyme, superoxide dismutase *(127)*. Smoking has been found to be a significant predictor of poor selenium status *(128,129)*.

The effect of cigarette smoking on calcium balance and bone has been studied more than other minerals and is associated with reduced bone mass and a higher rate of bone loss *(130)*. It is estimated that lifetime hip fracture risk is increased by 31% in women and 40% in men who smoke *(131,132)*. A decreased intestinal calcium absorption in smokers may be a contributing factor *(130)*.

An inadequate diet may compromise nutritional status in smokers. Data from the Second National Health and Nutrition Examination Survey *(133)* indicates that smokers are less likely than nonsmokers to consume fruits and vegetables, high fiber grains, low fat milk, and vitamin and mineral supplements. The high cancer risk associated with smoking may be compounded by a lower intake of cancer-protective nutrients. It is also possible that smokers have increased mineral and nutrient requirements. Interestingly, an epidemiological study *(134)* found that use of vitamin and mineral supplements may reduce fetal death risk associated with maternal smoking.

4.4. Illicit Substances

Consumption of nicotine and other addictive drugs such as cocaine and marijuana, affects food- and liquid-intake behavior, taste preference, and body weight. Also, there may be changes in specific nutrient status and metabolism. For example, heroin addiction can cause hyperkalemia *(135,136)* and morphine use can result in calcium inhibition *(137,138)*. Poor dietary habits and low zinc status has been observed among marijuana abusers *(139)*.

5. LIMITATIONS OF CURRENT DATA AND FUTURE RESEARCH NEEDS

Multiple drug use is common in the older population, making them especially vulnerable to an altered nutrient status. Studies to improve our understanding of polypharmacy and its effects on nutrient status are essential. In addition, with more foods being fortified, the effect on drug absorption and bioavailability should be examined. Investigations into drug–mineral interactions with the wide variety of nutritional and herbal supplements currently being consumed is also necessary in order to understand possible alterations, optimize the effectiveness and minimize the toxicities of these little-studied substances. In addition, there is limited information about genetic influences on mineral and/or drug absorption and metabolism and this should also be a goal of future studies. Finally, with new dangers of bioterrorism, investigations into how nutrient status is affected by potential biological agents and prophylactic antibiotics that would be distributed to prevent biological warfare, should be encouraged.

Given the relatively recent discoveries of beneficial effects of some trace and ultratrace elements, further studies of drug interactions with these minerals, about which little is currently known, is warranted. The use of stable isotopes to study minerals rather than radioisotopes should be encouraged. And although the costs of stable isotopes are high and require sophisticated laboratories with mass spectrometry, as technology is refined *(140)*, these techniques will become more standard.

6. CONCLUSION AND CLINICAL RECOMMENDATIONS

In general, drugs that induce malabsorption, should be taken 1–2 h before a meal. Drugs that interfere with metabolism will cause problems if taken on a long-term basis and supplementation of the affected mineral would be recommended. Other methods to maintain mineral status should also be implemented, such as using of probiotics (i.e., yogurt with live cultures) for drug-induced diarrhea (i.e., antibiotics) causing excessive mineral loss *(141)*.

The major drugs that influence sodium and potassium are the diuretics and these need to be monitored in most hypertensive and/or cardiac patients. Many other drugs may result in retention of sodium and potassium (Table 3). Adequate hydration is important to balance the electrolytes, as well as recommending the appropriate foods (Table 1) to either restrict or replace these minerals.

There are many drugs that may deplete body stores of calcium that affect a wide range of patients. For example, corticosteroids, antibiotics, sulfonamides, mineral oil, and bile acid sequestrants will all result in malabsorption of calcium, whereas loop diuretics, aminoglycosides, corticosteroids, anticonvulsants, isoniazid, and thyroid hormones will deplete calcium stores (Table 3) and increase the risk of osteoporosis. The beneficial effects of estrogens and thiazides on maintaining calcium balance should be considered when recommending these drugs to patients. Phosphorus is affected by fewer drugs, but its importance in maintaining bone health should not be underestimated. The number of patients at risk of an imbalance of these minerals essential for bone health is alarming and supplementation of calcium (about 1 g/d) should be considered.

Magnesium status, like calcium can be depleted by many drugs, although there are fewer that affect the absorption of magnesium (Table 3). Many patients are at risk of magnesium deficiency including those with asthma, hypertension, emphysema, heart conditions, tuberculosis, and diabetes. In addition, young women taking oral contraceptives are also at risk of magnesium deficiency, and alcoholics often present with deficiency signs associated with magnesium. Magnesium-rich foods or supplementation (~400 mg/d) can be recommended.

The trace minerals iron, copper, and zinc are also affected by many drugs (Table 3) and the appropriate mineral-rich foods should be recommended. Alternatively, clinicians can suggest supplements of these minerals in amounts equal to or less than their daily recommended levels (Table 1). The ultratrace minerals are important for health and many (i.e., chromium, selenium, iodine) also have interactions with drugs. For others, however, an excess rather than deficiency can be a problem.

As the use of a variety of nutritional supplements increases, including megadoses of vitamins and minerals, the need to assess for potential interactions between nutrient supplements and medications becomes more and more important. For most of these new drug–nutrient interactions, updated information should be addressed in appropriate reference sources (e.g., the Physician's Desk Reference for Nutritional Supplements *[107]* and others, and at professional sites on the internet). Older adults, whose mineral status is already compromised due to aging, and who generally take a number of different medications daily *(142)* must be questioned about all the medications and food supplements, and any major dietary changes with their prescribing practitioner. Furthermore, health education about medications should include warnings and information about potential interactions between food supplements and drugs. This could help improve the prognosis for drug interactions affecting mineral status, and minerals that affect drug absorption and activity.

ACKNOWLEDGMENTS

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V DRUG–NUTRIENT INTERACTIONS BY LIFE STAGE

18 Drug–Nutrient Interactions in Infancy and Childhood

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1. INTRODUCTION

Medical care is becoming increasingly complex, especially for the pediatric population in part because children with certain chronic diseases are living longer as a result of new medical treatments. Nutrition is exceedingly important in infants, children, and adolescents. Inadequate nutrition will directly affect growth, development, and puberty. Chronic medication use can result in depletion of certain nutrients, which in the growing infant, child, and adolescent can have long-term consequences. Drug–nutrient interactions (DNIs) occur between medications (prescription and nonprescription) and certain foods, fluids, and nutrient supplements. Many of these interactions are not significant, but some are serious. Health care professionals need to be aware of these interactions and must prevent their occurrence by educating themselves and their patients. It is through knowledge of these DNIs that one can help optimize therapeutic effects, prevent therapeutic failures, and minimize adverse drug events and DNIs *(1)*.

DNIs may be more frequent in children and infants because of the difficulty this population has in taking medications, especially those in tablet or capsule form. Crushing a tablet, opening a capsule, or making a liquid preparation from a solid dosage form may result in changes in drug efficacy. Mixing these forms with food to disguise poor palatability may lead to a DNI. Children with chronic illness receive multiple medications, thus increasing the likelihood of drug–drug and drug–nutrient interactions. These children receive certain medications for long periods of time that can affect growth and development. Parents are also treating their children with "nonpharmacological" agents and so are using "natural products," some of which are not clinically tested and can increase the likelihood of DNIs.

Although there are a large number of medications used in pediatrics, there are certain medications that are routinely prescribed. Table1 lists medications routinely used in pediatric patients and the DNIs associated with them *(2)*. There is a global lack of information regarding medication use in pediatrics, and the area of DNIs cannot be limited to

Table 1
Common Pediatric Diseases and Drug–Nutrient Interactions

Medical Conditions	Comments
Asthma	
Albuterol	• Caffeine administration increases albuterol's adverse drug reactions.
Theophylline	• Food may induce "dose-dumping" (sudden release) of sustained release preparations.
Cardiac Disease	
Digoxin	• Digoxin absorption decreases with foods high in fiber or pectin.
Hydralazine	• Chronic hydralazine use may cause a pyridoxine deficiency.
Inflammatory Bowel Disease	
Sulfasalazine	• Folate absorption is impaired.
Organ Transplants	
Cyclosporine	• Grapefruit juice increases cyclosporine concentrations.
	• St. John's wort decreases cyclosporine concentrations.
Tacrolimus	• Grapefruit juice increases tacrolimus concentrations.
Seizures	
Phenobarbital	• High doses of pyridoxine may decrease phenobarbital's effect.
	• Increased requirements of folate may be required with chronic use.
Phenytoin	• Bioavailability is decreased with tube feedings. Hold feedings for 2 h prior to and 2 h after phenytoin administration.
	• High doses of folate may decrease phenytoin bioavailability.
Valproic acid	• Carnitine requirements may be increased.

pediatric patients. DNIs may be divided into the following categories: effect of food on drug absorption (increased, decreased, or delayed), alterations of drug metabolism, effects of medications on nutrient absorption or use, and pharmacological interactions of medications with nutrients.

The majority of the available literature focuses on the effect of food on the absorption of medications (i.e., delaying absorption). We now know that nutritional components can have effects on the metabolism of medications, as is the case with the effect of grapefruit juice on the cytochrome P450 enzyme system. There is, however, little information

regarding the effects of many other food components on drug metabolism. Another area that needs further investigation is the site of absorption of medications. Chronically ill and critically ill patients often receive medications via a feeding tube. It is necessary to know where the drug is absorbed in order to know its extent of absorption when administered into a certain portion of the gastrointestinal (GI) tract. For example, a medication absorbed in the stomach will not be effective if administered post-pylorically. In this chapter, we discuss the requirements for growth and development in pediatric patients and the impact of nutritional status. We describe common DNIs in this age group, the limitations of current data, issues related to complementary and alternative medicine (CAM), provide recommendations for the management of DNIs, and suggestions for future directions related to DNIs in infancy and childhood.

2. GROWTH AND DEVELOPMENT

Growth and development starts from conception and needs to be closely monitored in infancy, throughout childhood, and into adulthood. Because of physiological changes that occur after birth, an infant will lose about 10% body weight in the first week of life and typically regain the weight by 8–10 d after birth. In the first year of life, the weight of an infant doubles by about 5 mo and triples in 1 yr; body length increases by 55% and head circumference by 40% *(3)*. Growth then slows through childhood and another growth spurt occurs during adolescence. During these periods of accelerated growth, many changes occur in the body including puberty, and nutrient needs change as well. There are a variety of medical conditions that can affect growth and development. Some of these conditions are treated with medications that may alter growth and development by a variety of mechanisms. These may include a direct effect of the drug on the body, secondary effect (i.e., anorexia from gastritis), or DNIs. Further discussion of specific conditions is beyond the scope of this section and is not discussed, although factors to consider for growth, development, and nutritional status are reviewed.

3. NUTRITION ASSESSMENT

Nutritional status is closely related to growth and development and may be complicated by difficult medical conditions. Pediatric patients with complex medical conditions will benefit from an assessment of nutritional status from a clinician who specializes in pediatric nutrition. Pediatric conditions that may be high risk for drug–nutrient or drug–drug interactions as a result of the medications used in the condition include childhood cancers, cystic fibrosis, congenital heart disease, bronchopulmonary dysplasia, inflammatory bowel disease, other GI disorders, end-organ failure requiring organ transplant, renal disease, seizure disorders, and other neurologic disorders. Table 2 provides a list of components to evaluate in the nutrition assessment of an infant or child. If a child does not have appropriate nutrition, his or her growth will be affected resulting in wasting, stunting, or obesity. All components need to be considered in order to have a comprehensive nutrition assessment to make the appropriate recommendations. Nutrition assessments, including growth assessments, need to be reassessed often as a result of the changing physiological status of a child. Body composition and nutritional requirements change with growth and development. These changes need to be accounted for in the evaluation of a patient's nutritional status because they will impact on drug action, metabolism, and excretion.

Table 2
Components of a Nutrition Assessment

Components	Key Questions
Medical History	What are the acute and chronic illnesses? Are there nutrition and growth implications?
	What diagnostic procedures, surgeries, medications, psychosocial issues (e.g., socioeconomic status), or other therapies (e.g., chemotherapy, radiation, immunosuppression) may have an impact on nutrition? *(4)*
Diet History	Is the diet age appropriate? Texture of foods, frequency, and amount of foods?
	Is there any oral feeding difficulty?
	Is there a history of food allergies or intolerances? If so what is the reaction(s)?
	Are there any foods that are avoided and why?
	Any recent changes in appetite or intake?
	How is the diet taken (by mouth, enteral feedings, supplements, parenteral nutrition)?
	Any issues with limited access to food?
	Is the assessment of the diet history adequate or inadequate?
Gastrointestinal History	Any problems with nausea, vomiting, diarrhea, constipation, or reflux?
Medications	Do any of the medications have potential drug–nutrient interactions, drug–drug interactions, or side effects affecting nutritional status?
	Is there a recent use of steroids, immunosuppressants, chemotherapy, anticonvulsants, anticoagulants, or gastrointestinal medications?
	What is the timing and dosing of the medications? Who administers the medications?
	Are there side effects from the medications that may affect dietary intake?
Vitamin/Mineral Supplements	Are there additional supplements being taken? If so, how much and how often? Are these appropriate given the diet history, medical history, and medication list?
Herbal or Other Non-Nutrient Supplements	Do any herbal supplements, which may interact with medications taken, contribute to gastrointestinal history, or have negative impact?
Available Labs	Are there abnormal lab values that can be attributed to the diet and a modification to the diet or supplement can be added?
	Any vitamin and mineral labs drawn as a result of possibility of deficiency?
Growth Parameters	What is the growth history? What is the current growth evaluation?
	Has there been recent weight loss or rapid weight gain?
	Is there stunting or wasting? Is the patient overweight?

(continued)

Table 2 (continued)

Components	Key Questions
Physical Assessment	Does physical assessment verify growth parameter assessment?
	Are there any signs of a vitamin or mineral deficiency? Is there skin breakdown?
	How is dental health?
Nutritional Needs	Does the diet provide all of the needed calories, protein, fluid, vitamins, and minerals? (*see* Tables 4–7 for guidelines).
	Are there specific nutritional needs based on medical history?
	Based on growth parameters and diet history is there a need for a change in the current diet?
Assessment	What is the assessment of the patient's nutritional status taking all of the above into consideration?
Recommendations	Are any modifications needed to promote normal growth and development?
	If the diet is found to be inadequate, what can be done to make the diet adequate?
	Are any changes or additions needed for vitamin and mineral supplementation?
	What monitoring methods are recommended (e.g., growth assessments, food records, laboratory values, compliance)?
	Are the recommendations, age-appropriate and feasible? How and in what time frame will the outcome be measured?
	Are appropriate referrals made (e.g., social work; speech therapy; occupational therapy; early intervention; Women, Infants, and Children [WIC] program; registered dietitian; behavioral psychologist, or other specialty physicians)?
Education	Is education needed? Verbal and written? Is it age- and culturally appropriate?
	Have all caregivers been educated?

It is important that regular growth measurements are taken at regular intervals after birth and plotted on growth charts, which provide a visual picture of overall growth. In 2000, the National Center for Health Statistics (NCHS), in collaboration with the National Center for Chronic Disease Prevention and Health Promotion, revised the previous NCHS growth charts and made them available on the internet (www.CDC.gov/growthcharts) for boys and girls for birth to 36 mo and 2 to 20 yr. The measurements needed for birth to 36 mo are weight, length, and head circumference. Standing height and weight are needed for the 2- to 20-yr growth charts. Incremental growth can be calculated from weight and length measurements obtained over a given period of time (e.g., 1 mo), and can be compared to recommended values (Table 3) *(4)*. Stunting is an indicator of chronic malnutrition, whereas wasting alone is an indicator of acute malnutrition. Table 4 shows the criteria and classification for wasting and stunting as defined by the Waterlow Criteria *(5)*. Growth measurements are only one component of the nutrition assessment. Another component is a review of medications for those that can impact nutritional status.

Table 3
Growth Velocity

Age	Weight (g/d)	Length (cm/mo)
< 3 mo	25–35	2.6–3.5
3–6 mo	15–21	1.6–2.5
6–12 mo	10–13	1.2–1.7
1–3 yr	4–10	0.7–1.1
4–6 yr	5–8	0.5–0.8
7–10 yr	5–12	0.4–0.6

From ref. *4*.

Table 4
Waterlow Criteria for Grading Malnutrition

Weight Assessment Percent of Median Weight for Height		*Length/Height Assessment Percent of Median Height for Age*	
(Wasting)	*Classification*	*(Stunting)*	*Classification*
90–110%	Within normal ranges	≥95%	Within normal ranges
80–89%	Mild wasting	90–94%	Mild stunting
70–79%	Moderate wasting	85–89%	Moderate stunting
<70%	Severe wasting	<85%	Severe stunting

From ref. *5*.

4. NUTRITIONAL REQUIREMENTS

The Recommended Dietary Allowances (RDAs) have been published since 1941 to provide guidance on dietary assessment. The RDAs have recently been revised and incorporated into a broad framework of nutrient standards referred to as the Dietary Reference Intakes (DRIs). These include RDAs but also three additional reference values, Adequate Intakes, Estimated Average Requirements, and Upper Tolerable Intake Levels. The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRIs) of the Food and Nutrition Board, Institute of Medicine of the National Academies is the committee responsible for creating the new DRIs. Table 5 includes selected DRIs (protein, fiber, iron, calcium, and vitamin D) for infants, children, and adolescents. Energy requirements can also be estimated by using prediction equations (e.g., World Health Equation [WHO]) to determine basal energy needs *(6)* (*see* Table 6). This value must then be multiplied by an activity/disease severity factor (1.1–1.3 for mild illness, bed rest; 1.3–1.5 for moderate illness, average activity; 1.5–1.7 for severe illness and above average activity) to determine total energy needs. Tables 7 and 8 list the new equations to determine Estimated Energy Requirements. For children over 3 yr of age,

Table 5
Selected RDA/AI for Protein, Fiber, Iron, Calcium, Vitamin D

Category	Age (years)	Protein (g/kg/day)	Fiber	Iron (mg/d)	Calcium (mg/d)	Vitamin D (µg/d)
Infants	0.0–0.5	1.52*	ND	0.27*	210*	5*
	0.5–1.0	**1.5**	ND	**11**	270*	5*
Children	1–3	**1.1**	19 g/day*	**7**	500*	5*
	4–8	**0.95**	25 g/day*	**10**	800*	5*
Males	9–13	**0.95**	31 g/day*	**8**	1300*	5*
	14–18	**0.85**	38 g/day*	**11**	1300*	5*
Females	9–13	**0.95**	26 g/day*	**8**	1300*	5*
	14–18	**0.85**	26 g/day*	**15**	1300*	5*

*Indicates Adequate Intakes (AIs): **Bold type** indicates Recommended Dietary Allowances (RDAs). AIs and RDAs can both be used as goals for individual nutrient intake.
ND, not determined. (From ref. *7*.)

Table 6
World Health Organization for Predicting Energy Expenditure From Body Weight

Age Range (yr)	Equation (Kcal/d) to Determine REE	
	Males	Females
0–3	$(60.9 \times wt [kg]) – 54$	$(61 \times wt [kg]) – 51$
3–10	$(22.7 \times wt [kg]) + 495$	$(22.5 \times wt [kg]) + 499$
10–18	$(17.5 \times wt [kg]) + 671$	$(12.2 \times wt [kg]) + 746$

REE, resting energy expenditure. (From ref. *6*.)

Table 7
Estimated Energy Requirement (EER): Infants and Young Children

0–3 mo	$(89 \times wt [kg] – 100) + 175$ (kcal for Energy Deposition)
4–6 mo	$(89 \times wt [kg] – 100) + 56$ (kcal for Energy Deposition)
7–12 mo	$(89 \times wt [kg] – 100) + 22$ (kcal for Energy Deposition)
13–35 mo	$(89 \times wt [kg] – 100) + 20$ (kcal for Energy Deposition)

EER, total energy expenditure plus energy deposition. (From ref. *7*.)

height, weight, and a determination of a Physical Activity coefficient is needed to use the equations. Note that these equations only provide a guideline for the initial estimation of energy needs. The patient's response (e.g., weight and length/height) to the energy intake, should be used to determine whether an adjustment to this caloric estimate should be made. Reports on the DRIs can be found on www.nap.edu. *(7)*. For fluid requirements see Table 9 *(8)*.

Table 8

Estimated Energy Requirements (EER): Boys and Girls

Boys' EER

Boys 3–8 yr	EER=88.5–61.9 × Age [y] + PA × (26.7 × wt [kg] + 903 × height [m]) + 20
Boys 9–18 yr	EER=88.5–61.9 × Age [y] + PA × (26.7 × wt [kg] + 903 × Height [m]) + 25
PA	PA = 1.00 if PAL is estimated to be ≥1.0<1.4 (Sedentary)
	PA = 1.13 if PAL is estimated to be ≥1.4<1.6 (Low Active)
	PA = 1.26 if PAL is estimated to be ≥1.6<1.9 (Active)
	PA = 1.42 if PAL is estimated to be ≥1.9<2.5 (Very Active)

Girls' EER

Girls 3–8 yr	EER=135.3–30.8 × Age [y] + PA × (10.0 × wt [kg] + 934 × height [m]) + 20
Girls 9–18 yr	EER=135.3–30.8 × Age [y] + PA × (10.0 × wt [kg] + 934 × Height [m]) + 25
PA	PA = 1.00 if PAL is estimated to be ≥1.0<1.4 (Sedentary)
	PA = 1.16 if PAL is estimated to be ≥1.4<1.6 (Low Active)
	PA = 1.31 if PAL is estimated to be ≥1.6<1.9 (Active)
	PA = 1.56 if PAL is estimated to be ≥1.9<2.5 (Very Active)

PA, physical activity coefficient; PAL, physical activity level or the ratio of total energy expenditure (TEE) divided by basal energy expenditure (BEE). (From ref. *7*.)

Table 9
Fluid Requirements in Pediatric Patients

Body Weight	*Baseline Fluid Requirements*
1–10 kg	100 mL/kg
11–20 kg	1000 mL + 50 mL/kg for each kg over 10 kg
>20 kg	1500 mL + 20 mL/kg for each kg over 20 kg

From ref. *8*.

5. MEDICATION ADMINISTRATION AND DRUG ABSORPTION

Pediatric patients use many of the same medications as the adult population, however, the specific method of drug administration may be different. Pediatric patients often cannot swallow tablets or capsules intact. Additionally, the milligram per kilogram dose that is appropriate for a pediatric patient may not be available in a tablet or capsule. This requires parents or caregivers to crush tablets or open capsules and mix them with a small quantity of liquid or food if a liquid preparation is commercially unavailable *(1)*.

5.1. pH Effects

By altering the integrity of the commercially available formulation, the medication may be affected by the pH in the stomach. An example of this is omeprazole, a highly acid-labile medication *(9)*. Omeprazole is formulated as a capsule containing enteric-coated granules designed to protect the drug from stomach acid by dissolving in the more

alkaline environment of the intestine where the drug is absorbed. Crushing the granules or dissolving them in an alkalotic liquid prior to administration will impair the integrity of the enteric coating and result in drug degradation in the stomach acid. There are three options for patients who cannot swallow an intact capsule. The first is to open the capsule and mix the granules with fruit juice. The second option is to prepare a suspension in a sodium bicarbonate base that buffers the stomach contents long enough for the medication to pass through to the intestine. The third option is to open the capsule and sprinkle the contents on a soft food.

5.2. Phenytoin and Enteral Feeds

Phenytoin presents multiple challenges secondary to its nonlinear pharmacokinetics and absorption issues. Phenytoin suspension adheres to polyvinylchloride found in feeding tubes. Also, the concomitant administration of phenytoin suspension and enteral formulas can decrease phenytoin bioavailability resulting in decreased serum concentrations *(10,11)*.

Marvel and Bertino *(12)* conducted a study evaluating a single dose of phenytoin suspension administered with Ensure and Vivonex and found no significant effect on the overall absorption of the suspension. Despite these findings, the majority of the literature suggests that absorption is impaired. If clinically feasible, the feedings should be interrupted for 2 h before and after the dose. It is also important to flush the feeding tube to remove any enteral feeds that may remain in the tube prior to medication administration.

5.3. Effect of Food on Drug Absorption

Palatability of liquid medications is another issue that is continually addressed in the pediatric population. To mask the taste of medications, they are often mixed with a liquid or soft food. As a result, the effect of food on drug absorption must be considered. Table 10 lists some medications whose absorption is affected by food *(11,13–19)*.

6. NON-NUTRIENT DIETARY SUPPLEMENTS

The use of non-nutrient dietary supplements is widespread in both adult and pediatric populations, increasing 380% from 1990 to 1997. One in six parents surveyed in one report admitted giving dietary supplements to their children *(20)*. Another study evaluated adult patients who commonly took prescription medications. The authors noted that 18.4% of those surveyed reported using at least one herbal product or high-dose vitamin therapy. More concerning is that 61.5% of those patients did not report their use to their physicians *(21)*.

A variety of reasons have been identified for the lack of patients' disclosure of non-nutrient dietary supplements to physicians. For example, some patients do not believe non-nutrient dietary supplements to be related to their medical care or think of them as medications. Others do not disclose non-nutrient dietary supplement usage to avoid scorn from their health care providers *(20)*.

Although non-nutrient dietary supplements have their utility, they are not without toxicities and interactions seen with more conventional medications. Tables 11 and 12

Table 10
Drug Absorption Affected by Food

Drug	Comments
• Erythromycin base (E-mycin®, EryTabs®, ERYC®)	• Administer on an empty stomach
• Erythromycin stearate (Erythrocin®)	• Administer on an empty stomach
• Fluorquinolones (i.e., ciprofloxacin)	• Drug chelates with divalent cations and becomes inactive
• Penicillins (i.e., penicillin V potassium)	• Administer 1 h before or 2 h after a meal
• Nitrofurantoin (Macrodantin®)	• Administer with food (increases absorption and minimizes gastrointestinal upset)
• Griseofulvin (Fulvicin®, Grifulvin V®)	• Administer with high-fat meal
• Theophylline (sustained-release products)	• "Dose-dumping" possible with high-fat meal

list some of the commonly used non-nutrient dietary supplements and their nutrient interactions.

7. MANAGEMENT OF DNIs

The management of DNIs includes identification, prevention, and management.

7.1. Identification

During the medical interview, all patients or their caregivers need to be asked what medications (prescription and nonprescription), and supplements they are taking including the method of administration. This is especially true if the patient is having an unexpected side effect or lack of therapeutic effect. The health care professional needs to have an open attitude so that patients feel comfortable and will disclose all medications they are using as well as share their health beliefs. Additionally, pharmacies dispensing medications should have software and appropriate upgrades to identify potential DNIs.

7.2. Prevention

The best way to prevent a DNI is by educating all staff and patients and their caretakers. Caregivers should be encouraged to obtain all medications through one pharmacy so that the pharmacist is able to identify interactions such as DNIs. Pharmacies and health care facilities should ensure that food–drug interaction software is current to help identify and prevent potential interactions. Health care professionals should ask patients about all medication and supplement administration. Hospitals and pharmacies need to set up systems so that cross-check mechanisms exist to identify DNIs, (e.g., use of labels, computer alerts, and educational materials) *(34)*. Protocols should be developed for medication administration in those patients with chronic disease. Those patients who are receiving several medications can benefit from a consultation with a pharmacist to help them develop a schedule for medication administration. The involvement of other health care professionals, especially dietitians, in prevention and education of a DNI is critical.

Table 11
Dietary Supplement–Drug Interactions

Dietary Supplement	Conventional Drug	Result of Interaction
Chromium (22)	• Calcium carbonate and other antacids	• Decreased chromium absorption
Garlic (20,21,23)	• Warfarin, NSAIDS, ticlopidine, dipyridamole, and other antiplatelet drugs • Protease inhibitors	• Garlic inhibits platelet aggregation and prolongs bleeding and clotting times • CYP450 interaction
Ginger (23)	• Anticoagulants • Antidiabetic medications	• Platelet dysfunction • Affects blood sugar levels
Ginseng (20,21)	• Anticoagulants • Alcohol	• Increases INR • Increases alcohol clearance
Licorice (21,23)	• Digitalis and cardiac glycosides • Corticosteroids and thiazide diuretics • Spironolactone	• Effects potentiated by increased potassium loss • Increased sodium retention, hypertension, and hypokalemia • Most licorice candies sold in the United States do not contain licorice
Ma Huang (23)	• Monoamine oxidase inhibitors • Methylxanthines (i.e., caffeine), cardiac glycosides, anesthetics	• Increased toxicity • Potentiates effects

NSAIDs, nonsteroidal anti-inflammatory drugs; CYP 450, cytochrome 450; INR, International Normalized Ratio.

Registered dietitians need to be aware of the patient's diet and drug therapy and can help prevent and identify DNIs. They can educate patients about the intake of certain foods as well as monitor the patient's daily intake of these foods.

7.3. Management

Once the DNI has been identified, the specific problem needs to be corrected. It may require changing the timing of medication administration, or checking a drug level. Another option is to select a therapeutic alternative medication, if appropriate. One mechanism to manage issues with medication absorption is to adequately separate feedings from medication administration. Some of the literature states that feedings should be held 2 h prior to and 2 h after medication administration. In pediatric patients, continuous enteral feeding is not uncommon, which makes medication administration difficult in cases where feedings must be held. One recommendation is to change the feeding regimen to bolus feedings, if appropriate, to eliminate nutritional losses resulting from holding the feedings. If the patient has a dual-lumen gastrojejunostomy enteral feeding tube, it is possible to continue giving the feedings post-pylorically, but the medi-

Table 12
Vitamin–Drug Interactions

Vitamin	Drug	Comments
Vitamin A (24)	• Cholestyramine • Mineral oil • Neomycin	} Decreases vitamin A absorption
	• Warfarin	• Increases hypoprothrombinemic effects
Vitamin B (19,25)	• Aminoglycosides • Aspirin • Phenobarbital • Phenytoin	} Decreases vitamin B_{12} absorption
	• Chloramphenicol	• Antagonizes the response to vitamin B_{12}
	• Vitamin C	• Destroys dietary vitamin B_{12} in vitro
Calcium (26,27)	• Digoxin	• Potentiates digoxin toxicity
	• Calcium • Iron • Quinolones	} Decreases drug absorption
	• Tetracycline	• Calcium absorption impaired by bran, oxalate containing foods, and whole-grain cereals
Folic acid (28)	• Chloramphenicol	• Decreases response to folic acid
	• Phenytoin	• Increases phenytoin metabolism
	• Sulfasalazine	• Decreased folic acid absorption
Iron (29)	• Antacids	• Binds to iron decreasing its absorption
	• Chloramphenicol	• Decreases the response to iron therapy
	• Quinolones	• Decreases quinolone absorption
	• Tetracyclines	• Decreases tetracycline absorption
Magnesium (30,31)	• Benzodiazepines • Ciprofloxacin • H_2-blockers • Iron • Phenytoin • Steroids • Tetracyclines	} Decreases drug absorption
Zinc (32)	• Calcium • H_2-blockers	} Decreases zinc absorption
	• Iron • Quinolones	} Decreases drug absorption
	• Tetracyclines	• Zinc absorption impaired by coffee, brans, whole-grain cereals, and legumes.

cation should be administered into the stomach if the site of absorption is unknown. Some patients will benefit from a medication administration schedule for use in an outpatient setting. In an inpatient setting, system and alerts need to be put into place to prevent the DNI from occurring.

8. CONCLUSION AND FUTURE DIRECTIONS

To fully understand the extent of drug–nutrient reactions, one needs to have a better understanding of the nutrients' effects on drug metabolism and clearance. With a larger portion of patients receiving medications via feeding tubes, it is important that the site of absorption of medications be more clearly defined. There is still a lack of information regarding the interactions between dietary supplements with conventional medications. Given the widespread use of dietary supplements, it is important that these interactions are identified and health care providers and patients are adequately educated about the potential risks of taking the medications concomitantly. Many drugs used in pediatric patients have not been adequately studied, especially in neonates. Much research still needs to be done to evaluate DNIs in pediatric patients with chronic diseases who take multiple medications. Although we do know about the effects of chronic disease on the nutritional status of the patients, little is known about the long-term effects of medications in pediatric patients with chronic illness who now have longer life expectancies. Research also needs to be done on the prevention of DNIs in pediatric patients.

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19 Drug–Nutrient Interaction Considerations in Pregnancy and Lactation

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1. INTRODUCTION

The risk of drug–nutrient interactions (DNIs) during pregnancy and lactation present a unique challenge to health care professionals. A clinician must be familiar with the potential teratogenic and developmental risks associated with prescribing medications to pregnant or lactating women. Most medications are prescribed for the benefit of the mother and the fetus or infant is an unintended recipient *(1)*. By prescribing medication, the clinician may also predispose the mother and fetus or infant to one or more interactions. Therefore, it is imperative that clinicians be familiar with DNIs and that they continue to educate themselves and the pregnant or lactating woman in order to optimize a drug's effectiveness and minimize the risk of toxicities or DNIs.

1.1. Considerations in Pregnancy

Until the 1940s, most physicians and researchers believed a fetus was protected from the external environment while in the mother's uterus. However, this belief was challenged in 1941 by Dr. N. M. Gregg who observed specific birth defects in infants born to mothers who had been exposed to rubella *(2)*. Then in the late 1950s, thalidomide was administered to pregnant women during the first trimester as an anti-anxiety agent. This drug had been evaluated for safety in several animal models and demonstrated no increased fetal risk in the animal species studied. Unfortunately, it took many years and thousands of limb deformities to establish the cause-and-effect relationship between thalidomide administration during the first trimester and subsequent birth defects *(2)*.

Today, the potential for causing harm to a fetus through exposure to medications, environmental chemicals, and some diseases is widely accepted. Drug use prior to conception and during pregnancy should be limited to what is medically necessary. Even with the current knowledge available regarding risks associated with medication administration during pregnancy, surveys indicate that as many as 80% of pregnant women take

prescription or over-the-counter (OTC) drugs *(1)*. Some cases involve inadvertent exposure to drugs in the period of time between conception and confirmation of the pregnancy. In other cases, medication use may be required throughout the duration of the pregnancy for the management of symptoms related to the pregnancy or for treatment of chronic medical conditions.

1.2. Classification of Drug Safety During Pregnancy

To enhance the safety of drug use during pregnancy, the Food and Drug Administration (FDA) maintains Use-in-Pregnancy ratings to rank drugs based on their potential for causing birth defects in infants born to women using the drugs during pregnancy *(2)*. Table 1 lists the categories included in this rating system. These ratings combine several risk factors into one assessment for both maternal and fetal risk *(3)*. Consequently, the pregnancy category must be used in combination with current research findings reported in the literature to establish the most accurate assessment of teratogenic risk. Unless a specific risk is identified during clinical trials, all new medications are classified as Category C.

1.3. Adverse Effects of Drug Use During Pregnancy

A drug that causes abnormal fetal development is considered a teratogen. This may include pregnancy loss, structural deformities, abnormal intrauterine fetal growth, abnormal neurological development, or long-term defects *(4)*. Effects may be evident at birth or manifest after a latency period. Diethylstilbestrol (DES) is an example of a drug with a long latency period. Children of women who took DES have an increased risk of adenocarcinoma of the cervix and vagina or male reproductive anomalies *(4)*. Many of these abnormalities were not discovered until exposed individuals reached adolescence or adulthood.

Many variables influence the risk for adverse fetal outcomes with drug use during pregnancy. Jennings *(3)* describes the following factors involved in determining teratogenicity from drug exposure:

- drug dose and route of administration
- timing of the drug exposure
- duration of drug exposure
- concurrent exposure of other drugs
- species susceptibility
- maternal absorption, distribution, and metabolism
- placental transport
- placental metabolism
- fetal metabolism and elimination

Additionally, maternal conditions including malnutrition, diabetes, seizure disorders, hypertension, and various infections also influence the risk of adverse fetal outcomes *(3)*. These risks may be even greater because of the drugs used to treat these disease states. Administration of drugs to a pregnant woman should be done cautiously. The patient and clinician must recognize that medication taken during pregnancy can affect the fetus. To minimize the risks of drug use during pregnancy, guidelines typically recommend giving medication only when a specific indication warrants pharmacological intervention and using the lowest effective dose for the shortest period.

Table 1
U.S. Food and Drug Administration Drug-Risk Categories

Category	Description
A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of a risk in later trimesters), and the possibility of fetal harm appears remote.
B	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal-reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester (and there is no evidence of a risk in later trimesters).
C	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.
D	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

From ref. *2*.

There are many sources of information available for clinicians listing the potential effects of drug use during pregnancy, such as product labeling, case reports, teratogen information services, and ongoing registries. Relatively few drugs have been proven to pose teratogenic risk to human fetuses. These include alcohol, selected chemotherapeutic agents, selected anticonvulsants, androgens, warfarin, danazol, DES, lithium, isotretinoin and other retinoids, as well as thalidomide *(3,4)*.

1.4. Drug–Nutrient Interactions

There are numerous causes of adverse pregnancy outcomes with nutrition playing a pivotal role *(5)*. In addition to the teratogenic risk of administering medication during pregnancy, DNIs may contribute to adverse outcomes for the mother and fetus. This triangular relationship between the mother and fetus, adequate nutrition, and drug administration has a significant impact on pregnancy outcome. There have been many studies demonstrating the negative outcome of diets low in protein and carbohydrates on pregnancy outcomes *(5)*. However, the effect of low intakes of selected micronutrients is not as clear. When a drug is prescribed to a pregnant woman, the effect it has on a selected nutrient may result in a deficiency for the woman, whereas it may have a teratogenic effect on the fetus. The triangular relationship must be considered when prescribing medications to a pregnant woman.

Failure to recognize a DNI may predispose both the mother and fetus to treatment failure, toxicity, or life-threatening adverse reactions. For example, a pregnant woman receiving phenytoin for a seizure disorder should be advised regarding its potential teratogenic effects. Additionally, the patient should be informed of the DNI between phenytoin and folic acid that increases the risk for folic acid deficiency and the need for supplementation.

DNIs can occur whether or not a woman is pregnant. However, many of the characteristics of a normal pregnancy, such as those listed in Table 2, increase the risk of a DNI *(1,6)*. Because maternal nutritional status governs fetal growth and development, DNIs that alter nutrient levels or utilization can have far-reaching clinical impact. If a drug must be given during pregnancy and a DNI has been reported, the clinician must determine if a change in dose for the drug or effected nutrient are necessary or determine if alternative therapy is warranted.

2. NUTRIENT CONSIDERATIONS DURING PREGNANCY

Nutritional requirements during pregnancy are determined by the maternal and fetal growth requirements. Fetal survival is correlated with birth weight, which largely depends on adequate maternal nutrition. Pregnancy increases daily energy requirements by 300 kcal during the second and third trimester *(7)*. With this increase in macronutrient consumption, which includes carbohydrate, protein, and fat, a corresponding increase in the amount of vitamins, minerals, and other micronutrients occurs. The Recommended Dietary Allowance (RDA) for most nutrients during pregnancy has been established *(7)*. When inadequate consumption of nutrients occurs, adverse consequences may result for both the mother and fetus. A summary of the consequences of nutrient imbalances during pregnancy is listed in Table 3 *(7–9)*. Pregnant women should also avoid mega-vitamin supplementation during pregnancy. As described in Table 3, there are also risks associated with excessive vitamin and mineral administration. Drugs that have a propensity to create an imbalance of nutrients that are critical to fetal development are most likely to result in a clinically significant DNI during pregnancy.

2.1. Special Nutrient Considerations: Folic Acid

Adequate folate intake is imperative prior to pregnancy as well as through the first trimester. A review of DNIs involving folate is presented elsewhere in this book. During pregnancy, a state of increased maternal and fetal cell proliferation, folate requirements are higher and the risk for deficiency greater. Folate deficiency may cause maternal megaloblastic anemia. Additionally, maternal deficiency has been associated with fetal neural tube defects, prematurity, spontaneous abortions, and low fetal birth weight *(10,11)*. Recently, folate deficiency and corresponding increased levels of homocysteine have been implicated in repeated spontaneous abortions, placental abruption, and pre-eclampsia *(12)*. A major drug–nutrient consideration centers on the use of anti-epileptic therapy during pregnancy because drug-induced reductions in folate levels may occur *(13)*. Folic acid supplementation reduces the risks of fetal defects. Supplementation with 0.4 mg per day is recommended prior to conception and continued for the first trimester. Significantly higher doses are recommended for patients who have had pregnancies

Table 2
Characteristics of Pregnancy That Increase the Risk for Drug–Nutrient Interactions

Characteristic	Clinical Implications
Elevated nutrient requirements	Potential for depletion of maternal nutrient reserves
Nausea and vomiting, food cravings and/or food aversions	Changes in eating patterns may predispose to nutrient imbalance
Body composition changes: increases in body weight, total body water, and fat stores	Alterations in volume of distribution and drug effect
Decreased plasma protein concentration	Potential to modify drug level and effect of protein-bound drugs
Delayed gastric emptying; prolonged intestinal transit	Can alter rate or extent of drug or nutrient absorption
Changes in metabolic activity in the liver	Variations in hepatic enzyme activity lead to changes in drug metabolism

From refs. *1,6.*

resulting in a child with a neural defect and for women taking anti-epileptic medications; dosage recommendations range from 4 to 5 mg per day *(10)*. If any potentially interacting drug is given to a pregnant woman, both mother and fetus may be at risk for folate deficiency and supplementation is warranted.

2.2. Special Nutrient Considerations: Iron

Iron deficiency during pregnancy results in maternal anemia. Deficiency during the first trimester, may result in a higher incidence of low birth weight babies *(14)*. In the third trimester, the mother may not be able to tolerate hemorrhage during labor and is more prone to infection *(15)*. The RDA for iron for the average adult woman is 18 mg per day. During pregnancy, it increases to 27 mg per day to avoid potential deficiency *(16)*. However, during pregnancy, the mother must avoid aggressive supplementation or iron overload may occur. High ferritin levels have been associated with increased risk of premature birth and neonatal asphyxia *(17)*. With the importance of maintaining adequate iron stores during pregnancy, the potential for DNIs must be monitored. For instance, the administration of an antacid may inhibit the absorption of iron *(18)*. If a medication is initiated that interacts with iron, adjustments in the dose of medication or iron may be necessary.

2.3. Special Nutrient Considerations: Treatment for Selected Conditions During Pregnancy

Pharmacological treatment for disease states occurring during pregnancy may need to be considered. Principles for treating the pregnant woman should include evaluating treatment options for the nonpregnant woman and then evaluate the relative safety of the treatment options for the mother and fetus *(19)*. Table 4 lists medical conditions that may require pharmacologic treatment in the pregnant women, the FDA's Drug-Risk Category, the most commonly prescribed drugs for the treatment of these conditions, and the DNIs that may result from the administration of the drugs *(1,4,20–22)*.

Table 3
Consequences of Nutrient Imbalance During Pregnancy

Nutrient	*Potential Consequences of Nutrient Imbalance*
Vitamin A	Teratogenic effects at doses exceeding 10,000 IU (3 mg)/d.
Vitamin D	Deficiency states result in fetal hypocalcemia, defective formation of bones and dental enamel. Excess vitamin D is associated with fetal hypercalcemia, growth retardation, aortic stenosis, and calcium deposits on the brain.
Vitamin E	Studies suggest a link between vitamin E deficiency and preeclampsia.
Vitamin K	Deficiency associated with neonatal bleeding tendencies.
Thiamine (vitamin B_1)	Acute deficiency leads to Wernicke's encephalopathy in women with severe nausea and vomiting of pregnancy.
Pyridoxine (vitamin B_6)	Vitamin B6 intake is used to treat nausea, vomiting of pregnancy. Low levels are associated with decreased APGAR scores.
Folic Acid (vitamin B_9)	Severe deficiency causes maternal megaloblastic anemia. Subclinical folate deficiency in early pregnancy contributes to fetal malformations including neural tube defects, oral clefts, and cardiac anomalies. Excess folic acid intake can mask vitamin B12 deficiency.
Ascorbic Acid (vitamin C)	Essential for optimal iron absorption. Studies suggest an association with preeclampsia and premature rupture of membranes. Excess intake may lead to "rebound scurvy" in neonates.
Calcium	Essential for fetal bone development.
Copper	Placental insufficiency and intrauterine death have occurred in association with deficiency states.
Iodine	Deficiency leads to mental impairment in infant (cretinism); may contribute to more subtle cognitive and developmental deficits; increases risk of miscarriage and stillbirth.
Iron	Iron deficiency anemia increases risk of low birth weight, preterm birth, perinatal mortality.
Magnesium	Supplementation reduces incidence of preeclampsia and intrauterine growth retardation.
Zinc	Inadequate zinc has been linked to intrauterine growth retardation, congenital malformations, perinatal death, impaired immunological, and cognitive development.

From refs. *7–9*.

Table 4
Pharmacologic Treatment of Medical Conditions During Pregnancy

Medical Condition	Common Drugs Prescribed in Pregnancy	FDA Drug-Risk Category	Drug–Nutrient Interaction Considerations
Hypertension	1) Methyldopa	1) B	1) ↓ methyldopa bioavailability with iron administration
	2) Hydralazine	2) C	2) Food increases hydralazine levels May ↑ pyridoxine requirements
	3) Labetalol, propranolol, metoprolol	3) C	3) Food enhances bioavailability of metoprolol and propranolol
	4) Nifedipine	4) C	4 a) Altered or diminished taste perception b) Grapefruit juice may ↑ nifedipine concentration
Diabetes	Insulin	B	Follow prescribed diet to avoid hypo/hyperglycemia
Nausea and Vomiting	1) Pyridoxine 2) Promethazine 3) Meclizine 4) Prochlorperazine 5) Metoclopramide	1) A 2) C 3) B 4) C 5) B	Treatment of nausea and vomiting may help prevent nutrient deficiencies
Dyspepsia and Gastroesophageal reflux	1) Antacids	1) B	1 a) ↓ iron absorption b) Aluminum-containing products ↓ phosphate c) Copper deficiency d) Folate malabsorption
	2) Sulcralfate	2) B	2) May ↓ fat soluble vitamin absorption
	3) H2 receptor blockers	3) B	3 a) Chronic use may lower B_{12} levels b) Hepatic vitamin D activity is reduced.
	4) Metoclopramide	4) B	
Constipation	1) Psyllium products 2) Docusate	1) B 2) C	1) Reduced absorption of riboflavin
Uncomplicated Urinary Tract infection	1) Sulfamethoxazole with trimethoprim	1) C (do not use near term)	1 a) Alcohol may cause disulfiram reaction b) Trimethoprim may interfere with folate metabolism
	2) Nitrofurantoin	2) B	2) Bioavailability increased by food
	3) Cephalexin	3) C	
	4) Amoxicillin with clavulanate	4) B	

From refs. *1,4,20–22.*

3. SUMMARY OF DNIs IN PREGNANCY

In pregnant women with poor dietary intake, deficiency of any vitamin or mineral may occur. However, a pregnant woman with good dietary intake may place herself and her fetus at risk for nutrient deficiency if a drug is administered and a DNI is not identified or recognized. When administering a drug to a pregnant woman, the risk to the fetus must be assessed. If a DNI has been reported with the prescribed drug, then management of this interaction is advised *(23)*. First, the short- and long-term clinical consequences of the interaction must be identified. If symptoms or laboratory changes are anticipated, the pregnant women should be monitored appropriately. Second, if dosage adjustments for the drug or affected nutrient are warranted, the necessary changes should be made and the mother should be monitored closely. Third, it should be determined whether alternative therapy is an option to help minimize the exposure of the mother and fetus to drug therapy and the potential DNI. Any unfortunate outcome of pregnancy should be investigated to include the possibility of a DNI as an etiologic factor. With a properly balanced diet, administration of a prenatal vitamin every day, exposure to drugs only when necessary, and recognition of DNIs, fetal growth is enhanced and the risk for pregnancy-related complications is minimized.

4. CONSIDERATIONS IN LACTATION

Although there are many drugs that cannot be taken during pregnancy without risking potential harm to the developing fetus, the risk may be less to the child if the drug is taken by the mother while breastfeeding. This section reviews information to consider when evaluating the use of medication in breastfeeding women and the nutritional implications. In most cases, the mother can be treated without harm to the baby while she continues to breastfeed, although more study is likely required for a number of drugs.

Because breastfeeding is important for the well-being of the mother and the baby, health care professionals need to be aware that very few maternal medications pose a problem for the breastfeeding baby. Babies who are fed artificial baby milk have more infections, are hospitalized more often, have more allergies, are more likely to be obese, are more likely to be diabetic, have more dental caries, and have more cancers. Mothers who do not breastfeed are at greater risk for osteoporosis, diabetes, urinary tract infections, rheumatoid arthritis, and gynecological cancers.

The American Academy of Pediatrics states that breastfeeding is the preferred feeding for all infants, including premature and sick newborns, with rare exceptions *(24)*. Babies should be fed human milk exclusively for 6 mo *(25)*. Human milk should be the major source of the baby's calories during the first year. Somewhere between 12 mo and 18 mo, other appropriate foods become the major source of the child's calories. For ideal nutrition and optimal health, breastfeeding should continue beyond the child's second birthday *(25)*.

During the childbearing years, various situations might arise requiring a woman to use a medication. Drugs will be detected in her milk *(26)*. For the most part, less than 1% of the maternal dose will reach the milk *(26)*. In general, medicines that can be given to an infant can be given to the breastfeeding mother. Very few maternal medicines are known to cause problems for the breastfeeding baby, although little data are yet available for

most drugs. This chapter focuses on the known and potential interactions that can occur in the setting of breastfeeding. This may include the increase or decrease in breast milk production in the mother as a result of drug use, the interaction between the milk components and drugs that appear in the breast milk, the altered bioavailability of drug or breast milk nutrients when administered to the baby simultaneously, and changes in the breastfeeding habits of the baby resulting from medication.

5. BARRIERS TO DRUG TRANSFER

5.1. Mechanisms to Protect the Baby

There are several factors that keep drugs from entering the baby's blood stream. The size of the molecule may be too large to pass into the milk such as with insulin and heparin. Drugs that bind appreciably to circulating protein (e.g., ibuprofen) may not pass into the milk in any significant amount. Drugs not orally bioavailable in adults, and administered by injection, may end up in breast milk with insignificant quantities being absorbed by the nursing infant (e.g., gentamicin). Some medicines are sequestered in the baby's liver. Inhaled and topical medicines usually do not enter the bloodstream of the mother in large amounts, and would not be considered likely to end up in the breast milk.

Although the level of medicine in maternal blood is often considered the most useful piece of information, much also depends on the drug's distribution from blood to breast milk, its residence time there, and the timing of blood levels relative to drug administration along with the frequency and duration of nursing. All this would help in estimating the amount of the drug that could actually reach the baby. When the drug is eliminated from the maternal blood, it is less likely to appear in the milk. Knowing when the drug peaks can help in the timing of when to take the medicine. This may be less helpful in cases of chronic medication use when therapeutic levels are maintained throughout the dosing interval. It is preferable to avoid breastfeeding when the drug level in the maternal blood is at its highest. In general, the best plan is to take the medicine right after breastfeeding so the peak will come before the next feeding. Drugs available to the infant through the breast milk that possess a long half-life in the infant can potentially accumulate (e.g., meperidine and caffeine) because the baby cannot excrete them rapidly. It is better to use medications with a short half-life, and it is best to stay away from time-release drugs. Some drugs such as iodides concentrate in breast milk, and can cause hypothyroidism in the breastfed infant (27).

5.2. Age of the Baby

The newborn liver is immature. As the baby grows and the organs mature, drugs are assimilated better. A premature or ill infant can be at a greater risk. Once the baby is 6 mo old and taking other foods in addition to milk, there is less concern than when human milk is the only source of nourishment.

During the first 4 d after birth, large spaces between the alveolar cells in the breast allow for drugs to pass directly into the milk. Gradually the spaces decrease so that usually by the 14th d postpartum, tight junctures between the alveolar cells block this pathway. If drugs enter into the milk, they must travel through the cells.

6. DRUGS TRANSFERRED INTO BREAST MILK

The American Academy of Pediatrics publishes a list of medications and their impact on the breastfeeding infant about every 5 yr *(28)*. The most recent publication groups the drugs into the six following categories:

1. Cytotoxic drugs that may interfere with cellular metabolism of the nursing infant.
2. Drugs of abuse for which adverse effects on the infant during breastfeeding have been reported.
3. Radioactive compounds that require temporary cessation of breastfeeding.
4. Drugs for which the effect on nursing infants is unknown but may be of concern.
5. Drugs that have been associated with significant effects on some nursing infants and should be given to nursing mothers with caution.
6. Maternal medication usually compatible with breastfeeding *(28)*.

6.1. Cytotoxic Agents

Chemotherapy drugs (cyclophosphamide, cyclosporine, doxorubicin, and methotrexate) may cause immune suppression and an abnormal decrease in the number of neutrophils in the blood. These drugs can pose problems for the breastfeeding infant. Some women can return to breastfeeding between chemotherapy treatments depending on the drug used and the dosing schedule.

6.2. Drugs of Abuse

Women taking street drugs should not breastfeed as drugs of abuse (amphetamine, cocaine, heroin, and marijuana) are detrimental to the baby. There are reports of vomiting, irritability, seizures, and death. In the past, mothers on methadone treatment were told they should not breastfeed. More recent research has shown low levels detected in the breast milk, so today more and more mothers on methadone maintenance therapy are breastfeeding their babies *(29,30)*.

6.3. Radioactive Compounds

Radioactive compounds require temporary cessation of breastfeeding. Many studies can be done without using a radioactive material. However, if nuclear studies are indicated, the nuclear medicine physician can select the radionuclide with the shortest excretion time in breast milk. Before the study, the mother should collect the extra milk that is in the breasts after breastfeeding and gradually over several days or weeks store enough milk in the freezer for feeding the infant until the radioactive material would no longer be in her milk. After the study, to maintain her milk production, the mother should pump her milk *(28)*. This milk can be stored in the freezer until it is no longer radioactive *(31)*. Milk samples can be screened by the radiology department for radioactivity before resumption of breastfeeding *(28)*.

6.4. Specific Drugs of Concern

The effects of drugs on the breastfed infant are in some cases known, but in others unknown. As a result, some suggestions can be made. For analgesic agents, ibuprofen is preferred to aspirin, and morphine is preferred to meperidine.

Pseudoephedrine may reduce the milk supply. One study showed the mean milk volume was reduced 21% after taking a single dose (60 mg) of pseudoephedrine *(32)*.

Therapeutically equivalent agents (e.g., cromolyn and topical nasal steroids) would be preferred *(30)*. Loratadine and cetirizine would be the antihistamines of choice because they have a minimal sedative effect on the baby *(30)*.

Sulfonamide drugs are used much less than they once were. They should not be given to breastfeeding mothers of infants under 1 mo of age, particularly to premature or acutely ill neonates, because they may increase free bilirubin, the form that enters the central nervous system. "Infants with glucose-6-phosphate dehydrogenase (G6PD) deficiency should never receive sulfa drugs directly or via the breast milk" *(26)*, as these infants are unable to conjugate bilirubin for lack of the proper enzyme.

Oral contraceptives may reduce milk supply and nitrogen content. Nonhormonal forms of birth control are preferred during lactation. If a woman wants to use a hormonal method while breastfeeding, she should wait for at least 6 wk until her milk supply is well established *(33)*. The baby needs to be monitored closely for weight gain. The progestin-only mini pills are preferred. Once the woman begins the mini pill, if there is an impact on milk production, she can discontinue use. The issue with injections and implants is that they cannot be easily discontinued once administered. Birth control containing estrogen is not recommended, because it may reduce the milk supply. Estrogen-containing patches and vaginal rings are not recommended for lactating women, nor is emergency contraception with estrogen.

There are some drugs that increase milk production as a side effect. Metoclopramide and domperidone are both dopamine antagonists that increase prolactin levels, so some women experience an increase in milk production. Metoclopramide has the side effect of causing severe depression for some people, so domperidone is preferred (not currently available in the United States). One study of 16 mothers of premature babies reported a daily milk volume increase by 43% after 7 d on domperidone *(34)*.

7. OTHER INTERACTIONS TO CONSIDER DURING LACTATION

Foods to avoid while breastfeeding are individual in nature; however, some common sensitivities are noted here.

7.1. Flavors of Foods

Flavors and odors of foods the mother eats also enter the breast milk and transfer to the infant. Mennella found that babies exposed to the variety of smells and flavors from breast milk were more accepting of foods when first introduced into their diets *(35,36)*. In fact, when milk had a garlic smell, babies drank more milk than usual *(37,38)*.

Foods in the cruciferous family such as broccoli, cauliflower, and cabbage have been reported to cause colic symptoms in some young infants *(39)*. This same report also implicated onions, cow milk, and chocolate. However, most women find they can consume these foods without problems for their babies.

7.2. Allergy

Casein, the chief protein in cow's milk, can cause gastrointestinal discomfort for sensitive infants *(40)*. Peanut allergies are becoming more prevalent. If there is a strong family history of specific food allergies on either side of the family, it would be prudent

for the mother to avoid these foods during pregnancy and lactation *(41,42)*. Food allergies on the whole are less common in breastfed infants as compared to formula-fed infants *(43)*.

7.3. Ethanol

Alcohol goes directly to the blood and directly to the milk. However, one of its metabolites, acetaldehyde, does not apparently distribute into the breast milk. When mothers ingest alcohol, babies take less milk and sleep for a shorter length of time *(44,45)*. One alcohol-containing beverage on a full stomach and sipped over several hours should not be a concern for breastfeeding. When the alcohol level decreases in the bloodstream, it also decreases in the milk; therefore, a woman does not have to express her milk just to get rid of the alcohol. Some women express milk before consuming alcohol and use previously pumped milk to bottle-feed the infant. If they miss a feeding or two, they express their milk at the same time as their babies are being fed the previously pumped milk. Expressed milk that is pumped immediately after consuming a beverage quickly will contain alcohol and should be discarded. The general recommendation is to wait 2 h per drink. A drink is defined as 12 ounces of beer, 8 ounces of wine, or 1.5 ounces of hard liquor. Because alcohol alters judgment, a mother who is drinking at home should have a nondrinking adult care for her baby.

7.4. Caffeine

Caffeine is a stimulant and does enter breast milk in small amounts. Excessive intake by the lactating mother can cause the caffeine to accumulate in the infant who excretes caffeine poorly and may cause irritability and restlessness in the infant. Many women can consume caffeine in moderation (approx 300 mg/d) without adverse affects to their breastfed infants once the infants are over 2 mo old and are able to excrete it better. Coffee, tea, green tea, cola, and chocolate are the most commonly consumed foods in this category (Table 5). Decaffeinated varieties are readily available in the United States and should be used in place of caffeinated varieties whenever possible.

Many lactation professionals will recommend that a mother pump and discard the next feeding if excessive caffeine has been consumed. Although this should not be a regular practice, it certainly reduces the risk of passing unwanted caffeine to the breastfed infant. Previously pumped milk can be used in its place. If the mother does not have any previously expressed milk, occasional intake of breast milk with caffeine would be healthier for the baby than an artificial baby milk, so the mother should breastfeed.

7.5. Environmental Contaminants

Another concern during lactation is environmental contaminants. Consumption of fatty fish with high levels of mercury should be avoided. Foods heavily treated with pesticides that are not on the generally recognized as safe list should be avoided as well. When in doubt, the practitioner should discourage use of questionable foods or substances. Organic foods do not contain chemicals or the risk of pesticides and are considered a safe and reasonable choice during lactation.

7.6. Smoking

Smoking is strongly discouraged for breastfeeding mothers. Research shows that lactating women who smoke produce less milk, and the milk has a lower fat content than from mothers who do not smoke *(46)*. Smoking while breastfeeding also puts the infant

Table 5
Caffeine Content of Foods and Beverages

Food	Amount	Type	Caffeine
Coffee	5 oz cup	Brewed:	
		Drip	110–150 mg
		Percolated	40–70 mg
		Decaffeinated	2–5 mg
		Instant:	
		Freeze dried	40–108 mg
		Decaffeinated	2–3 mg
Tea:	Steeped for 1 to 5 min	Hot or iced	20–50 mg
Colas:	per 12 oz container		20–75 mg
Chocolate:	5 oz hot chocolate		2–50 mg
	1 oz chocolate		
	1 cup chocolate ice cream		

at risk for other harmful factors such as burns and second-hand smoke inhalation. Because the need for vitamin C is greatly increased in smokers, women who smoke and breastfeed should be sure to include extra sources of vitamin C or supplement to meet their needs. Of course, supplementation cannot correct a poor lifestyle habit. When assessing risks vs benefits, it is important to note that breastfed children who live in homes with smokers have fewer pulmonary problems than those who are formula fed, so it is better for the infants to be breastfed *(31)*.

8. NUTRIENT DEFICITS

Vegan mothers are those who consume only plant foods—grains, legumes, vegetables, and fruits. All animal products are eliminated including eggs and dairy products. A vegan mother needs to include a source of vitamin B_{12} in her diet, so her breastfed infant will not have permanent neurological damage *(47)*. Anemia in the infant born to a mother with low B_{12} stores will develop over a period of 3 to 6 mo. Vitamin B_{12} is a water-soluble vitamin, but unlike other water-soluble types it is stored in the liver and can be retained by the body for long periods.

The reports of megaloblastic anemia associated with vitamin B_{12} deficiency are inconsistent *(48)*. It may take several years to develop this deficiency. The richest source of B_{12} is found in meats or animal flesh. Eggs and milk can also provide a lesser quality source. Vitamin B_{12} is naturally found in manure, so foods fertilized with manure may actually contain microorganisms rich in B_{12} and therefore be inadvertently consumed by humans (depending on the degree of sanitation associated with the preparation and food handling). Fermented soybean products, tofu, miso, and tempeh, provide some vitamin B_{12} to vegetarians *(49)*.

A totally breastfed infant may need a vitamin D supplement, if the infant is not exposed to sunlight or is dark-skinned and living in a northern climate *(50)*.

9. USE OF HERBAL MEDICINES

The use of herbal teas and treatments is becoming more popular in the mainstream and can be a great concern during lactation. Many herbs are found in OTC products and

remedies, but the FDA does not regulate medicinal herbs. The misconception is that a "natural" herbal constituent is safe, but herbs can be dangerous if not used properly. A knowledgeable health care professional should be consulted before taking any herbs.

Several herbs are considered to be galactagogues (milk increasing)—such as *Allium sativum* (garlic) and fenugreek. Others are antilactagogues (milk decreasing)—such as *Salvia officinalis* (sage). Some herbal constituents such as berberine notably present in Goldenseal and Oregon Grape are known to cross the blood–milk barrier. Berberine is noted to displace bound bilirubin and high doses have been considered to increase the risk of neonatal kernicterus *(51)*.

An herbal remedy should be researched thoroughly before consumption to avoid unpleasant or dangerous side effects. For example, excessive amounts of licorice can alter potassium levels and ginseng alters consciousness *(31)*. It is important to note that certain herbs interact with many medications as well. Therefore, even if the herb is considered safe during lactation, it may not be compatible with a prescribed medication or an OTC preparation. To reiterate, the advice from a knowledgeable health care professional can be most valuable when it comes to individual products, their safety and interaction potential.

Some health care practitioners disregard herbal therapies; however, some herbal preparations have been the basis for pharmaceutical development and can have quite serious side effects. A complete screen should include questioning patients on use of herbals, teas, other remedies, and diet, so that proper education can be conducted. Also, reserving personal comments on the topic and maintaining professionalism could make all the difference in establishing good patient–professional relationships and improving outcomes.

10. SURGERY

After anesthesia, breastfeeding mothers can safely breastfeed once they feel awake and alert *(30)*. Because human milk is digested rapidly, the breastfeeding infant requiring surgery needs to fast for only 3 h *(52–54)* before surgery.

11. SUMMARY OF INTERACTION CONSIDERATIONS IN LACTATION

It is recommended that the health care practitioner consult several of the resources listed in Table 6 before prescribing a drug for a breastfeeding woman. It is considered detrimental to tell a woman she must stop breastfeeding to take a needed drug, because in most cases there is a safe alternative. Her milk is medicine for her baby, and all energies should be expended to assure her child receives her milk, unless the drug in the milk would pose more of a problem to the infant than the known risks of not receiving his own mother's milk. Also the health risk–benefit ratio for the mother should be taken into consideration. There are many studies showing healthier outcomes for women who have breastfed. It is rare for a woman to need to wean in order to take medication.

Available resources for information are listed in Table 6. More information is awaited on the large number of drugs used during breastfeeding and interaction potential in terms of milk production, nutrient components of milk, drug bioavailability in the presence of breast milk, and changes in breastfeeding habits due to medication use in the infant.

Table 6
Additional Resources for Clinicians

Articles
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Textbooks
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5. USP DI®. Volume I: Drug Information for the Health Care Professional, Micromedex/Thomson Health Care, Greenwood Village, CO, 2003.

CONCLUSION

Consideration needs to be given to the potential for DNIs in all pregnant or lactating women. This is especially important in those with marginal nutritional status or requiring several medications. The effect of each drug on the fetus or the nursing infant should be evaluated prior to administration, while recognizing that much information has yet to be generated. Any required adjustment to therapy or monitoring suggested by the available data should be performed to limit the risk of adverse outcome. Addressing or preventing an interaction can optimize outcome of the fetus or infant.

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20 Drug–Nutrient Interactions in the Elderly

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1. INTRODUCTION TO DRUG USE AND THE ELDERLY

1.1. Definitions and Demographics

The elderly are more prone to experience drug–nutrient interactions (DNIs) given their higher use of medication, chronic and cumulative disorders, and the likelihood of marginal nutritional state. The elderly, arbitrarily defined as those 65 yr of age and older, constitute approx 14 % of the US population. By the year 2030, the elderly cohort will grow to approx 20% of the nation's population, with the "old-old" cohort, aged 85 yr and older, being the most rapidly growing segment of the population [1]. Elder adults are the most heterogeneous population with respect to physical, social, and health status [2]. The rate at which an individual ages is variable, and how well an individual ages is also variable, being dependent on both genetic and environmental factors [2]. For instance, one 75-yr-old gentleman may be viewed as being a frail elder if he is suffering from chronic disease and disability, whereas another 75-yr-old gentleman may be viewed as having aged "successfully" if he has limited disease and disability [3,4]. Frailty refers to a loss of physiologic reserve that makes a person susceptible to disability from minor stresses [5]. Rockwood and colleagues evaluated the many different proposed definitions of frailty by different authors and suggest that any definition that is used must include multisystem impairment, instability, change over time, an association with aging, and an associated increased risk of adverse outcome [6]. Successful aging has been described as a process by which deleterious effects are minimized and function is preserved [4]. Therefore, chronological age is not as descriptive as physiological age when assessing the health status of an individual.

The elderly have the highest rate of acute illness, as well as chronic illness and disability [7,8]. The prevalence of chronic disease states increases with age [9], with 80% of the elderly population having at least one chronic condition at any point in time [10]. Chronic conditions that lead to disability include heart disease, stroke, chronic obstructive pulmonary disease, diabetes, arthritis, osteoporosis, and visual and hearing impairments [11].

The use of medications can often accomplish prevention, cure, or palliation of disease. Because the elderly are often afflicted with multiple chronic disease states and related disability, they use a disproportionate amount of medication.

1.2. Medication Usage in the Elderly

Older adults use approx 33% of the nation's prescription and nonprescription medications *(12)* even though they only comprise about 14% of the U.S. population. A newer statistic suggests the average elderly uses 40% of all over-the-counter (OTC) medications sold in the United States *(13)*.

Data on drug use in the elderly may vary with clinical setting, cohort age, and year of evaluation. A detailed regional survey of both institutionalized and ambulatory elderly conducted nearly two decades ago revealed that drug use was significantly higher in the former with 9% taking 10 or more drugs daily *(14)*. The impact of drug use on nutritional status was discussed with virtually all the most frequently used medications of that time associated with nutritional alterations *(14)*. Unfortunately, no simultaneous assessment of nutritional status was performed in the patients surveyed. Even 10% of rural elderly use five or more prescription drugs at a given point in time *(8)*. Indeed, as has been repeatedly shown since, the average number of agents used increases with age with an average of 4.4 drugs for those 80 yr old and above. The number has increased over the years, too. Recent data indicate that 91–94% of ambulatory adults age 65 and older use medications, 44–57% using 5 or more, and 12% using 10 or more medications *(15)*.

Given the commonplace finding of multiple medication usage in the elderly, it would seem difficult to fathom that medications may be underutilized in the aged. Yet, there is a lot of literature to support the fact that some effective medications are actually underused in the elderly in certain instances. Much of such data exists in the cardiovascular literature including the underuse of β-blockers, angiotensin-converting enzyme inhibitors (ACEIs), and warfarin despite evidence to support their efficacy in reducing cardiovascular events in the elderly and despite consensus statements advocating their use *(16–24)*.

The type of medication most commonly used by the elderly depends on the setting. Studies examining community-dwelling elders found they use analgesics, diuretics, cardiovascular medications, and sedatives often, whereas nursing home residents use psychoactive medications most often, followed by diuretics, antihypertensives, analgesics, cardiovascular medications, and antibiotics *(8,9,25–27)*. One well-known study sought to examine the pharmacoepidemiology of prescription medication use in community-dwelling elderly living in rural Pennsylvania. The authors found that among more than 900 participants, over 71% reported taking at least one prescription medication. The old-old participants reported taking more cardiovascular agents, anticoagulants, vasodilating agents, potassium supplements, and diuretics than the younger elderly *(8)*.

Self-treatment with OTC medications is common, especially for chronic disease states whose prevalence increases with age, such as arthritis and constipation. The most frequently used OTC medications are analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), insulin, and gastrointestinal (GI) products such as laxatives, and dietary supplements.

In addition to high utilization of prescription and OTC medications, use of dietary supplements is also increasing. Dietary supplements, as marketed in the United States,

encompass products that contain nutrients (e.g., vitamins, minerals, amino acids), herbals (e.g., ginkgo, St. John's wort, garlic), and other substances (e.g., glucosamine, chondroitin, melatonin). Common dietary supplements include multivitamins, vitamin E, vitamin C, calcium, gingko, ginseng, garlic, saw palmetto, and St. John's wort *(28–31)*. Reasons listed for increasing popularity and utilization include high prices of medications and patient dissatisfaction with conventional medication and treatment *(32,33)*. One study that investigated the use of dietary supplements in older veterans found that 50% of respondents reported using one or more such products (vitamins, minerals, and herbals) within the previous 3 mo *(31)*. Another such study found that 17% of elderly patients were currently using a vitamin, mineral, or herbal supplement and that 29% of patients had tried such a product within the past 3 yr *(29)*. Although many elderly may consume nutrient-type supplements, this cannot be viewed as replacement for an inadequate diet. Certainly, many of the beneficial compounds found in food are not vitamins or minerals but phytochemicals whose combination in the diet may not be duplicated in a pill. Vitamin and mineral supplement intake is often highest in those with the best dietary intakes of those nutrients, setting the stage for potentially deleterious effects of excessive dosing. For example, although pharmacologic doses of vitamin E may play a role in modulating insulin action in the elderly, it may also increase the risk or severity of infection in older individuals *(34,35)*.

Additionally, many of the non-nutrient dietary supplements, including the herbal medicines, are not regulated closely for safety and product quality and may increase the risk to elders. A recent survey identified that 40% of Americans use vitamins/minerals and 14% use herbal and other non-nutrient supplements *(15)*. A closer look at the ambulatory elderly population revealed that 47–59% use vitamins/minerals and 11–14% use non-nutrient supplements *(15)*. Other recent surveys of the elderly provide similar findings of supplement intakes between about 25 and 50% *(36–38)*.

Given the large number of medications consumed by the elderly, their potential risk for drug–supplement–nutrient interactions may be significant. A recent report identified that 54% of elderly patients using non-nutrient dietary supplements with their medication regimen were taking at least one drug–supplement combination that could cause an interaction *(36)*. These patients consumed an average of six prescription medications and three dietary supplement products. The most commonly used supplements in this group of elderly included garlic, glucosamine, ginkgo, saw palmetto, chondroitin, and coenzyme Q. It bears keeping in mind that many interactions involving dietary supplements are based on case reports or theoretical grounds, and that no prospective evaluation exists to identify the true prevalence or clinical relevance of many of these interactions (*see* Chapters 11 and 12).

1.3. Barriers to Health Care

Although the use of medication can benefit elders, the aged are presented with many barriers to health care. The following barriers are interestingly similar to recognized barriers to adequate nutritional status. These barriers include lack of transportation, being too ill and immobile to seek treatment, lack of adequate health insurance, misperception that certain symptoms and problems are normal with aging, perceived unresponsiveness by the medical system (inadequate parking, abbreviated encounters with clinicians, inconve-

nient office locations), depression, denial, isolation, and atypical presentation of illness leading to underrecognition and underreporting of disease. An excellent example of atypical presentation of illness is offered by Williams *(39)* in which the presence of arthritis masks heart failure owing to inability to ambulate and to stress the heart. Another example is that of angina. Canto and colleagues examined the health records of 4000 elderly patients with a diagnosis of unstable angina, which characteristically presents with crushing, substernal chest pain. In their study, more than 50% of patients with confirmed unstable angina had no chest pain. Rather, they presented with other symptoms, such as nausea and labored breathing and these patients tended to be treated less aggressively *(40)*.

1.4. Drug-Related Problems in the Aged

In addition to the aforementioned general barriers to healthcare and nutrition, the elderly are also at risk of specific drug-related problems (DRPs). These can include adverse drug reactions, withdrawal events, medication error, overdose, therapeutic failure, nonadherence and inappropriate medication use, and drug interactions that may encompass DNIs *(41,42)*.

1.4.1. Risk Factors for Adverse Drug Events

An adverse drug event (ADE) is an adverse event, expressed as a sign, symptom, or laboratory abnormality, in which a drug is suspected and plausible *(43)*. Several definitions also exist for adverse drug reactions—a subset of ADEs *(44–48)*. The geriatric population is at particularly high risk of developing ADEs, including DNIs, for several reasons. The most consistently reported risk factor for ADEs in the literature is polypharmacy and the risk of ADE increases exponentially as the number of medications increases *(43,49–52)*. Other associated or suspected risk factors for ADEs include comorbidity *(53,54)*, history of ADE, changes in pharmacokinetics *(53)* and pharmacodynamics, nonadherence and fragmented health care *(43)*. It is controversial whether age, in and of itself, is a risk factor for ADEs and is probably not *(55,56)*.

The prevalence rates of ADEs in the community has been shown to range from 2.5% to as high as 50.6%; in long-term care, 9.5–67.4%; and in the hospital setting, 1.5–44% *(43,49–52,54,57–59,61,62)*. Analysis of self-reported ADEs in community veterans showed that cardiovascular (33.3%), central nervous system (27.8%), musculoskeletal (9.7%), respiratory (5.6%), endocrine (4.2%), and GI (2.8%) medications were most likely to cause an ADE *(57)*. Analysis of ADE associated with hospital admissions in patients 50 yr and older showed medications associated with ADE and hospitalization were corticosteroids, digoxin, NSAIDs, antihypertensives, and benzodiazepines. The number of medications was also associated with a risk of ADE leading to hospitalization ($r = 0.77$, $p < 0.001$). The number of diseases on admission has also been correlated to risk of hospitalization ($r = 0.81$, $p < 0.026$) *(52)*.

The cost of ADEs has been studied. It is estimated that for every dollar spent on medication in a nursing facility, \$1.33 is spent treating a DRP *(63)* and that in the ambulatory setting, the cost of DRPs was approximated to be \$76.6 billion *(64)*. Clearly, DRPs are common in the elderly and costly to the health care system *(65)*.

Many ADEs are thought to be preventable. A study of hospitalized elderly showed that compared to their younger counterparts, the elderly had a higher rate of preventable ADEs (5.3 vs 2.8% in their younger counterparts, $p = 0.001$). The authors suggest this was

the result of more complex medical issues in the elderly rather than of less aggressive or appropriate care *(55)*.

1.4.2. MEDICATION APPROPRIATENESS

Because the elderly utilize a disproportionate percentage of medications and are at risk of developing a host of DRPs, a panel of geriatric experts developed a list of medications they feel should best be avoided in the elderly. This list, developed by Beers and colleagues, is known as the Beers' criteria *(66)*. Using the Beers' criteria, nearly 25% of community-dwelling elderly patients received potentially inappropriate medications *(65,67–69)*. Based on an evaluation of a national database, it is estimated that the elderly are prescribed at least one potentially inappropriate medication at 4.5% of the more than 10 million outpatient visits they make *(70)*. If we turn our attention to nursing home residents, we find that ADEs occur in 22% with as many as 20,000 life-threatening or fatal events annually in the United States, many of which are preventable *(71)*. Often, the drugs themselves are not so much the problem as is the way in which they are used *(72)*. One potentially confounding issue is that many of the drugs found listed in the Beers' criteria are now seldom used. Newer agents may need to be accounted for, and the influence of many of these medications has not been as well documented vis-à-vis nutritional implications. Patients in long-term care facilities can be at considerable risk for DNIs, where drug use averages five agents per patient per month placing them at risk for about two potential interactions in that time *(73)*. Many of the interactions identified relate to the GI tract or those that impact upon electrolyte status.

Medication appropriateness in the elderly is a concept popular with the provision of pharmaceutical care *(74–80)*. The screening and evaluation of drug interactions is one component in ensuring medication appropriateness, and should encompass screening for DNIs *(81,82)*. Because drug interactions are common, it is important for the clinician to be knowledgeable about an interaction, to recognize an interaction, to understand its potential implication, and to determine an appropriate course of action in the management of a potential interaction.

Recognizing the benefits and risks associated with medication therapy, the goal of pharmacotherapy is to promote successful aging by maintaining functional independence, preventing disability and iatrogenic disease, and increasing the health-related quality of life of patients. As mentioned earlier, polypharmacy, and changes in physiology, pharmacokinetics and pharmacodynamics can potentially lead to the development of DRPs and require further discussion.

2. REVIEW OF BASIC SCIENCE

2.1. Changes in Physiology

Age-related changes in physiology that occur result in a functional decline of organ systems and homeostatic mechanisms, at variable rates in different patients *(2,39,83,84)*. The resultant decline in reserve capacity can impair an individual's ability to respond to physiologic stress and to "bounce back" from illness. Functional decline ensues and progresses and independence is jeopardized. The clinical implication of some of these physiologic changes is readily apparent and impacts on the provision of safe medication therapy, whereas others less directly affect medication therapy. What follows is a select

Table 1
Age-Related Physiologic Changes

Organ System	Physiologic Change
Body composition	↓ Total body water
	↓ Lean body mass
	↑ Body fat
	↓ Albumin
	↑ α_1-acid glycoprotein
Integument	↓ Collagen and elastin leading to epithelial and dermal thinning and wrinkling
	Changes in pigmentation due to loss of melanocytes
	↓ Number of melanocytes in the hair bulbs
	↓ Number of hair follicles
Skeletal system	Osteopenia
Sensory changes	↓ Accommodation of the eye lens, causing presbyopia
	↓ Peripheral vision from glaucoma and night-time vision
	Macular degeneration leading to loss of central vision
	Cataracts
	Presbycusis (high-frequency hearing loss)
	↑ Threshold for smell, taste, pain, and temperature
Central nervous system	↓ Brain mass and increase in neuronal apoptosis
	↓ Neurotransmitters (some)
	↓ Cognitive abilities (some)
Cardiovascular system	↓ Cardiac mass
	Loss of myocytes and subsequent hypertrophy
	↓ Myocardial sensitivity to β adrenergic stimulation
	↓ Baroreceptor function
	↓ Maximal cardiac output with exercise
	↑ Total peripheral resistance
	Delayed diastolic relaxation
Pulmonary system	↓ Lung mass
	↓ Respiratory muscle strength
	↓ Chest wall compliance
	↓ Functional alveolar surface area
	↓ Tidal volume leading to decreased response to hypercapnia and hypoxia
	↓ Forced expiratory flow rates
Oral changes	Altered dentition
	↓ Ability to taste sweet, sour, and bitter
Gastrointestinal system	↓ Lower esophageal sphincter pressure
	Potential ↑ in gastric pH
	Delay in gastric emptying
	↓ Gastrointestinal blood flow
	↓ Intestinal mucosal surface area

Table 1 (continued)

Organ System	Physiologic Change
Liver	↓ Liver mass
	↓ Blood flow leading to decreased presystemic metabolism of medications with high extraction ratios
Renal system	↓ Renal mass and blood flow
	↓ Renal tubular function (secretion)
	↓Glomerular filtration
	↑ Filtration fraction
Genitourinary system	Atrophy of the vagina
	Hyperplasia of the prostate
	Potential predisposition to urinary incontinence
Endocrine system	Atrophy of the thyroid gland and ↑ incidence of thyroid disease
	↑ Incidence of diabetes mellitus
Immune system	↓ Cell mediated immunity

From refs. *2,3,39,85–106*.

review of changes that are clinically evident and/or that have an impact on nutritional status and the delivery of pharmacotherapy, namely the GI, hepatic, renal, CNS and sensory changes (Table 1).

2.1.1. GASTROINTESTINAL SYSTEM

Oral ulcers and poor dentition occur often in the elderly although they are probably secondary to poor hygiene and other diseases rather than to aging itself *(3)*. Nonetheless, 50% of elderly patients have an ulcerative, hyperplastic, or atrophic oral lesion *(3)*. The occurrence of these can have an impact on pharmacotherapy because some medications can contribute to oral disease such as phenytoin, corticosteroids, immunosuppressants, and certain antibiotics. Oral ulcers and poor dentition may also affect nutritional status due to decreased oral intake.

Xerostomia, or dry mouth, is also common in the elderly and can be exacerbated by any medication exhibiting anticholinergic properties such as antihistamines, decongestants, ipratropium, antipsychotic agents, certain antidepressants, and urinary anticholinergic/antispasmodic agents, among others. Xerostomia is problematic in the elderly because it is particularly disturbing to patients, it can contribute to dental caries and it can cause difficulty in swallowing medications and food *(95)*.

Other changes in the GI tract include achlorhydria, delayed gastric emptying, and a modest decrease in the intestinal mucosal surface area *(3,96)*. Theoretically, these changes may affect the extent or rate of absorption of certain medications. However, in most instances, this is not of clinical relevance. Moreover, one study by Hurwitz and colleagues suggest that basal gastric hypoacidity in healthy elderly may not be as common as previously thought *(97)*.

2.1.2. HEPATIC SYSTEM

Hepatic mass declines by approx 40% by age 80 *(2)*. This decrease in mass and in hepatic blood flow has the potential to decrease the metabolism of certain medications

(96,104). Medications that are most affected include those that undergo a large first-pass metabolism (e.g., fentanyl, propranolol) *(107)*, whereby the medication is metabolized by the liver before it is absorbed systemically. Medications with a large first-pass metabolism primarily rely on (hepatic mass and) blood flow for systemic clearance. In the case of decreased hepatic blood flow and decreased first-pass metabolism, the extent of absorption of these medications may be increased. Conversely, medications with a low hepatic extraction *(107)* (e.g., phenytoin, warfarin, valproic acid), primarily rely on hepatic size and enzymatic activity for systemic clearance. Changes in hepatic physiology as a result of aging itself are difficult to quantify as diet, ethanol, tobacco use, and medications also contribute to changes in drug metabolism *(108)*.

2.1.3. RENAL SYSTEM

The physiological decline of the kidney and its implications are probably the most evident of organ systems with respect to altered medication handling. With age, there is a decrease in renal blood flow, kidney mass, and number of functioning glomeruli *(102,109)*. There are also renal tubular and vascular changes that lead to declining renal function *(102,109)*. In general, creatinine clearance starts to decline in the fourth decade of life at a rate of approx 1 mL/min/yr *(110)*. The serum creatinine concentration may appear normal or unchanged in the aged despite true renal dysfunction *(111)*. This is observed because a decrease in the clearance of creatinine is offset by a decrease in creatinine production, owing to a decline in muscle mass in the aged *(109)*.

2.2. Changes in Pharmacokinetics

Pharmacokinetics is the study of medication absorption, distribution, and elimination from the body. The changes in physiology described here are, in part, responsible for changing the way the elderly body handles the absorption, distribution, metabolism, and excretion of medications. Thus, the study of aging on pharmacokinetic parameters was undertaken in the early 1970s *(104)*. According to Crome and Flanagan, pharmacokinetic studies were and are conducted in the aged for three main reasons: (a) to study the effect of aging on metabolism, (b) to facilitate an appropriate choice of dose and dosing interval of a medication, and (c) to minimize the risk of toxicity from the medication in clinical practice *(104)*. This information may be utilized to identify risk factors for DNIs in the elderly.

When pharmacokinetic studies were first conducted, little was known about pharmacokinetic changes in the elderly because the participation of elderly patients in clinical and pharmacokinetic trials was very limited. When the elderly were included in pharmacokinetic studies, the percent of elderly participating was small; healthy elderly were enrolled; and single-dose pharmacokinetic studies were employed, which in most instances did not reflect the clinical scenario in which the medication would be used.

Presently, the US Food and Drug Administration (FDA) mandates that the elderly are represented in clinical trials so that more can be learned about the differing pharmacokinetic effects of a particular medication in the young and the old. It also mandates that pharmacokinetic and pharmacodynamic information derived from studies (either formal pharmacokinetic studies or pharmacokinetic screens) in the elderly be described in the product labeling under a specific section devoted to geriatric use of the medication *(112)*.

The study of the pharmacokinetic profiles of medication in the elderly has increased substantially since the 1970s. What is more, present pharmacokinetic studies are, in general, employing more multicenter, multidose designs. A literature search for pharmacokinetics in the elderly identified many entitled "Pharmacokinetic Study of [drug] in the Elderly" *(113–117)*. Despite this, the number of elderly included relative to young patients is still very small and those studies evaluating only elderly patients are very small studies, often with less than 20 patients. Moreover, the elderly included are rarely 75 yr and older. This is important to recognize given the known heterogeneity of the population. Moreover, clinical recommendations made on the basis of limited pharmacokinetic data is difficult. Sproule and colleagues highlight this disconnect in their review of lithium pharmacokinetics in the elderly *(115)*. They highlight that even though there is some pharmacokinetic data on lithium in the aged, there have been no placebo-controlled studies of lithium in the elderly so clinical recommendations are based on extrapolation of small pharmacokinetic studies and anecdotal reports of lithium use in the geriatric patient *(115)*. Likewise, Solomon and Gurwitz reviewed available pharmacokinetic data of different NSAIDs and found inconsistent findings when comparing pharmacokinetic data of a particular NSAID in different studies *(118)*. They suggest nonuniform assay techniques and study design may be some reasons why the data were inconsistent. They also state that there are no clinical or epidemiological studies to support the pharmacokinetic data, making clinical recommendations about the role of age as an independent risk factor for NSAID-induced complications unclear *(118)*. Indeed, much more information is needed about pharmacokinetic changes in the elderly, the implication of those changes and how to recommend changes in clinical therapy based on this information. What follows is a review of what is known about basic pharmacokinetic changes in the elderly (Table 2).

2.2.1. ABSORPTION

As described earlier, there are several GI changes that occur with aging. The effects that these changes have on drug absorption are thought to be minimal in most instances, as few drugs have been demonstrated to have a significantly decreased rate or extent of absorption *(166)*. There is also little evidence to suggest that such changes in absorption have a clinically significant effect on pharmacological efficacy or safety.

An exception to this are medications absorbed by active transport (e.g., calcium) whose decrease in absorption may be significant *(96,123,124)*. Some researchers suggest the decreased absorption of calcium is associated with decreased production and activation of vitamin D, or resistance to its effects *(125,126)*. Water-soluble vitamins are probably absorbed normally, including the absorption of vitamin B_{12} in patients without gastric atrophy *(96)*.

Little is known about the transdermal absorption of medications in the elderly. One small study analyzed the pharmacokinetics of a transdermal fentanyl patch in elderly patients vs young patients and found that the elderly patients required early patch removal because of side effects that were not observed in their younger counterparts. The study also found that higher serum concentrations accompanied the side effects observed in the elderly patients *(127)*. Finally, the absorption of medications with high first-pass metabolism may be increased and this is addressed further in the discussion of changes in drug metabolism.

Table 2
Summary of Pharmacokinetic Changes in the Elderly

Pharmacokinetic Parameter	Pharmacokinetic Change
Absorption	Rate of absorption affected more than extent of absorption
	Passive absorption unaffected
	Active absorption may be affected
	↑Bioavailability of medications with high first-pass effect
	Little evidence to suggest absorption changes result in clinically meaningful changes in outcome. Rarely is the dose adjusted prospectively
Distribution	↓ Albumin leading to increased free concentration of acidic medications that are highly protein bound (≥90%)
	↑ a_1- Acid glycoprotein leading to decreased free concentrations of basic medications
	↑ Distribution of lipid-soluble medications potentially leading to lower blood concentrations and longer half-lives
	↓ Distribution of water-soluble medications potentially leading to higher blood concentrations
	Changes in volume of distribution primarily impact on the loading dose of a medication with a dose-related response
	Rarely is dose adjusted prospectively
Metabolism	Medications with high extraction rates are most affected in the elderly; a decrease in extraction occurs leading to higher bioavailability (e.g., fentanyl, propranolol, verapamil) Rarely is dose adjusted prospectively
Excretion	Pharmacokinetic parameter most clinically affected
	Decline in estimated creatinine clearance despite potentially "normal" serum creatinine value; "normal" serum creatinine reflects decrease in production of creatinine rather than normal renal function
	Dose is commonly adjusted prospectively for decreased estimated creatinine clearance

From refs. *107,108,119–122.*

2.2.2. DISTRIBUTION

With age, body composition changes such that there is an increase in total body fat and a decrease in total body water and lean mass in the elderly. This change in composition affects the distribution of medications in the elderly. Although there are exceptions, in general, the volume of distribution of water-soluble medications such as digoxin *(116)*, ethanol *(116)*, cimetidine and lithium *(115)* is decreased because of the decrease in total body water *(108)*. This leads to higher plasma concentrations of these medications and the potential need for lower initial doses. Sproule and colleagues reviewed the differential pharmcokinetics of lithium in elderly patients *(115)*. Their study suggests that lithium pharmacokinetics are influenced by age with the elderly requiring approx 30% less of a dose to achieve similar concentrations as those observed in the young *(115)*. This observation is likely the result of changes in volume of distribution, namely an increase in body

fat and a decrease in body water resulting in a smaller volume of distribution of this water soluble medication. The opposite is generally true of lipid soluble medications. Because there is a relative increase in total body fat in the aged, the distribution of these medications can be increased and the plasma concentrations decreased but they are slower to leave the fat compartment for excretion. Thus, the half-life of these medications can sometimes be increased (depending on other variables as well, such as blood flow) and accumulation can occur. Examples of such lipid-soluble medications are diazepam and chlordiazepoxide.

Changes in protein binding also affect the distribution of medications in the elderly. A decrease in albumin concentration, owing to age itself or more commonly, chronic disease, can result in higher free concentrations and increased clearance of otherwise highly protein bound (>90%), acidic medications. Often times, this is of little clinical significance. However, there are a few acidic, highly bound medications in which the increase in free concentration is noteworthy, including that of naproxen, phenytoin, valproate, and warfarin *(108)*. Highly bound medications (>90%) have the potential to interact with other medications via competitive protein binding and they often possess other physicochemical properties, such as low extraction by the liver, and small volumes of distribution that together create a profile of a medication known as a narrow therapeutic index. Medications with narrow therapeutic indices are medications in which the difference between blood levels needed to achieve efficacy and toxicity is small. Phenytoin, valproate, and warfarin are classic examples of such medications with a narrow therapeutic index. Thus, vigilant monitoring of patients on these medications is the standard of care.

2.2.3. Metabolism

The metabolism of some medications in the elderly is decreased, whereas that of others is largely unaffected. Hepatic metabolism is affected by changes in hepatic mass, hepatic blood flow, and hepatic enzyme activity. In general, the metabolism of medications that undergo phase I reactions (such as oxidation, reduction, dealkylation, and hydroxylation) is decreased, whereas medications undergoing phase II reactions (such as glucuronidation, sulfation, and acetylation) are unaffected *(103,107,108)*. For example, some of the benzodiazepines such as diazepam and chlordiazepoxide, are metabolized by phase I oxidation. The metabolism of these medications appears to be prolonged and thus these agents can accumulate in the elderly, potentially leading to toxicity (an increase in volume of distribution without changes in clearance can also increase half-life). However, lorazepam, oxazepam, and temazepam do not undergo phase I reactions and are not expected to accumulate. They are, therefore, the preferred benzodiazepines for use in the aged, although it is important to note that the elderly are particularly sensitive to the anxiolytic and sedative effects of all benzodiazepines as a result of changes in pharmacodynamics, which will be discussed later *(108)*.

As mentioned earlier, some medications, when administered orally, are metabolized by the intestines and liver before they are able to reach the blood stream for distribution and effect. This process is called first-pass metabolism. In the elderly, however, a decrease in metabolic capacity and hepatic blood flow leads to an increase in bioavailability of these medications with high extraction ratios (e.g., fentanyl, propranolol, verapamil) *(108)*. Because these medications are highly extracted from the liver,

clearance is primarily dependent on (hepatic mass and) blood flow. Medications that have a low extraction rate from the liver rely on liver mass and functional activity of hepatic enzymes for clearance. Medications with intermediate hepatic clearance rely on hepatic enzyme activity, hepatic mass, and blood flow for hepatic clearance *(107)*. Medications that are usually highly extracted from the gut into the liver for metabolism in the young are those that are most affected by a decrease in presystemic metabolism and an increase in absorption in the aged. Examples of these medications include propranolol, verapamil, and fentanyl.

In the cytochrome P450 (CYP) enzyme system, CYP3A4 is the most prevalent isozyme and is responsible for metabolizing the largest percentage of medications. It is important to know which medications are metabolized by the 3A4 isozyme and other isozymes, so that drug–drug interactions and DNIs can be identified. The clinician could also check for other factors that are known to affect the metabolism of certain medications, such as diet, tobacco, and ethanol use.

2.2.4. EXCRETION

As discussed earlier, the age-related decline in renal function and therefore the renal elimination of medications is of great clinical importance. Glomerular filtration is decreased in the elderly and its decline can be estimated by measuring the creatinine clearance *(108,119–121)*. An actual measurement of creatinine clearance via the 24-h collection of urine is often not feasible and may produce inaccurate results in patients with urinary incontinence and urinary retention. Therefore, the decline in glomerular filtration is often estimated using a creatinine clearance equation *(128)*.

A decrease in the clearance of renally eliminated medications in the elderly may lead to an increase in the area under the concentration-time curve (AUC), an increase in half-life, and an increase in steady-state concentrations, which may lead to toxicity. Therefore, many medications need to be dose-adjusted based on the extent of decline in the creatinine clearance *(108,119–121)*. Examples of such medications include allopurinol, gabapentin, many antibiotics, histamine$_2$ receptor antagonists (H$_2$RAs), digoxin, amantadine, and pramipexole, to name a few.

2.3. Changes in Pharmacodynamics

Pharmacodynamics is the study of the effect of a medication on its target site at a given concentration *(49,108)*. The study of pharmacodynamics in the elderly is limited to only a few medications or medication classes, most notably the benzodiazepines, β-adrenergic agents, calcium channel antagonists, opiate analgesics, and warfarin, however, most clinically relevant DNIs involve changes in pharmacodynamics *(108,129)*. The pharmacodynamic changes that are observed with these medications in the aged are thought to be the result of changes in the intrinsic sensitivity of the elderly to these agents, rather than to changes in pharmacokinetics. Such changes in intrinsic sensitivity are thought to occur at the drug–receptor complex, such as changes in receptor number, receptor affinity or alterations in postreceptor events. It is here that interactions, including DNIs, may take place mechanistically *(84,122)*. The clinical effect of these changes is either an increased response or a decreased response to the above agents or classes.

Elderly patients are thought to exhibit an increased response to benzodiazepines, opioid analgesics, and warfarin *(84,103,108,130,131)*. They have been shown to inhibit more vitamin K-dependent clotting factor synthesis at similar plasma warfarin levels

than their younger counterparts and are often able to achieve a therapeutic international normalized ratio (INR) at lower doses than younger patients *(132)*. The clinician should routinely check for drug–drug interactions and DNIs as many medications and foods are known to inhibit the metabolism of warfarin and increase the risk of bleeding.

Conversely, the elderly tend to exert an attenuated response to β-adrenergic agonism and antagonism and are therefore less responsive to β agonist and β antagonist medications *(84,103,122,133)*. Finally, the effects of calcium channel antagonists are also changed in the elderly. Although the elderly possess a heightened response to the anti-hypertensive effects of calcium channel antagonists, they also exhibit an attenuated response to the effects of calcium channel antagonists on cardiac conduction, as evidenced by a decreased atrioventricular node blockade *(84,108,129)*.

In a guidance document, the FDA states that the number of pharmacodynamic differences to date is too small to warrant separate pharmacodynamic studies in the elderly as a routine requirement. Yet, one can argue that the reason why there is little known differences in pharmacodynamics between the young and old is because there has been little investigation into potential differences. The FDA does recommend separate studies in sedative/hypnotics, psychoactive medications, and in instances in which phase II/III studies suggest large differences in safety or efficacy in elderly vs younger patients *(134)*.

Presently, more clinical studies are being conducted in the elderly to examine the effects of a particular medication in the aged. Sometimes, these studies compare the effects of the medication in the young vs the old so they employ a large age range in the study, and other studies evaluate geriatric patients only. One such example is a study done by Antonicelli and colleagues; they conducted a small, open-label, crossover study evaluating the effectiveness of extended-release felopidine on controlling 24-h ambulatory blood pressure. They employed 35 elderly patients (mean age 69 ±4 yr) *(135)*. Although the study was open-label and small and did not include patients 75 yr and older, their commitment to evaluating elderly patients was promising. Another recent study specifically studied the tolerability of candesartan and hydrochlorothiazide in patients exclusively over 75 yr of age in a multicenter, double-blind, randomized, parallel group study *(136)*. Given the increased attention to the growing elderly population in the United States and around the world, and to the increased attention of the need to increase geriatric participation in clinical trials, we will likely see more controlled studies evaluating greater numbers of the elderly in the future.

2.4. Changes in Nutritional Status

Social, psychological, and environmental factors are all considered in assessing the elderly beyond the traditional patient history and physical examination. As eluded to earlier, an assessment of functional status is critical. Similarly, nutritional status is central to all these pieces of the patient assessment and needs to be included for each individual. All health care professionals involved in the care of geriatric patients can at least screen them for poor nutritional status when a clinical nutrition expert is unavailable.

Malnutrition is evident in many older persons for a variety of reasons—some physiological and others pathological *(137)*. Addressing malnutrition can prevent morbidity including the increased risk of infection, pressure ulcers, poor wound healing, weakness, falls, osteopenia, macular degeneration, disturbed drug metabolism, cognitive deficits, and mortality that is associated with poor nutritional status. The ability to identify those

with malnutrition or at risk for malnutrition is therefore important. Serum albumin levels, an independent risk factor for all-cause mortality, likely reflect frailty and disease severity more than they reflect nutritional status in the elderly *(138)*.

A number of screening tests are available to help identify poor nutritional status in the elderly. These range from the simple SCALES evaluation (Table 3), to slightly longer screening tools. The DETERMINE checklist using a 10-item form, can be used easily even by a non-health care provider. The level I screen that follows that checklist, although still easy, requires a health care provider *(139)*. The Mini-Nutritional Assessment (MNA) is another rapid yet more sophisticated tool useful for identifying elderly patients with poor nutritional status *(140)*. The MNA has excellent sensitivity and specificity while being both reproducible and easy to administer *(141)*. Furthermore, it may be applied to healthy, frail, and sick elderly. A comparison of several screening tools is available *(141)*. Any of these tools can be used to quickly identify those at risk for poor nutritional status. Most screening tools include "medication use" as a vital portion of the overall score. Pharmacists practicing in community settings are more likely than others to routinely engage the elderly and are therefore in a good position to screen their nutritional risk and identify DNIs. Given the relationship between malnutrition and poor outcome, all efforts at assessing nutritional status in the elderly are necessary and must include evaluation of DNIs.

Poor nutritional status may be defined by protein-calorie undernutrition, overnutrition, dehydration, or imbalances of specific nutrients determined by clinical history, physical examination and laboratory findings. Clinically trained pharmacists can also provide nutrition assessments in elderly patients under their care *(142)*.

2.4.1. Rates of Malnutrition in the Elderly

Both institutionalized elderly and those dwelling in the community are at risk for malnutrition, global or nutrient-specific. It has been estimated that malnutrition, defined predominantly as protein-calorie undernutrition, occurs in about 15% to as high as 25% of community-dwelling elderly, in as many as 65% of hospitalized elderly, and 85% of those in long-term care institutions *(137,143,144)*. This does not include those with micronutrient (electrolyte, vitamin, and mineral) deficits or excesses. With age, there may be decreased nutrient absorption, distribution, metabolism, and excretion. Deficits in dietary intake of micronutrients are more likely than macronutrients in elderly subjects living in institutions *(145)*. More than 90% of these subjects did not meet the Recommended Dietary Allowance (RDA) for vitamin E, calcium, and folate, whereas additionally more than 80% of the men did not meet the RDA for pyridoxine and zinc. Rates of poor vitamin A or zinc status in the elderly may approach 20 and 25%, respectively *(144)*. Together, these alterations in nutritional status can impact negatively on immune function, contributing to the risk of infection in this population *(144)*. For example, a study of community-acquired pneumonia in the elderly suggest that as many as 85% of the patients were malnourished *(146)*. A prospective follow-up study of elderly patients admitted emergently to a hospital for non-cancer medical reasons revealed not only that 20% were malnourished, but also that the mortality rate at 9 mo in the malnourished group was 44% compared to 18% in the nonmalnourished patients ($p < 0.001$) *(147)*.

Although protein-calorie and micronutrient deficits are associated with increased morbidity and mortality, the obese elderly are also at risk for morbidity and diminished

Table 3
Screen for Malnutrition

S—Sadness
C—Cholesterol < 4.14 mmol/L (160 mg/dL)
A—Albumin < 40 g/L (4 g/dL)
L—Loss of weight
E—Eating problems (cognitive or physical)
S—Shopping problems, or inability to prepare a meal

From ref. *137.*

Table 4
Etiology of Weight Loss

M—Medication(s)
E—Emotional problems (depression)
A—Alcoholism, anorexia, or abuse of elders
L—Late-life paranoia
S—Swallowing problems (dysphagia)

O—Oral problems
N—No money for food, counseling, or care (poverty);
       nosocomial infections

W—Wandering, and other dementia-related behavior
H—Hyperthyroidism, hyperparathyroidism, hypoadrenalism
E—Enteric problems, including malabsorption
E—Eating problems, including inability to feed oneself
L—Low-salt, low-cholesterol and other therapeutic diets
S—Social problems, including ethnic preferences, isolation, etc.
       Shopping and meal preparation problems

From refs. *105,137,143,148.*

quality of life. Data suggest the presence of a dysregulation of the feeding response with age *(148)*. There is also a decrease in lean body mass (sarcopenia) with aging. This may be accounted for in part by the physiological anorexia of aging with central and peripheral mechanisms *(148)*.

Aside from general protein-calorie deficits and altered hydration, many elderly individuals have micronutrient deficiencies. The latter include the vitamins pyridoxine, cobalamin, calciferol, and folic acid, and the minerals calcium, magnesium, and zinc. These nutrient deficits can result from reduced food intake, or altered nutrient absorption, metabolism and excretion, or both. The nonphysiologic causes of malnutrition, identified through weight loss, can be the result of social, psychological, and/or medical causes. A popular pneumonic for identifying the major treatable causes of malnutrition in the elderly, MEALS ON WHEELS (Table 4) begins with "Medication" *(105)*. At the most basic level, those drugs implicated in weight loss in the elderly can be identified among virtually all pharmacological classes. They include drugs that induce anorexia, malabsorption, or hypermetabolism (Table 5).

Table 5
Medications That May Produce Weight Loss in the Elderly

Mechanism of Weight Loss	*Medication*
Dysphagia	Aldendronate
	Anticholinergics
	Antineoplastics, immunosuppressants
	Corticosteroids
	Iron
	NSAIDs
	Potassium
	Quinidine
Nausea, vomiting,	Amantadine
diarrhea or anorexia	Amiodarone
	Anesthetics
	Antibiotics (most)
	Antineoplastics
	Cimetidine
	Colchicine
	Digoxin
	Erythromycin
	Iron salts
	Levodopa
	Lithium
	Metformin
	Metronidazole
	NSAIDs
	Nutritional supplements
	Opioids
	Phenothiazines
	Potassium salts
	SSRIs
	Spironolactone
	Theophylline
	Tricyclic antidepressants
	Vitamin D
Altered gastric emptying	Anticholinergics
Delayed gastric emptying	Caffeine
	Calcium channel blockers
	Clonidine
	Dicyclomine
	Iron
	Meperidine
	Nitrates
	Opiates
	Oxybutynin
	Theophylline
	Tricyclic antidepressants
	Verapamil

Table 5 (continued)

Mechanism of Weight Loss	Medication
Increased gastric emptying	Bethanachol
	Erythromycin
	Laxatives
	Metoclopramide
	Misoprostol
Altered taste or smell	Albuterol
	Allopurinol
	Amiloride
	ACEIs
	Antihistamines
	Aspirin
	Bismuth
	Captopril
	Carbamazepine
	Chloral hydrate
	Chlorpropamide
	Digoxin
	Diltiazem
	Dipyridamole/aspirin
	Enalapril
	Flurazepam
	Iron
	Levodopa
	Lithium
	Metformin
	Metronidazole
	Nifedipine
	Opiates
	Penicillin
	Phenytoin
	Propranolol
	Thioridazine
Drowsiness (missed meals)	Antidepressants
	Antiemetics
	Antihistamines
	Antipsychotics
	Benzodiazepines
	Skeletal muscle relaxants
Depression	Anticonvulsants
	Barbiturates
	Benzodiazepines
	Beta blockers
	Clonidine
	Digoxin
	Levodopa
	Neuroleptics

Table 5 (continued)
Medications That May Produce Weight Loss in the Elderly

Mechanism of Weight Loss	Medication
Dry mouth	Antihistamines
	Anticholinergics
	Antipsychotics
	Benzodiazepines
	Diuretics
	Decongestants
	Tricyclic antidepressants
Malabsorption	Cholestyramine
	Colchicine
	Ganglionic blockers
	Laxatives, including sorbitol
	Methotrexate
	Neomycin
Hypermetabolism	Pseudoephedrine
	Theophylline
	Thyroxine, thyroid extracts, tri-iodothyronine

NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; ACEIs, angiotensin converting enzyme inhibitors. (From refs. *137,253–255*.)

Among homebound elderly, the intake of several nutrients (magnesium, vitamins E and C, zinc, vitamin B_6, folate, vitamin B_{12}) is inadequate relative to the estimated average requirement in at least 25% of subjects *(149)*. Most concerning was that 95% of women did not meet the adequate intake level for calcium, and all but one subject had vitamin D intakes below the adequate intake level. Vitamin D deficits are associated with declines in muscle function, which impacts upon mobility and increases the risk of falls in the elderly *(150)*.

2.4.2. Risk Factors for Poor Nutritional Status in the Elderly

Risk factors for poor nutritional status in the elderly are numerous, with some data suggesting that two-thirds of independently living elderly are at significant risk *(151)*. Given that more than 9.5 million elderly live alone in the United States, and their risk of being found helpless or worse in the home is 3.2% per year, there is clearly more to be done in terms of assessing this population more seriously *(152)*. The risk of malnutrition in the elderly occurs with depression, oral disorders, dementia, concurrent illnesses, and the medications used to manage them. Poor micronutrient status in turn may be responsible for some of the cognitive dysfunction seen in the elderly *(153,154)*. Given the fortification of the U.S. food supply with folic acid in recent years, concerns have arisen about potentially irreversible neurologic dysfunction in the elderly with marginal vitamin B_{12} status without apparent hematologic signs *(155)*. The increasing costs of prescription drugs for the elderly may be associated with reduced spending on food. Although this interaction does not meet the definition for a DNI, it remains a relevant issue in the current U.S. health care system.

2.4.3. Altered Nutrient Disposition in the Elderly

Although knowledge about optimal nutrition for the elderly is far from complete, differences between the young and old are seen. Indeed, in recent years more attention has been directed at specific nutrient-dosing standards for the elderly *(156)*, which have for the most part been reflected in the most recent dietary reference intake volumes *(157)*. Coming to a consensus on requirements in the elderly necessitates reviewing and interpreting the available data in the elderly. Interpreting biochemical indices of nutritional status in the elderly may be difficult because of the confounding by disease and by medications that are being used *(158)*. Many nursing home residents are reported to have low vitamin blood levels, which may be accounted for by poor intake as well as drug-induced alterations *(159)*. The clinical consequence of low circulating levels is likely less important than low levels of functional indices of vitamin status. For example, despite serum vitamin B_{12} levels in the normal range, many elderly may have clinically manifest, functional cobalamin deficits based on serum methylmalonic acid and homocysteine levels *(160,161)*. Although pyridoxine status is reported to decline with aging, the data suggest that decreased intake, bioavailability, or total body clearance are unlikely to explain the alteration *(162,163)*. Depending on the assay method used, the prevalence of vitamin B_6 deficits in the elderly may be as high as 86% *(164)*. There exist age-dependent differences not only in nutrient requirements per se, but in the established ratio of one nutrient to another. For example, the dose of vitamin B_6 required per gram of protein intake is lower for the elderly than for younger individuals *(165)*. Does this relationship change when consuming medications that alter pyridoxine status? What about the growing number of genetically engineered foods that may contain higher amounts of one or more nutrients in them?

Drug-induced nutritional problems can occur as a result of decreased food intake (inability to shop and prepare food owing to altered mental status, as well as drug-induced oral problems and anorexia), malabsorption, altered metabolism, and excretion. These are more likely to occur in individuals with marginal nutritional status to begin with. The elderly are at high risk for many reasons including prolonged and chronic illnesses, the regimens used to manage them, and reduced dietary intake with age. Drug reactions could include altered taste and smell, which would impact on food selection and intake. Drug reactions that include lightheadedness, breathlessness, joint pain, or impaired visual acuity could restrict food shopping or preparation, whereas loss of appetite and adverse drug effects on the GI tract can limit food intake and absorption *(142)*.

Energy expenditure decreases with advancing age because of less physical activity and a lower metabolic rate. The latter is partially owing to sarcopenia seen in many. Energy requirements can be met at intakes of about 25 kcal/kg daily on average, whereas protein requirements remain at about 1 g/kg daily for the elderly. Fluid (water) needs of about 30 mL/kg per day remain important for the elderly to prevent significant consequences of dehydration. Compared with younger adults, the elderly have different requirements for a number of micronutrients (e.g., higher calcium, vitamin D, vitamin B_6, and vitamin B_{12} requirements, lower chromium and vitamin A requirements) based on altered absorption, circulating levels, physiological measures, metabolism, or excretion.

The effects of food/nutrients on drug disposition and effect in the elderly was extensively summarized at an international conference on nutrients, medications, and aging *(166)*. In that conference, the authors described the effects of food on absorption, diet components on enzyme induction, protein on metabolism, and malnutrition on metabolism *(167)*.

Drug-induced malnutrition is concerning given the findings of marginal nutritional status in many elderly. What follows includes a review of those medications consumed by many elderly that can affect food intake, nutrient absorption, nutrient metabolism, and nutrient excretion. Alcohol and caffeine are considered as pharmacologically active substances as well.

3. CLINICAL EVIDENCE

3.1. Mechanisms and Consequences of DNIs

DNI is an interaction, which results from a physical, chemical, physiological, or pathological relationship between a drug and a nutrient, multiple nutrients, or food in general. The interaction is considered significant from a clinical perspective if therapeutic response is altered or if nutritional status is compromised (168). The elderly are at risk for DNIs because they use a disproportionate amount of prescription and OTC medications, and they often are instructed to take their medications with breakfast and dinner to increase adherence. DNIs may occur via multiple mechanisms. The presence of food may alter drug bioavailability, in which case the rate and or extent of absorption may be affected. In most instances, food alters the rate at which a medication is absorbed, whereas the extent of absorption remains largely unaffected. A delayed rate of absorption is only important if it is necessary to achieve a rapid effect or if a high peak concentration is required quickly. For most chronic therapies, the rate of absorption is less important because a steady-state blood level is likely attained and maintained. In general, if rapid, high blood levels are needed, medication can be taken 1 h before or 2 h after food to avoid an interaction.

The mechanism of DNI may be by food acting as a physical barrier to drug absorption, by altering gastric emptying rate, or by reacting physicochemically with the drug (chelation, precipitation). In general, fatty meals decrease motility and gastric emptying rate, increasing the time the medication spends in the stomach. This may be important if the drug is unstable in an acidic environment or if rapid absorption is required. Conversely, small meals and liquid meals empty rapidly and may decrease time available for absorption.

The effect of food on altered drug metabolism or excretion can also serve as the mechanism between DNIs (169–176).

DNIs in elderly diabetics (177) and elderly cardiac patients have been reviewed and guidelines provided (178). The risks vary not only depending on the medications used, but also on dietary patterns and organ function. The consequence of these interactions in the diabetic, for example, includes hyperglycemia, hyperosmolar hyperglycemic state, neuropathies, and hypoglycemia with risk of pseudostroke (177). In patients with cardiovascular disease, multiple risks for DNIs exist that involve reduced drug absorption, as well as drug-induced edema, anorexia, and micronutrient deficits (178).

3.2. Ethanol, Nicotine, and Caffeine DNIs

Alcoholism is a problem that is underrecognized in the elderly population (179), when in fact, widowers over 75 yr of age have the highest rate of alcoholism in the country (180). Prevalence rates of alcohol-related problems in the aged vary depending on the definition, and method of measurement. Estimates range from 1 to 6% for community-

dwelling elderly, 7 to 22% for hospitalized elderly, from 28 to 44% in patients admitted to psychiatric units *(181)*. Detecting alcohol-related problems in the elderly is often difficult because symptoms may be confused with other medical conditions and using changes in social and work functioning as an indicator of alcohol abuse is often not applicable in the aged *(181)*. Several scales and questionnaires have been developed to detect alcohol abuse and have been assessed specifically in the elderly *(182–184)*.

Alcohol is related to a myriad of health problems including liver disease, alcoholic dementia, neuropathy, depression, insomnia, loss of libido, late-onset seizure disorder, incontinence, diarrhea, myopathy, heart failure, poor self-care, hypertension, and falls/ fractures. Alcohol can also cause poor nutrition as a result of poor oral intake, which can lead to the depletion of micronutrients such as folate, thiamine, pyridoxine, zinc, magnesium, and selenium. Alcohol also affects lipid metabolism and can lead to the development of adverse reactions owing to alcohol–drug interactions *(181,185)*.

Reid and colleagues suggest that theoretically there are many mechanisms in which alcohol can cause functional impairment in the elderly including trauma, osteoporosis, malnutrition, lack of control of chronic disease states, and drug–alcohol interactions. Functional impairment owing to alcoholism can lead to DNIs by way of decreased self-care abilities that lead to decreased food acquisition, preparation, and intake. The authors suppose that alcohol and DNIs can impair physical, cognitive, and functional abilities in elderly patients so they sought to examine the relationship between alcohol use and functional disability in cognitively impaired patients (Mini Mental State Examination [MMSE]). The authors retrospectively investigated the use of alcohol in 242 patients in a hospital-based geriatric center and found that heavy drinkers (>14 drinks/wk) had higher basic activities of daily living scores and lower instrumental activities of daily living scores. Of note is that only 6% of the patients were heavy drinkers. Moderate drinkers (>1 and <14) had higher basic and instrumental activities of daily living scores. They state their study suggests that the effects of alcohol in elderly patients with cognitive impairment is complex. The authors recorded concomitant medications but did not comment on potential drug–alcohol interactions. Because these patients were cognitively impaired, it is likely that some of the patients would have been on psychoactive medications that would presumably interact with alcohol *(185)*. Such ethanol–drug interactions can in turn contribute to the development of DNI. For example, any psychoactive medication has the potential of interacting with alcohol by augmenting its CNS effects, such as sedation and confusion, which could lead to inadequate food preparation and intake and altered nutritional status.

Nicotine interacts with several medications that in turn, interact with foods. For instance, nicotine increases blood viscosity and fibrinogen levels, and it thereby decreases the effectiveness of warfarin, an anticoagulant *(186)*. Warfarin also interacts with many vitamin K-containing foods. Vitamin K is needed to produce clotting factors, thus foods containing vitamin K decrease the effectiveness of warfarin. Ingestion of warfarin with nicotine and foods high in vitamin K may lead to suboptimal anticoagulant effect.

Caffeine is probably the most frequently and widely consumed drug *(187)*, but it is often thought of as a dietary constituent rather than a drug and is therefore thought of as being generally safe. Yet, caffeine (1,3,7-trimethylxanthine) is a CNS stimulant that has been implicated in various diseases and can be associated with toxicity when taken in excessive amounts. Effects of caffeine taken in excess include GI effects, headaches,

palpitations, angina, nervousness, insomnia, delirium and seizures, and decreased appetite, all of which can decrease nutritional intake. Caffeine is not only present in many foods and drinks, but it is also present in some migraine medications and OTC medications, particularly pain relievers. Therefore, it can be easily taken in excess in various forms.

Not only is caffeine a common substance in foods and medication, making cumulative intake easy, but it can interact pharmacokinetically and pharmacodynamically with many medications. Caffeine is metabolized primarily by the CYP1A2 isozyme. Therefore, it has the potential to interact with many medications also metabolized by the same isozyme *(187)*.

Pharmacodynamic caffeine interactions include increased risk of hypokalemia with other medications known to cause hypokalemia, such as diuretics and corticosteroids; increased GI side effects of medications such as NSAIDs, corticosteroids, and ethanol, which may lead to changes in appetite; and increased CNS stimulation with other stimulants such as theophylline, β-agonists, and decongestants, which may also affect appetite *(186)*.

3.3. Grapefruit Juice DNIs

Grapefruit juice, a common beverage consumed by many, carries the American Heart Association's healthy "heart check" food mark and contains compounds that may both reduce atherosclerotic plaque formation and inhibit cancer cell proliferation *(188,189)*. In recent years, grapefruit juice has been shown to interact with many medications *(188–192)*. Because grapefruit juice is often consumed with breakfast when most medications are given, a scenario is set for many potential or actual DNIs to occur. The most notable drug interactions with grapefruit juice are its effects on cyclosporine, some dihydropyridine calcium channel blockers, and some HMG-CoA reductase inhibitors. (*See* Chapter 9 for a more complete discussion.)

Grapefruit juice is believed to be an inhibitor of the CYP3A4 intestinal enzyme, but not in the liver, for several reasons. First, grapefruit juice is known to interact with medications that undergo metabolism by the CYP3A4 in the small bowel. Second, grapefruit juice increases AUC, with minimal if any change in clearance or half-life. Third, in standard doses, grapefruit juice has no effect on the pharmacokinetics of medications administered intravenously. Wide interpatient variability exists in the effects of grapefruit juice. Patients with the highest concentrations of CYP3A4 in the intestine display the greatest effects from grapefruit juice.

Although the majority of grapefruit juice studies have been conducted in healthy, young patients, the interaction between felodipine and grapefruit juice has been evaluated in the elderly population *(192)*. Twelve healthy elderly people (70–83 yr of age) were evaluated in an unblinded, crossover study. Subjects were administered 5 mg felodipine extended release (ER) with grapefruit juice or water in a single-dose study. Six of these then received 2.5 mg felodipine for 2 d followed by 5 mg felodipine for 6 d with 250 mL grapefruit juice or water. Steady-state concentrations of felodipine, and concentrations of felodipine metabolite, dehydrofelodipine were measured as were blood pressure and heart rate for 24 h after single dosing and after repeated dosing. Mean AUCs were 2.9-fold ($p < 0.001$) and 4-fold ($p < 0.05$) greater with grapefruit juice in both studies. Interindividual variability in the extent of the interaction was high. Half-life was not altered. Systolic and diastolic blood pressures were lower with grapefruit juice in the

single-dose study ($p < 0.01$ for systolic blood pressure and $p < 0.001$ diastolic blood pressure), whereas they were not different between groups at steady state. Heart rates were higher with grapefruit juice in both studies but this effect was greater and more prolonged at steady state ($p < 0.01$). This study demonstrates an instance in which a pharmacokinetic and a pharmacodynamic DNI with grapefruit juice occurred.

The authors concluded that normal dietary amounts of grapefruit juice produced a pronounced, unpredictable sustained interaction with felodipine by reducing its presystemic metabolism in the elderly. The study suggests that the elderly should be cautioned about concomitant grapefruit juice and felodipine ingestion. Because the elderly are more susceptible to hypotensive events, the authors state it is particularly important to caution against periodic consumption of grapefruit juice with felodipine. This warning would apply to any time of day during drug therapy as an interaction can still occur with a normal amount of grapefruit juice consumed as much as 24 h before felodipine *(192)*.

3.4. Warfarin DNIs

Warfarin is an anticoagulant used to prevent thromboembolic events. Elderly people are widely thought to be at increased risk for warfarin-related bleeding and are often less likely to be treated with warfarin, in part because of concern regarding adherence with monitoring and bleeding risk *(193–195)*. Pharmacodynamic studies in the elderly suggest geriatric patients are intrinsically more sensitive to the anticoagulant effects of warfarin than are their younger counterparts *(84,103,108)*. Thus, elderly patients often necessitate a lower dose of warfarin than younger patients to achieve the same goal INR *(194)*. The elderly patient who is at risk for falls or who has a history of falls is often not perceived to be a good candidate for warfarin because a resultant bleed can occur after a fall *(17)*. Elderly patients may be nonadherent with either warfarin administration or with blood testing needed for INR monitoring.

Warfarin interacts with numerous medications and foods. Thus, it is important to identify patients who may not comply with warfarin therapy or other drug therapies because sporadic use of medications or foods that interact with warfarin can lead to clinically important changes in the INR, resulting in bleeding or a thromboembolic event. Warfarin inhibits vitamin K-dependent clotting factors, which is the basis of its interaction with foods containing vitamin K, such as green leafy vegetables, vegetable broths, and vegetable oil-based salad dressings. Food interactions may be harder to manage than drug–drug interactions because the astute clinician is able to anticipate drug–drug interactions with warfarin and is knowledgeable in managing drug interactions with warfarin.

Food interactions may be harder to manage because less may be known about the amount and timing of intake of the interacting food. Therefore, rather than counsel patients to decrease their intake of vitamin K-containing foods, which may lead to vitamin deficiencies, it is wise to counsel patients to maintain a consistent intake of vitamin K. It is the change in vitamin K intake, as opposed to the absolute vitamin K intake, that can lead to variability in maintaining a goal INR.

Wells and others reviewed the literature on warfarin–drug and food interactions and rated the evidence behind the proposed interaction, using two independent raters. Of 120 original articles reporting a drug or food interaction with warfarin, the authors suggest that 43 foods or drugs were highly probable in causing a clinically important interaction with warfarin ($k = 0.67$) Among the reports possessing strong evidence for a clinically

relevant interaction with warfarin were foods high in vitamin K, large amounts of avo-
cado and enteral feeds, which likely contained high amounts of vitamin K *(196,197)*. New
formulations of enteral feeds usually contain no more than the RDA for healthy elderly,
and rarely cause warfarin insensitivity *(169)*. When educating patients about warfarin–
food interactions, it is important to relay to patients that they need not avoid foods high
in vitamin K, rather they should attempt to remain consistent in their intake of foods with
vitamin K.

Beyth and colleagues developed a multicomponent comprehensive program for man-
agement of warfarin therapy aimed at improving control of warfarin's effects and reduc-
ing events that may precipitate bleeding. They randomized 325 patients 65 yr and older
(mean +/– *SD* = 74.9 +/– 6.9 intervention and 74.5 +/– 6.6 control) to usual care or
intervention, consisting of among other things, education about drug–drug and DNIs in
which patients were trained about changes in lifestyle and diet. At 6 mo, major bleeding
was more common in the control group, whereas more time was spent at goal range INR
in the intervention group. Mortality was similar in both groups *(193)*. More recently,
warfarin has been known to interact with vitamin E, gingko, ginseng, and garlic, resulting
in an increase in INR *(36,170,198,199)*.

3.5. Phenytoin DNIs

Phenytoin is a common antiepileptic agent used in the elderly. It is considered to be
a narrow therapeutic index medication, meaning the concentration difference between
that which produces a therapeutic effect and that which produces toxicity is small. Pheny-
toin also has a saturable absorption and metabolism. At low levels, it possesses linear
pharmacokinetics such that an increase in dose produces a proportional increase in plasma
concentration of phenytoin. However, at higher concentrations, the same increase in dose
will produce a disproportionately greater increase in plasma concentration *(200)*. Owing
to phenytoin's narrow therapeutic index and nonlinear pharmacokinetics, phenytoin–
food interactions can markedly influence plasma concentrations and therefore drug safety
and effectiveness *(201)*.

Wilder studied potential food-associated differences in absorption between 100 mg of
Mylan's ER phenytoin sodium capsules and Parke-Davis' 100 mg Dilantin Kapseals®.
A single-dose, two-way crossover study was conducted in 24 healthy subjects (18–70 yr
old) to determine the influence of a high-fat meal on the pharmacokinetics of these two
formulations. The impact of switching products at steady-state levels was investigated
using a simulation method of pharmacokinetic data previously obtained from 30 epileptic
patients. Based on AUC, the bioavailability of the Mylan product administered with food
was 13% lower than that of Dilantin Kapseals®. Simulations of substituting the Mylan
product with Dilantin Kapseals® suggested that the 13% decrease in bioavailability
would result in a median 37% decrease in phenytoin concentrations when given with
food; in 46% of patients, concentrations would likely fall below the normal range. Simu-
lations of substituting Dilantin Kapseals® for Mylan suggested an increase of 15% in
bioavailability would occur and result in a median 102% increase in phenytoin concen-
trations, with 84% of patients having concentrations above the therapeutic range. Results
suggest that when taking phenytoin sodium with food, product switches may result in
either side effects or loss of seizure control *(201)*.

Yet another study by Cook and peers examining the effect of food on the bioavailability of Dilantin Kapseals® in a nonblinded, single-dose, randomized, crossover study in healthy patients 29–69 yr old after a fast and a high-fat meal suggested there were no clinically relevant changes in bioavailability and that patients may take Dilantin Kapseals without respect to meals *(202)*.

Based on the results of these two studies, it seems prudent to avoid switching phenytoin products in patients stabilized on a particular formulation and to recommend taking phenytoin consistently with respect to food. It is important to pay particular attention to elderly patients and those requiring high concentrations of phenytoin to maintain seizure control.

Phenytoin may interact with tube feedings and several mechanisms have been proposed, including binding of phenytoin suspension to the tube, or binding of phenytoin to the nutrient formula. The type of formula may affect the extent of this interaction *(203,204)*. However, a study of the effects of elemental formula (Vivonex TEN®) and lactose-free formula (Ensure®) on the absorption of phenytoin suspension was conducted in 10 normal volunteers. No difference in AUC, peak concentrations, or time to peak was observed with either formula *(204)*. Likewise, the bioavailabilities of phenytoin sodium solution and acid suspension were not found to be affected by continuous nasogastric adminstration of Isocal® *(205)*. Phenytoin is primarily absorbed in the duodenum. Using jejunal feedings tubes may therefore also impair absorption of phenytoin because the primary site of absorption is bypassed *(206)*. Despite the frequent use of phenytoin and nutritional supplements, there appears to be little information regarding outcomes relating to phenytoin–enteral feed interactions in the elderly population who would be likely to encounter such a potential interaction.

Phenytoin and folic acid also interact with one another; phenytoin can decrease folic acid levels and folic acid can, in turn, decrease phenytoin concentrations. Although the exact mechanism of the interaction is unknown, phenytoin may induce a metabolism that uses folate as a cofactor *(207)* and folic acid may affect the affinity of phenytoin to the enzymes responsible for metabolizing phenytoin *(208,209)*. Thus, long-term phenytoin use can decrease folic acid levels. But subsequent supplementation with folic acid is controversial because folic acid supplementation can decrease phenytoin levels to the point of seizure breakthrough *(207)*, and a dose increase in phenytoin may be needed.

Older studies examining the interaction were small *(210,211)* and administered large doses of folate (10 mg/d) daily. The smaller quantities of folic acid found in typical multivitamins are not likely to cause a clinically significant interaction with phenytoin. Yet, one recent case report describes a 79-yr-old man with severe folate deficiency who developed aplastic anemia while on phenytoin therapy. The authors suggest the aplastic anemia was the result of phenytoin and folate deficiency because of the existence of a temporal relationship, discontinuation of phenytoin and folate replacement, which corrected hematological values, and absence of other recognizable causes for the anemia *(212)*. For a more complete discussion of anticonvulsants and DNIs, *see* Chapter 15.

3.6. Monoamine Oxidase Inhibitor DNIs

Nonselective monoamine oxidase inhibitors (MAOI) represent the prototypical medication class known to interact significantly with food. Although they are rarely used in the current management of depression in the elderly, it is still noteworthy to briefly

discuss their interaction with food. Nonselective MAOIs, such as tranylcypromine, phenelzine, and isocarboxazid, inhibit the activity of monoamine oxidase A and B in a sustained and unpredictable manner, thereby decreasing the metabolism of amines such as epinephrine, norepinephrine, and dopamine for a period of time, from several days to several weeks after discontinuation of the drug *(213)*.

There are numerous foods that contain tyramine, an amine as well. Ingesting these foods concomitantly with a MAOI can lead to the accumulation of these amines, and consequential blood pressure elevation potentially resulting in fatal hypertensive crisis, with severe headache and stiff neck, palpitations, and nausea and vomiting *(213,214)*. Therefore, patients need to avoid the myriad of foods that contain tyramine. Examples of foods that contain tyramine include aged cheeses and wines, processed and cured meats, and chocolate, to name a few.

Selegiline is a selective monoamine oxidase B inhibitor used in elderly patients with Parkinson's disease (PD). At recommended doses for PD, selegiline does not interact with tyramine *(215)*. However, when taken above the recommended dose of 5 mg orally twice daily, selegiline loses its selectivity and may interact with tyramine-containing foods to cause a hypertensive crisis. It is important to counsel patients to adhere to selegiline dosing to avoid this potentially significant DNI.

3.7. Enteral DNIs

Strategies to improve adherence with drug regimens in community-dwelling elderly may include recommendations to take all their medications with their morning or evening meal. Strategies to improve nutritional status of the elderly particularly in transitional care settings may increase the risk for DNIs. For example, the use of liquid meal substitute formulas in place of water or juice with each medication administration may increase the total nutrient intake but can alter the bioavailability of some drugs. Likewise, frequent feedings throughout the day may not allow for an appropriate environment to administer drugs that should be administered on an empty stomach. The mixing of some medications in various beverages to increase drug-regimen adherence should not be undertaken without evaluating the potential for pharmaceutical interaction between the drug and beverage. Many elderly patients with cerebrovascular disease, dementia, aspiration, GI disorders, and failure to thrive in general receive enteral feeding. Many DNIs exist between enteral formulas and medication and these are reviewed in more detail in Chapter 26.

3.8. Dietary Supplement DNIs

The indiscriminant use of dietary supplements does not necessarily improve outcomes in the elderly, and has the potential to interact with other medications. For example, the impact of vitamin A or vitamin E supplementation on the immune response of the elderly can be deleterious, and potentially counterproductive in the face of vaccination or antimicrobial regimens *(216,217)*.

An examination of the literature on herbal supplements used by the elderly for dementia identified a series of papers describing the potential drug–supplement interactions that would place the elderly at risk for an ADE *(218)*. Twenty-eight articles were identified that examined five herbals—St. John's wort (11 articles), ginseng (7), kava (5), ginkgo (4), and valerian (1). These herbals are marketed in the United States as dietary supplements. Besides a few studies and reviews, most of the papers were case reports. St. John's wort is reported to interact with theophylline, cyclosporin, warfarin, indinavir, digoxin,

and the selective serotonin reuptake inhibitors (SSRIs). Digoxin, warfarin, and phenelzine interact with ginseng. Aspirin, warfarin, and trazodone may interact with ginkgo. Both kava and valerian may interact with sedatives, including benzodiazepines and barbiturates.

A recent study was conducted that specifically evaluated the DNIs between dietary supplement use and prescription medications used in a cohort of 285 patients in a Veterans Affairs geriatric clinic. The mean age of patients in this study was 78 yr. Patients were taking a mean of six prescription medications, excluding vitamins and minerals, and a mean of three dietary supplements (vitamins, minerals, herbals). The investigators found that 54% of patients were taking at least one dietary supplement and prescription medication that could potentially interact. Forty-five potential and possible interactions were found; these mainly involved the interaction with an antiplatelet or anticoagulant with garlic, gingko, and ginseng leading to increased risk of bleeding; garlic and an antihypertensive leading to increase blood pressure lowering effect; or decreased absorption of medication with flaxseed or psyllium *(36)*.

3.9. Proton Pump Inhibitor DNIs

Proton pump inhibitors (PPIs) are very commonly used in the elderly to manage gastritis, gastroesophageal reflux disease, and to prevent NSAID-induced ulcers. The currently available PPIs are omeprazole, lansoprazole, esomeprazole, rabeprazole, and pantoprazole. The PPIs are acid-labile medications that are degraded in neutral and basic media. They are formulated such that enteric-coated granules traverse the stomach intact and the medication is released in the less acidic medium of the duodenum. The administration of PPIs with nonacidic juices may impair their absorption. Thus, it is recommended that these agents be administered with an acidic juice like apple juice or orange juice, and not with milk *(219)*. Rabeprazole and pantoprazole tablets should be swallowed whole and unaltered. They should not be chewed or crushed. Lansoprazole, omeprazole, and esomeprazole capsules can be opened and their granules given with acidic juices. There is little data regarding the PPI in the elderly *(219)*. Among the data that are available in the elderly, there is no information to suggest that the absorption of PPIs is impaired to any clinical extent due to achlorhydria or impaired gastric acid secretion *(219,220)*. Food may decrease the maximum plasma concentration of the PPI but the AUC is not significantly affected. Still, it is best to counsel patients to administer their PPI about 30 min prior to meals if practical. If this is not possible, counsel patients to take their PPI at the start of the meal *(219)*.

An acidic medium is required for vitamin B_{12} to be released from dietary sources. Thus, long-term use of H_2RAs and PPIs may contribute to vitamin B_{12} deficiency *(221)*, particularly in the elderly who tend to be at higher risk *(222)*. Force and investigators conducted a retrospective, case-control study in middle-aged and elderly patients (mean age 71.2 +/– 20.8) and found that the need for vitamin B_{12} supplementation was preceded by chronic acid suppression therapy with H_2RAs and PPIs in more cases than controls (18.4 % vs 11% OR 1.82, p = 0.025) *(223)*.

3.10. Bile-Acid Sequestrant DNIs

Cholestyramine, colestipol, and colesevelam are lipid-lowering agents that decrease GI pH and bind bile salts to prevent their reabsorption in the ileum. They are then excreted and may cause steatorrhea and fat malabsorption *(169)*. Malabsorption of fat-soluble vitamins A, D, E, and K can occur because the absorption of these vitamins is usually facilitated by bile acids *(174,224,225)*.

3.11. Laxative DNIs

The elderly use many laxatives, which may lead to fluid and electrolyte imbalances and nutrient depletion *(174)*. Mineral oil is well known by the elderly as an old remedy for constipation. When used as a laxative long term, it may deplete fat-soluble vitamins by forming micelles and acting as a vehicle for lipid soluble moieties *(169,174,175,226)*.

3.12. Metformin DNIs

Metformin, a biguanide used for the management of type 2 diabetes mellitus, may cause vitamin B_{12} malabsorption, especially in the presence of atrophic gastritis *(169)* and with long-term therapy. Metformin has been used in Europe much longer than in the United States. Thus, reports of metformin-induced vitamin B_{12} deficiency in Europe dates back to the 1970s when it was predicted that approx 10–30% of patients on metformin therapy would develop vitamin B_{12} deficiency *(227)*. The incidence of clinically significant vitamin B_{12} deficiency is not known. It has been estimated that it takes less than 9 yr to up to15 yr on metformin therapy to develop associated vitamin B_{12} deficiency *(228,229)*.

Several mechanisms have been proposed by which metformin causes vitamin B_{12} deficiency. These include alterations in the motility of the small intestines, a direct effect on the absorption of vitamin B_{12}, bacterial overgrowth, and alteration in the calcium-dependent uptake of B_{12}- intrinsic factor complex at the ileum *(228–230)*. Based on this hypothesis, adminstration of calcium should decrease the severity of vitamin B_{12} deficiency associated with metformin. This was tested by Bauman and colleagues in a small study of 21 patients originally on sulfonylurea therapy without vitamin B_{12} deficiency. They switched half of the patients to metformin therapy on study entry (in a 2:1 ratio based on study entry date). They measured baseline and serial vitamin B_{12} levels and holotranscobalamin levels, which measures early, subclinical negative vitamin B_{12} balance even before serum vitamin B_{12} levels decrease. Patients were given calcium carbonate 1200 mg/d 3 mo into metformin therapy. The authors concluded that calcium supplementation reversed the decline in holotranscobalamin levels and had no impact on serum vitamin B_{12} levels *(230)*.

One recent case report in the United States describes a 63-yr-old man on metformin (dose unknown) for 5 yr who developed a probable metformin-induced vitamin B_{12} deficiency. The patient had no history of bowel surgery and had a balanced nonvegetarian diet. No glossitis, paresthesias, or other neurological abnormalities were found on examination. Laboratory findings included a mean corpuscular volume of 114 fl, a hematocrit of 33.6%, a vitamin B_{12} level of 109.7 pg/mL (normal 187–1059 pg/mL), and a folate level of 750 ng/mL (normal >190 ng/mL) and intrinsic-factor antibody findings were negative. A Schilling test was suggestive of intestinal malabsorption of vitamin B_{12} (recovery of radiolabeled vitamin B_{12} of 2.5 and 3.4%). The patient's metformin therapy was stopped and oral vitamin B_{12} was instituted at 1000 mcg/d for 2 mo. A repeat Schilling test was suggestive of normal vitamin B_{12} absorption, with and without intrinsic factor (17.5 and 17.7%).

Andres and colleagues share their experience with metformin and vitamin B_{12} deficiency. They describe 10 European patients with documented metformin-induced vitamin B_{12} deficiency. The mean age of these patients was 69 (range 52–84). Patients were using metformin for an average of 9 yr (range 3–10 yr) at an average dose of 2015 mg

(range 1400–2550 mg). Clinical symptoms were present in a few patients and included asthenia, peripheral neuropathy, and edema. One patient required blood transfusions. Average serum vitamin B_{12} levels were 148 pg/mL. Patients had normal creatinine and folate levels, and no patient had antibodies to intrinsic factor. The average hemoglobin level was 11g/dL. Nine of 10 patients had normal Schilling tests. One patient had atrophic gastritis and one patient had chronic diarrhea. All patients were treated with a maximum of 1000 mcg of oral or intramuscular vitamin B_{12} and vitamin B_{12} levels and blood counts normalized within 3 mo of treatment. An additional interesting finding in this case series is that the investigators found elevated homocysteine levels in these patients. Homocysteine is a potential risk factor for vascular disease *(231,232)*.

These case reports suggest that long-term metformin therapy can cause vitamin B_{12} deficiency, but in most cases, it is asymptomatic. In some instances, metformin therapy was continued and in other instances, it was not. Whether metformin therapy should be discontinued or not remains to be determined but treatment with oral vitamin B_{12} appears to reverse the deficiency within 2 to 3 months.

3.13. Levothyroxine DNIs

Antacids, iron sulfate, high-fiber diets, and calcium have all been shown to decrease the absorption of levothyroxine *(233–237)*. A case report of a 63-yr-old woman with long-standing hypothyroidism clinically euthyroid on levothyroxine revealed that chronic use of aluminum and magnesium antacids decreased absorption of levothyroxine, resulting in elevated thyroid stimulating hormone (TSH) levels despite levothyroxine 2000 mcg/d. Discontinuation of the antacids resulted in normalization of TSH and return to the previous dose of 50 mcg/d levothyroxine *(238)*.

Singh and colleagues recently further investigated the effects of calcium carbonate on the absorption of chronic levothyroxine in veterans aged 27–78 yr and found that calcium carbonate reduced thyroxine absorption. The proposed mechanism of this DNI is adsorption of levothyroxine to calcium carbonate *(237)*.

3.14. Bisphosphonate DNIs

The oral bioavailability of alendronate and risedronate, used for the prevention and treatment of osteoporosis, is poor (0.64% for alendronate and for 0.63% risedronate) and is significantly further decreased with food. Small studies of alendronate and risedronate revealed their bioavailabilities were reduced by 40% and 55%, respectively when administered shortly before a meal as opposed to in the fasting state *(239,240)*. Even orange juice and coffee were found to reduce the bioavailability of alendronate by 60% *(239,240)*. The bisphosphonates can also cause a local irritation of the GI tract leading to esophagitis, esophageal ulcers, and esophageal strictures in rare instances, especially when taken inappropriately *(239–241)*. Therefore, they are contraindicated in patients with esophageal disease. Clinical studies suggest that the incidence of GI events, including dysphagia and esophagitis, are similar to placebo *(242–245)*, but these studies were efficacy studies in which safety and tolerability were not primary endpoints and clinical experience suggests that many patients do not tolerate the oral bisphosphonates well. One study evaluating early case reports of alendronate and adverse event reporting to the manufacturer suggests that about 16% (199 of 1213) of reported events were related to the esophagus, and 26% of those were considered serious. Alendronate was taken inappropriately

in 61% of cases in which administration technique was known. Most patients were elderly and symptoms developed within 2 mo of starting alendronate *(241)*.

Because of their poor oral bioavailability and their risk of esophagitis, very specific administration instructions needs to be adhered to, to maximize bioavailability and decrease the risk of esophagitis. Alendronate and risedronate should be taken with 6–8 ounces of plain water only, first thing in the morning at least 30 min before any food, drink (besides plain water), or medication has been consumed, and patients must remain upright for 30 min after taking alendronate or risedronate and until food is consumed to decrease the risk of reflux and esophageal irritation. These complicated administration instructions can be difficult for elderly patients to follow, especially if they have cognitive impairment, functional immobility, or are on many medications. Moreover, calcium and vitamin D supplementation is recommended in patients taking bisphosphonates to maximize their effectiveness. But like all other medications, the administration of calcium/vitamin D with the bisphosphonates needs to be staggered *(239,240)*.

3.15. Levodopa DNIs

The interaction between levodopa and food and dietary protein has been evaluated in several small studies *(246,247)*. Levodopa is absorbed in the small intestines and is extensively metabolized in the periphery prior to uptake in the basal ganglia, where it is needed to exert its effect. Two mechanisms have been proposed for these interactions. One proposed mechanism is that food delays and decreases the absorption of levodopa from the small intestines, by delaying gastric emptying, and increasing exposure of levodopa to degradative enzymes in the stomach and intestines. Another proposed mechanism involves the ability of levodopa, an amino acid, to compete with large neutral amino acids in the diet for transport across the blood–brain barrier (BBB). Whatever the mechanism, this interaction is likely to be more significant in patients with progressive Parkinson's disease (PD) who experience motor fluctuations like "on–off," as opposed to patients without existing motor fluctuations *(246)*. Although the redistribution of dietary protein is cited as a management option for patients experiencing motor fluctuations *(248)*, this DNI is not likely to be a clinically significant interaction in early staged Parkinson's disease (PD) patients because large amounts of protein are needed (2 g/kg) to cause a significant interaction *(246,259)*. Vitamin B_6 may also decrease the effects of levodopa; it is a codecarboxylase, which may decrease blood levels of levodopa by increasing the peripheral metabolism of levodopa before it can cross the BBB for uptake into the basal ganglia *(173–175)*. However, levodopa is almost always co-administered with a dopa decarboxylase inhibitor (carbidopa) nowadays and this likely minimizes the significance of this interaction.

3.16. Antibiotic DNIs

Tetracycline and some fluoroquinolones classically interact with antacids and other products containing calcium, aluminum, magnesium, and iron by chelating with these polyvalent cations, resulting in a decrease in the absorption of the tetracycline or fluoroquinolone *(175,225)*.

Food, especially that containing dairy products, can decrease the absorption of tetracycline, and to a lesser extent, doxycycline. The effects of Ensure®, an enteral feeding product, on ciprofloxacin and ofloxacin was studied in healthy volunteers *(250)*. The

authors found that it decreased the absorption of both ciprofloxacin and ofloxacin when compared to water ($p < 0.01$), but also suggested that ciprofloxacin was significantly more affected than ofloxacin ($p < 0.005$). The relative bioavailability of ciprofloxacin was 72 ±14% ($p < 0.005$) of that when given with water *(250)*. For a more complete discussion about antibiotic DNIs, *see* Chapter 24.

3.17. Medications Associated With Unintentional Weight Loss

In the long-term care setting, there is a growing regulatory focus on unintentional weight loss as a marker of poor nutritional status. The impact of substantial weight loss on quality of life and overall health status can be significant. Pressure ulcers, falls, fractures, decreased resistance to infection, impaired wound healing, increased skin friability, osteopenia, anemia, and cognitive problems can occur. Studies show that undernutrition is associated with increased morbidity and mortality *(251,252)*.

The Center for Medicare and Medicaid Services has identified nine new quality indicators in nursing homes, one of which is unintentional weight loss *(253)*. Thus, nursing homes and surveyors will be paying more attention to pressure ulcers, malnutrition, and dehydration, all potentially linked with consequences of unintentional weight loss. Numerous causes of weight loss in the elderly can be explained with medications foremost among them. Besides evaluating the potentially offending agent, its mechanism of weight loss and duration of use should be considered. It is unlikely that a 10-d course of antibiotic therapy will have a substantial impact on weight. On the other hand, chronic use of a taste-altering medication could have a major impact.

Medication regimens may cause cognitive disturbances (e.g., psychotropics, clonidine, metoclopramide), anorexia (e.g., digoxin, antidepressants, theophylline), GI irritation (e.g., aspirin, erythromycin, NSAIDs), constipation (e.g., opioid agonists, calcium channel blockers), diarrhea (e.g., sorbitol-containing medications), and altered metabolism (e.g., theophylline, thyroxine). Medications can cause weight loss indirectly by causing dysphagia, GI side effects, delayed gastric emptying, early satiety, altered taste or smell, sedative effects leading to lack of desire to eat or napping and missed meals, or they may cause depression *(253,254)* (Table 5).

3.18. Medications Associated With Unintentional Weight Gain

Many psychoactive medications classically cause significant weight gain. The mechanism involved is complex but is probably multifactorial, involving the metabolic, endocrine, and neurochemical systems (histaminergic, serotonergic, and cholinergic) *(255)*. Reports of weight gain associated with antipsychotics date back to the 1960s *(256)*. Many of those older antipyschotics are rarely used today, but the newer atypical antipsychotics (clozapine, olanzapine, quietapine,risperidone, ziprasidone), developed and marketed for their improved side-effect profiles, all have the potential to cause weight gain that can potentially be significant (>7%) *(257)*. Olanzapine and clozapine may have the potential to cause more weight gain than other atypicals, as evidenced by direct comparative trials *(258,259)*.

Most studies evaluating weight gain with psychoactive agents employed younger patients with schizophrenia. But because these agents are widely used in elderly patients for neuropsychiatric symptoms, it is important to research their weight-gaining proper-

ties in the elderly who likely have concomitant cardiovascular disease and diabetes, which may make weight gain more problematic. Allison and colleagues conducted a recent meta-analysis in studies utilizing patients with a wide range of ages and found that mean weight change at 10 wk was +1.08 kg with haloperidol, +4.45 kg with clozapine, + 2.1 kg was risperidone, +4.15 kg with olanzapine,+2.18 with quetiapine (at 6 wk), and +0.04 with ziprasidone *(260)*. In general, the weight gain that occurs with psychoactive agents is usually centrally distributed, occurs early in the course of therapy and has been associated with altered adherence to therapy *(255,256,259,260)*.

Antidepressants can also cause a significant weight gain. Tricycylic antidepressants (TCAs) stimulate appetite and cause carbohydrate cravings *(256)*. Amitriptyline, typically avoided in the elderly, may cause the most side effects including weight gain. The weight gain associated with TCAs is dose- and duration-dependent. The SSRIs, the antidepressants of choice in the elderly, are less likely to affect weight significantly. In fact, there is often an initial weight loss associated with the SSRIs, which may be followed by a return to base weight. Therefore, the overall weight change associated with them tends to be negligible. A fairly new antidepressant, mirtazapine, is also a well-known inducer of weight gain *(261,262)*. In short-term studies employing a large range of patient ages, it has been shown to cause a greater than 7% weight gain in 7.5% of patients *(263)*. Long-term studies are under way to further investigate weight gain associated with mirtazapine. Lithium can also cause significant weight gain. Patients on lithium can gain up to 20–25 pounds in their first several years of therapy *(264,265)*. Other psychoactive medications that can cause weight gain include some anticonvulsants, such as valproic acid and carbamazepine.

Other medications that can cause weight gain include antidiabetic medications, particularly sulfonylureas, repaglanide, netaglanide, and insulin and corticosteroids. Antihistamines and NSAIDs can cause some fluid retention, but clinically significant weight changes are rare *(256)*.

3.19. Medication-Induced Laboratory Abnormalities

3.19.1. DIURETICS

The elderly are prone to fluid and electrolyte imbalances owing to changes in the renin-angiotensin-aldosterone system and antidiuretic hormone. They also possess altered thermoregulatory function, baroreceptor function, and have an altered thirst drive. Therefore the aged may be prone to DNI between diuretics and electrolytes. It is widely known that potential effects of thiazide diuretics include hyponatremia and hypokalemia, hyperlipidemia, hyperglycemia and hypercalcemia, although these metabolic disturbances are not as clinically relevant at doses used today. A retrospective review of elderly patients, 65–99 yr old, investigated the need for lipid-lowering therapy following the initiation of thiazide diuretics compared with other antihypertensives. The use of low-dose thiazides was not associated with an increased need for lipid-lowering therapy *(266)*. The effects of diuretics on serum sodium and potassium are described here.

3.19.2. DRUG-INDUCED HYPONATREMIA AND HYPERNATREMIA

Many medications, including carbamazepine, valproic acid, tricyclic TCAs, trazadone, venlafaxine, antipsychotics, SSRIs, and thiazide diuretics, can cause hyponatremia*(267–*

273). Booker describes the cases of six elderly patients with severe symptomatic hyponatremia (Na 112+/– 5.5 mmol/L) in which a thiazide diuretic was suspected of causing the electrolyte abnormality. The patients were 65 to 87 yr of age and had serum sodium concentrations ranging from 105 to 121 mmol/L. Symptoms developed within 4 d of thiazide initiation in the majority of instances. In two patients, hyponatremia was corrected and recurred upon thiazide rechallenge and in another two patients, hyponatremia recurred without rechallenge, perhaps suggesting that elderly patients with concomitant conditions are at risk of hyponatremia from various causes, including stress. Proposed mechanisms of thiazide-induced hyponatremia include volume contraction and decreased glomerular filtration rate, and increased reabsorption of sodium and water *(268).*

SSRIs (fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram), used for depression can also cause hyponatremia by causing a syndrome of inappropriate antidiuretic hormone (SIADH). The incidence is rare, but because these medications are widely used in the management of depression in the elderly, the prevalence of SIADH increases *(267).* Guay reviewed a series of SSRI-induced SIADH in elderly patients (mean age 75 yr old). The majority of patients developed hyponatremia within 14 d of SSRI therapy, although hyponatremia with SSRI therapy can occur at any time. Only 20% of patients were symptomatic (mean sodium level 120 mmol/L). Serum sodium normalized within several days of discontinuing the SSRI. Christe and Vogt described eight cases of SSRI-induced SAIDH in elderly patients with a mean age of 86 (range 78–89). The development of SIADH occurred within the first 3 mo of SSRI therapy, and as quickly as 3 d. Three patients were also on concomitant diuretic therapy. Three-quarters of the patients were symptomatic (nausea, diarrhea, dizziness, confusion). The hyponatremia resolved within 17 d after discontinuation of the SSRI in five cases. No rechallenge was offered, but despite this, one patient develop recurrent hyponatremia, suggesting as Booker did, that concomitant conditions can place elderly patients at risk of electrolyte abnormalities *(270).* A survey of spontaneuous reporting of adverse events associated with antidepressant therapy found that hyponatremia with antidepressant therapy occurred primarily in elderly females, in the summer, and during the first few weeks of antidepressant therapy *(271).*

Other case reports of SIADH caused by citalopram, and valproic acid, lisinopril, and amiloride/hydrochlorothiazide have been described in elderly patients *(272–275).*

Stress, hypothyroidism, and hypoadrenalism can also impair diuresis, leading to hyponatremia. The elderly are susceptible to these disease states and are on many medications that can alter sodium levels. Additionally, signs and symptoms of hyponatremia in the elderly are often subtle and nonspecific (including somnolence, headache) and do not occur until the serum sodium falls below 125 or 130 mmol/L or lower. Progress to coma and seizures can occur, so it is important that clinicians recognize this important DNI *(267,269,276).* Medications that can cause hypernatremia include those that can induce diabetes insipidus, including lithium, amphotericin B, and demeclocycline.

3.19.3. Drug-Induced Hypokalemia and Hyperkalemia

Many prescription medications can interact with potassium status, leading to hypokalemia or hyperkalemia. Loop diuretics (e.g., furosemide), thiazide diuretics (e.g., hydrochlorothiazide), and corticosteroids can all cause hypokalemia (K < 3.5 mmol/L).

Diuretic-induced hypokalemia can be significant enough to warrant potassium supplementation. Unlike the diuretics just listed, potassium-sparing diuretics (e.g., spironolactone, amiloride) can cause hyperkalemia, as can many other medications.

Medications can cause hyperkalemia (K > 5 mmol/L) by three main mechanisms: increase in potassium intake, decrease in potassium excretion, or a shift of potassium from the intracellular fluid to the extracellular fluid *(277)*. Medications that increase potassium intake include enteral nutrient formulas and oral nutrient supplements, oral potassium supplements, and penicillin G. Salt substitutes, often used in the elderly cardiac patient trying to avoid a large sodium intake, can also contribute to hyperkalemia, so it is important to inquire about the use of salt substitutes in patients on other medications that can increase potassium levels.

Medications commonly used in the elderly that decrease potassium output include ACEI, angiotensin II receptor antagonists, heparin, and NSAIDs. Medications that shift potassium extracellularly include β-blockers and digoxin.

In addition to the elderly using combination medications that contribute to hyperkalemia, they also suffer from diseases that can increase hyperkalemia as well, including diabetes mellitus secondary to insulin deficiency, metabolic acidosis, and renal insufficiency. Reardon and Macpherson conducted a case-control study to analyze hyperkalemia in patients on ACEIs. They found that 11% of 1818 patients (mean age 67 yr) developed hyperkalemia on ACEIs and that concomitant risk factors included renal insufficiency and heart failure *(278)*. Therefore, it is important to know which medications and disease states can alter potassium levels; to inquire about enteral supplements, salt substitutes, and other OTC medications that can cause hyperkalemia (such as NSAIDs); to monitor potassium levels in patients on chronic medications that can alter potassium levels; and to educate patients on the signs and symptoms of hyperkalemia (paresthesias and muscle weakness) *(277,279)*.

3.19.4. OTHER

Many medications can affect the absorption of vitamin B_{12}, often by interfering with intrinsic factor, which is necessary for vitamin B_{12} absorption. Examples include metformin and the PPIs (which were discussed in more detail previously), cholesytramine, ethanol, cimetidine, allopurinol, and potassium *(255)*.

Particular care needs to be exercised with use of corticosteroids chronically or in high doses. Corticosteroids can cause hyperglycemia or glycosuria that may affect diabetic control and can lead to dehydration, sodium retention, and potassium-wasting. Corticosteroids can also cause calcium depletion, enhancing the risk of osteoporosis and fractures *(169)*.

Case reports have suggested that antipsychotics may impair glucose tolerance and predispose patients to the development of diabetes mellitus. However, it is difficult to determine whether this is because of the disease state for which the antipsychotic is being used (schizophrenia, bipolar disorder), to the antipsychotic therapy itself or to confounding factors such as obesity or concomitant cardiovascular disorders. Despite antipsychotics being commonly used in the elderly for agitation associated with dementia, case reports that exist are primarily in younger patients being treated for schizophrenia. Therefore, it is premature to determine whether antipsychotics used in the elderly are associated with clinically important changes in glucose tolerance in the elderly *(280–285)*. Anticonvulsants

may decrease the activation of vitamin D_3 to 1,25-hyroxycholecalciferol *(225)*. Antacids reduce the absorption of selenium, chromium, iron, calcium, zinc, folate, magnesium, and vitamin B_{12} *(225)*. Thiazide diuretics can cause angina-like effects that are precipitated by foods containing monosodiumglutamate *(175)*.

4. LIMITATIONS OF THE DATA

How well does the existing data describe DNIs in the elderly? In 1994, the FDA issued a guidance document regarding studies in support of special populations including the geriatric population *(112,134)*. The document states that drugs that are to be used substantially in the elderly should be adequately studied in the elderly. The guideline further encourages the inclusion of patients 75 yr and older in clinical studies and recommends that geriatric patients with concomitant disease not be excluded from studies unnecessarily. However, this was a recommendation only, not a requirement. Furthermore, no stipulation was made to identify DNIs.

In 1997, the FDA established the geriatric use subsection of product labeling to inform clinicians about the use of medication in the elderly *(112,134)*. Under the geriatric labeling regulation, most prescription products need to include recommendations for use in the geriatric population and the data supporting the recommendation also needs to be included. Specific information that is supplied includes information about use of a medication in the elderly and relevant data supporting it, a statement declaring whether a sufficient number of geriatric patients were included in studies or not, differences in safety or effectiveness and supportive data, known pharmacokinetic and pharmacodynamic data in the elderly, determination if the medication is substantially renally excreted and information describing potential hazards with use in the elderly. Evidence is required that supports a recommended dose and dosing interval and modification of the dose or interval in the elderly. Finally, if there is no geriatric data pertinent to product labeling, the sponsor must provide reasons for omission. DNIs are not included. OTC medications need not submit geriatric use information *(286–288)*. Although the FDA mandates a geriatric use section of the product information, it requires little with respect to the actual data analysis of information included in this section. Specifically, the FDA merely recommends an adequate number of geriatric patients be included in clinical trials, with no actual percent inclusion mandated. It offers suggestions for pharmacokinetic analyses, including the option to perform pharmacokinetic screening involving trough blood level determinations at steady state from geriatric and younger patients to detect a difference, or from formal pharmacokinetic analyses, which can be done in either healthy geriatric patients or volunteers. It does not recommend formal pharmacodynamic studies be conducted unless other phase II/III studies suggest large differences in efficacy or safety between geriatric and other adult patients. The FDA recommends drug–drug interaction studies be completed in the elderly if an interaction is likely and for certain medications, including digoxin, oral anticoagulants, medication extensively metabolized hepatically but again, it makes no mention of DNIs. Most recently, in 1998, the FDA issued its "final rule" requiring sponsors to tabulate the number of elderly patients they include in trials. It does not address requirements for the conduct of clinical studies nor does it require sponsors to perform additional studies to include more geriatric patients.

It merely requires sponsors to submit existing data that had already been collected *(288)*. The FDA is currently developing a guidance document addressing drug interactions, yet there is no mention of DNI in this draft document *(289)*.

5. FUTURE RESEARCH NEEDS

The elderly comprise the fastest growing segment of the population and they use a disproportionately higher percentage of medication. It is important for clinicians to be aware of the changes in physiology that accompany aging and the effects that these changes have on drug disposition in the elderly patient. Health care providers need to keep in mind that advancing by chronological age is not a clinical disease. Although much is made of the demographics of the elderly focusing on alterations based on chronological age, the variability in physiologic function with age is more important to determine. Physiological function will relate more directly to nutrient and drug disposition. This may help one to better understand, predict, or address the clinical relevance of the interactions between nutrients and drugs. It is essential to evaluate the nutritional implications of each of the most frequently used medications for chronic conditions in the elderly. Although it is unlikely to become a requirement of the drug-approval process, it should be considered critical in the drug usage process. It is also important to identify the alterations in drug disposition in physiologic subgroups of the elderly with the use of oral meal replacements, vitamin and mineral supplements, soy protein and amino acid supplements, as well as herbal and other non-nutrient dietary supplements.

Crome and Flanagan address the future needs of pharmacokinetic studies in the elderly. They state that the elderly should be included in more phase I and phase II studies so that pharmacokinetic and pharmacodynamics can be collected early on. They advocate conducting pharmacokinetic dose-ranging studies in elderly patients to better determine appropriate doses for later clinical trials (phase III and IV). They also recommend using a parallel, placebo arm to collect controlled information about pharmacodynamics and to be able to directly compare the groups *(104)*.

Because the majority of studies, including DNI studies, are conducted in younger individuals, little data exist about DNIs in the elderly per se. However, a few studies have been conducted evaluating the implementation and outcome of DNI-tracking programs *(60,98)*. These studies suggest that DNIs are common and identifiable, and preliminarily suggest that intervention programs can decrease the incidence of DNIs. More of these studies are needed.

6. CONCLUSION AND RECOMMENDATIONS

Changes in geriatric physiology, pharmacokinetics, pharmacodynamics, and nutritional status, in addition to other factors such as polypharmacy, nonadherence, and suboptimal prescribing can lead to atypical disease-state presentation, and increased susceptibility to ADEs, including drug–drug interactions and DNIs *(260)*. The goals of geriatric pharmacotherapy are to maintain functional independence, prevent disability and iatrogenic disease, and to increase health-related quality of life *(290)* by promoting the use of rational drug therapy when drug therapy is indicated. Hanlon and colleagues developed the Medication Appropriateness Index, an instrument with demonstrated

reliability and validity that should be used by pharmacists in the routine evaluation of drug therapy, including DNIs *(81,82)*.

A comprehensive geriatric assessment is the standard of care in geriatric medicine *(7,260,291)* and is often conducted using a team approach. Components of the comprehensive geriatric assessment include a functional assessment, cognitive assessment, and social and nutritional assessment, in addition to the standard history and physical. An organized assessment of nutritional status, comprehensive medication use and DNI should be performed routinely *(290,292)*. Meal supplements and dietary supplements should be used cautiously in the elderly as they have the potential to adversely influence drug disposition and nutritional status.

Routinely educating oneself, patients, other clinicians, health professional students and federal agencies about changes in the elderly and DNIs should occur. Specifically, one should become knowledgeable about changes in physiology and drug disposition that occur in the elderly, and the mechanism, likelihood, severity, and the management of specific DNIs. Periodic review of the literature, contribution to the literature, development of continuing education programs, inclusion of geriatric and DNI topics in health professional curriculums, and patient health fairs and like programs should serve to increase recognition and knowledge of geriatric issues and DNIs.

Research has shown education to be effective in preventing DNIs. For example, Byeth and colleagues demonstrated that patient education about warfarin, including DNIs, was effective in preventing bleeding complications in the elderly. Strategies that were reported by Byeth were both successful and can and should be replicated in practice. These included assessment of warfarin indication and risks, as well as the provision of patient education. The patient education intervention used a workbook formatted for older adults and used coaching techniques to teach the elderly to take an active role in their care and to communicate necessary health information to their health care providers *(193)*.

Likewise, strategies to address DNIs in long-term care facilities have been identified in the literature and should be replicated *(73)*. They include education of health care providers (particularly about timing of food with drug regimens), establishing administrative policies and protocols based on limiting the occurrence of preventable DNIs, and regular monitoring of nutritional status, medication profiles, and laboratory data to evaluate the potential for interactions. The American Society of Health-System Pharmacists issued guidelines for pharmacists involved in home health care, which includes the responsibility to counsel and manage DNIs *(293)*. Clinicians can utilize some of the successful strategies outlined in the few studies available.

Promotion of geriatric patient inclusion in clinical trials and research incentives may also increase our recognition and knowledge about geriatric pharmacotherapy and DNIs. Once we have become proficient in the understanding of geriatric DNIs, we need to translate that knowledge into implementable skills that can be used in clinical practice, with vigilant monitoring conducted to prevent adverse DNIs in the elderly.

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VI DRUG–NUTRIENT INTERACTIONS IN SPECIFIC CONDITIONS

21 Drug–Nutrient Interactions in Patients With Cancer

Todd W. Canada

1. NUTRITIONAL STATUS IN CANCER

Nutrition has a major role in both cancer prevention and its therapy. In fact, dietary choices and physical activity are the two major modifiable determinants of cancer risk. The evidence suggests that one-third of the more than 500,000 cancer deaths in the United States can be attributed to these two factors each year *(1)*. The recent observation of improved 5-yr survival rates for all cancers is encouraging because much of the research into early cancer detection and treatment appears to be invaluable *(2)*. Unfortunately, the increase in 5-yr survival over time (1950 to 1990) had little relationship to changes in the mortality from cancer. There are several reasons that the 5-yr survival rates have increased. These include improvements in the treatment of established cancer, earlier identification of patients in their disease course, and early effective treatment regimens. Naturally, if more effective treatments of existing disease and more cancers are found early and treated, then mortality rates should decrease. The major explanation for improved 5-yr survival rates without improved mortality is simply changes in the diagnosis of cancer, including detection of subclinical cancers. However, epidemiological studies of populations whose diets are high in vegetables and fruits and low in animal fat, meat, and total calories have shown reduced risks for some of the most common types of cancer *(3)*.

One of the most important factors in the response to cancer treatment and mortality is the overall condition of the host at the time of diagnosis. Approximately 50% of patients experience weight loss at the time of cancer diagnosis and this unfortunately conveys a poor prognosis. By the time of death, virtually all cancer patients will experience loss of their lean body mass although their weight may actually increase from fluid retention (e.g., anasarca) or underlying tumor burden. Additionally, cancer has one of the highest incidences of protein-calorie malnutrition among hospitalized patients. The protein-calorie malnutrition is often related to the underlying disease itself, treatments related to the cancer, or a combination of the two. In a study done at M.D. Anderson Cancer Center approx 30 yr ago, the major causes of death in more than 800 cancer patients were infections and organ failure associated with the underlying malignancy *(4)*. Interestingly, 10% of these patients were characterized at autopsy to have extreme degrees of debilitation, malnutrition, and electrolyte imbalance. Most of these cancer patients experi-

enced greater than 25% loss of their body weight and represented one of the earliest reports of the syndrome of cancer-related cachexia. It also emphasized the important role of malnutrition in the pathogenesis of cancer and how nutrition therapy is often over-looked in this patient population *(5)*.

Cancer-related cachexia is a syndrome characterized by progressive, involuntary loss of body cell mass or lean body mass *(6,7)*. Clinical features of cachexia include host tissue wasting with skeletal muscle atrophy, anorexia, anergy, fatigue, anemia, hypoalbumin-emia, and ultimately debilitation. Patients with nearly identical primary cancers and disease stages may vary significantly in terms of the development of cachexia. Although cachexia is often seen in patients with advanced malignancies, it may already be present in the early stages of tumor growth. The development of cachexia may be related to variations in tumor phenotype and host response although the precise etiology is cur-rently unknown.

The primary determinants of weight loss in cancer represent a multifactorial process as depicted in Fig. 1. The most common rationales for weight loss are typically decreased oral intake of nutrients, increased requirements either from the tumor or its associated treatments, and inefficient use of nutrients *(8)*. Tumors of the gastrointestinal (GI) tract may present a physical obstruction or induce a malabsorptive state thereby reducing oral intake or its absorption. There are several reasons for decreased oral intake and the frequent observation of GI symptoms in cancer patients may influence weight loss. In a study to identify the primary symptoms responsible, the following were evaluated in approx 250 cancer patients: constipation, diarrhea, nausea, vomiting, abdominal full-ness, abdominal pain, milk-product intolerance, difficulty swallowing, mouth pain, mouth dryness, taste changes, denture problems, and difficulty chewing *(9)*. After obtaining a complete nutritional assessment including dietary and weight history, it was observed that the most common symptoms were abdominal fullness (61%), taste changes (dysgeu-sia) (46%), constipation (41%), mouth dryness (40%), nausea (39%), and vomiting (27%). The effects of these symptoms were compared in patients with greater than 5% weight loss to those with less than 5% weight loss. Interestingly, constipation and nausea were not statistically significant between the groups; however, they may have been clinically significant in terms of inducing weight loss given the frequent use of narcotics for cancer-related pain.

During simple starvation, the host is normally able to adapt by reducing energy expen-diture, conserving protein, and utilizing fatty acids and ketone bodies derived from fat as an energy source. These adaptations are attenuated or absent in cancer-related cachexia, where energy expenditure may be increased and ongoing protein losses occur. Increased requirements may be a direct effect of increased energy expenditure. Resting energy expenditure (REE) in cancer patients represents a heterogeneous description from hypometabolism to hypermetabolism. In an evaluation of 200 cancer patients, the mean measured REE was 98.6% of predicted using the anthropometric based formula of Harris and Benedict *(10)*. However, it was noted that 33% were hypometabolic (measured REE <90% of predicted), 41% were normometabolic (measured REE 90–110% of predicted), and 26% were hypermetabolic (measured REE >110% of predicted). Patients who were characterized as hypermetabolic had a longer duration of disease than the normometabolic patients (32.8 vs 12.8 mo), indicating that duration of malignancy may have some impact on energy metabolism.
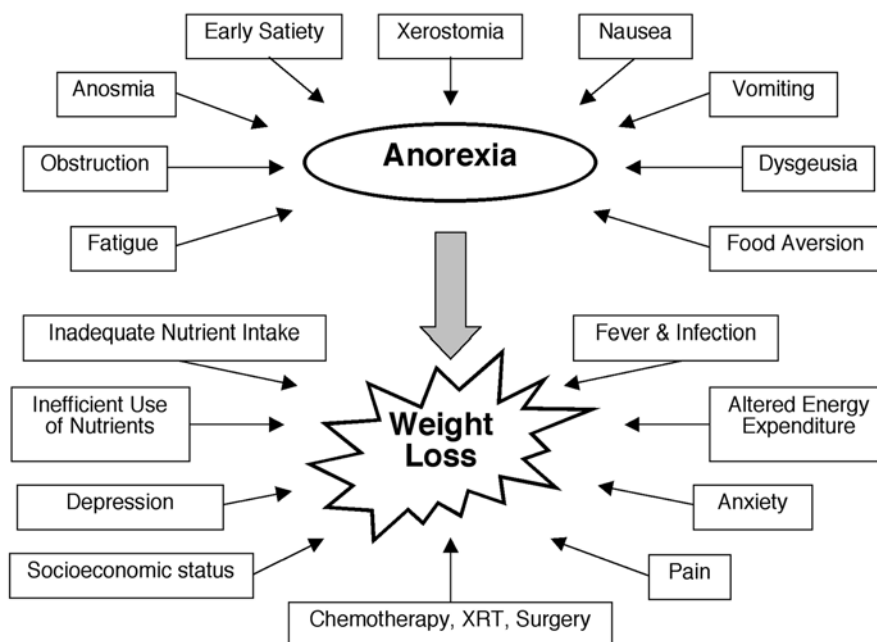
Fig. 1. Factors associated with weight loss in cancer.

Several changes in nutrient metabolism have been described in patients with cancer-related cachexia. These changes have been ascribed to a number of tumor-derived factors (e.g., proteolysis-inducing factor, lipid-mobilizing factor) as well as pro-inflammatory cytokines derived from the immune system (e.g., tumor-necrosis factor, various interleukins, interferon). These patients exhibit glucose intolerance and insulin resistance with increased rates of glucose production and recycling via lactate (from the Cori cycle) *(8)*. Lipolysis rates have not been found to be significantly increased and lipogenesis appears to be reduced. Whole-body protein turnover has been observed to be increased in most advanced cancer patients compared to starved normal individuals and weight-losing non-cancer patients *(8)*. As expected with progression of disease, protein turnover appears to increase further. Cancer patients with advanced disease and weight loss appear to exhibit an impaired adaptability to simple starvation, because fat mobilization is impaired and muscle proteolysis persists. All of these metabolic alterations observed in cancer have been referred to as an inefficient use of nutrients. Additionally, if surgery is required as part of the cancer treatment, it may cause further alterations in nutrient metabolism, such as an increased energy expenditure and protein requirements. It becomes apparent that reversing the metabolic defects observed in cancer patients is not a simple process.

Nutritional assessment of cancer patients is routinely accomplished by taking a medical and nutrition history while conducting a thorough physical exam guided by subjective global assessment *(11)*. Several factors that may place cancer patients at nutritional risk include other underlying acute or chronic diseases, inadequate food and nutrient intake patterns, multiple medications, and poor psychological or socioeconomic status. Whether

patients have new or recurrent cancer diagnoses, their current stage of cancer, and the presence of voluntary or involuntary weight loss are especially informative for nutritional assessment in the cancer population. Serum albumin may also be helpful, as it has been shown to be of prognostic significance *(12)*.

2. THERAPEUTIC MODALITIES IN THE CANCER PATIENT

Chemotherapeutic agents may contribute to host malnutrition by a variety of direct and indirect mechanisms including nausea, vomiting, mucositis, GI dysfunction, and learned food aversions (Table 1). The adverse nutritional effects of chemotherapy may be compounded in the host who is already cachectic from the tumor or who has received prior or concurrent radiation therapy. Fortunately, the adverse effects of chemotherapy are relatively short-lived, but repeated courses within 2–4 wk intervals generally do not allow the host to recover fully. Most patients usually have 1–2 wk of fatigue, GI symptoms, and poor oral intake after each course of chemotherapy followed by 1–2 wk of suboptimal oral intake and slowly improved activities of daily living. These durations may be prolonged depending on the host's functional and socioeconomic status, depression, narcotic use, and concurrent radiation therapy.

Weight loss in cancer patients can be of prognostic significance. The effects of weight loss in cancer was originally described from the Eastern Cooperative Oncology Group in more than 3000 patients *(13)*. The prognostic effect of weight loss on response to chemotherapy and survival along with the frequency of weight loss in a variety of tumor types was evaluated. Chemotherapy response rates were lower overall in the patients with weight loss. Within each tumor type evaluated, survival was shorter in the patients who had experienced weight loss compared to those patients who had not. The study noted 46% of patients had experienced no weight loss in the previous 6 mo and were comprised of non-Hodgkin's lymphoma, breast, acute nonlymphocytic leukemia, and sarcoma tumor types. The remaining 54% of patients had lost between 0 and 5%, 5 and 10% or greater than 10% of their body weight. Of the patients reporting greater than 10% weight loss, most had GI cancers primarily of pancreatic or gastric origin. These study findings emphasized the importance of pre-existing malnutrition in patients about to undergo chemotherapy and signifies how early recognition and intervention to prevent worsening of cancer-related cachexia may afford the best opportunity to prevent its debilitating consequences *(12)*. It could be argued in a broad sense that the poor drug response in the malnourished patients is itself an adverse drug–nutrient (drug–nutritional status) interaction (DNI) in these patients with cancer.

3. SPECIFIC DNIs IN PATIENTS WITH CANCER

Despite the wealth of information regarding malnutrition in cancer from reduced intake of nutrients, there are very few reports that have specifically focused on DNIs and their impact in this population *(14,15)*. The actual incidence and clinical significance of DNIs in oncology are likely patient- and cancer-dependent owing to the variations in age and treatment modalities. The combination of chemotherapy, radiation therapy, and/or surgery may induce specific nutrient deficiencies, appetite suppression, altered taste perception, and impaired nutrient absorption, metabolism, and excretion. One of the

Table 1
Chemotherapy-Related Effects in Cancer

Head and Neck
    Oropharyngeal ulcerations/stomatitis
    Anosmia/dysgeusia
    Anorexia
    Learned food aversions
Esophagus
    Esophagitis
Stomach
    Nausea and Vomiting
Small and Large Intestine
    Enteritis/colitis
    Typhilitis (neutropenic enterocolitis)
    Diarrhea
    Protein-losing enteropathy (BMT regimens)
Other
    Depression/grief
    Pain
    Anemia/fatigue

BMT, bone marrow transplant.

reasons for few reports of DNIs in cancer may be related to the route of administration, namely intravenously, of most chemotherapeutic agents used clinically; however, there are exceptions as some are taken orally, such as busulfan, melphalan, hydroxyurea, procarbazine, capecitabine, and temozolomide. The bioavailability of these oral drugs has generally been the major focus of the published DNIs where most have shown reduced absorption when administered with food *(14)*.

Several issues have gained greater importance to cancer patients and clinicians, including the older age now seen at diagnosis and lack of information on the benefits of current treatments with this aging population. The physiological and metabolic changes of aging have important implications for potential DNIs in the cancer patient. The elderly often exhibit subclinical or overt signs of malnutrition, including deficiencies of visceral proteins (e.g., albumin), minerals (e.g., calcium), and vitamins (e.g., vitamin D). Chronic vitamin D deficits have been associated with the incidence of some cancers. Furthermore, many of the elderly will have altered organ function, chronic diseases, and a poorer socioeconomic status, which may influence their nutritional well-being. The potential impact of oncological treatments on the worsening of nutritional status in the elderly is a major area of future research.

One of the few trials to examine specific nutrients in the plasma of breast cancer patients prior to a diagnostic biopsy and then 3–4 mo after diagnosis showed some interesting results *(16)*. Although this study was not designed to evaluate DNIs, it did show that women with breast cancer who received chemotherapy (agents not specified) had higher concentrations of retinol and α- and γ-tocopherol compared to those with

benign breast disease. The changes observed in these patients were small and may have had statistical significance; however, it is not clear what physiologic or clinical effects this truly represents. It may reflect the common use of nutrient supplements or dietary alterations in the oncology population after diagnosis because this is one of the few interventions patients feel they have some control over in their disease. Another study that evaluated the effects of vitamin and trace element supplementation in lung cancer patients was unfortunately unable to show any significant differences in the serum concentrations of the nutrients tested in survivors or those dying during or after their treatments, which included chemotherapy (cyclophosphamide, doxorubicin, vincristine) and irradiation *(17)*. Again, this trial was small and not designed to evaluate DNIs, but did emphasize that nutrient concentrations changed only slightly with supplementation and did not appear to affect overall mortality.

The observation that chemotherapeutic agents induce cell damage and destruction intuitively leads clinicians to believe nutrient supplementation is beneficial in cancer patients. One trial examined this phenomenon in patients with various tumor types from osteosarcoma to testicular cancer who underwent various plasma antioxidant testing prior to and 8–15 d after chemotherapy *(18)*. The chemotherapy consisted of either cisplatin and doxorubicin, cisplatin and etoposide ± bleomycin, and cisplatin with 5-fluorouracil (5-FU) or methotrexate. The plasma concentrations of vitamin C and vitamin E and copper decreased, whereas vitamin A and β-carotene increased from the baseline to the 8–15 d later values. Interestingly, all of the mean values obtained throughout the study were within the normal ranges for the testing laboratory. As a clinician, it is difficult to interpret the results of this trial given the lack of physiological or clinical relevance of the alterations in the antioxidant concentrations.

The study of depriving malignant tumors of their copper supply as a potent antiangiogenesis strategy for stabilizing patients with advanced cancer is one of the true DNIs in oncology. The use of the investigational agent tetrathiomolybdate to lower total body copper in patients with advanced stages of metastatic breast, kidney, colon, lung, skin, and pancreatic cancer did show that those able to achieve a mild copper deficiency had longer survival periods and stable disease *(19)*. Another impressive DNI was observed when gastric cancer patients received 5-FU and parenteral nutrition that was depleted of L-methionine *(20)*. This study evaluated the effects of 7 d of a L-methionine-depleted diet with chemotherapy (5-FU) and found marked degeneration of the gastric cancer postoperatively. The depletion of L-methionine apparently enhanced the therapeutic effects of 5-FU in this gastric cancer study.

4. LIMITATIONS OF CURRENT DATA

The obvious major limitation of the current data is the lack of published studies to guide oncologic clinicians and patients in their identification, prevention and treatment of DNI. Most clinicians are unaware of any clinically important interactions as few have been the subject of short- or long-term oncologic research. The development of new treatment regimens or combinations of chemotherapeutic agents to cure cancer has a greater precedent for reduction of mortality than the observance of decreased nutrients

in various bodily fluids from a potential DNI. Furthermore, most of the research devoted to studying the relationship between dietary habits and cancer has used case-control designs. These are often limited given the potential for dietary interviews or questionnaires to misclassify patients based on their nutrient intake, use of supplements, or other factors.

The biochemical measurement of circulating nutrients to identify toxicities or deficiencies has been a promising research potential for oncology. However, the interpretation of these measurements is often complicated by the underlying malignancy or its treatment in altering the concentrations *(16)*, not to mention the cellular control and interaction not captured by serum markers. Many of the studies have enrolled cancer patients after surgery, during chemotherapy and radiation treatment, or shortly after these have ended. Consequently, this leaves clinicians to question the etiological relevance of the findings. Some study designs have collected blood samples of various nutrients at different times in a patient's disease course that may include hospital admission, months after treatment has ended or just begun. What is uncertain is the time required for these patients to return to their baseline concentrations of the nutrients tested after resumption of their normal dietary habits (if possible).

5. FUTURE RESEARCH

Research in the area of DNIs for the cancer population is vastly unexplored. The observation that cancer can occur at any age and many patients are now survivors of cancer greatly impacts researchers as this does not entirely make them normal physiologically to compare with healthy controls. The following areas are suggested as potentially valuable research areas for DNIs:

1. Pediatric/elderly populations and the impact of oncologic treatments on nutritional status.
2. Acute and chronic vitamin and trace-element toxicities or deficiencies with chemotherapy (including commonly used regimens), radiation therapy, surgical resections of the GI tract, or any combinations of the above.
3. Protein (e.g., methionine) or trace-element (e.g., copper) restriction diets in newly diagnosed and end-stage cancer patients as a potential treatment option.
4. Impact of micronutrient supplementation (or other non-nutrient supplements) on clinical efficacy and toxicity of chemotherapy regimens.
5. Defining the time course for alterations in nutrients at diagnosis, prior to and after treatments, during unexpected hospital admissions, and when clinically cured or no other treatment options available.

6. CONCLUSION AND RECOMMENDATIONS

Despite the absence of published studies of DNIs in oncology patients, there are some clinically important DNIs that deserve attention. Drug-induced alterations in nutrient substrate utilization (protein, carbohydrate, or fat) may alter the interpretation of response to any form of nutrition support (Table 2). Clinicians need to be familiar with the drugs listed in Table 2 as these often result in worsening malnutrition (propofol is the exception)

Table 2
Common Drug-Induced Alterations in Nutrient Substrate Utilization

Nutrient Altered	Interfering Drug(s)
Glucose metabolism	
•Hyperglycemia, altered insulin sensitivity	Corticosteroids
	Catecholamines (epinephrine, norepinephrine, dopamine)
	Megesterol
	Diuretics
	Octreotide
	Tacrolimus
Glucose metabolism	
•Hypoglycemia	Pentamidine (increased insulin secretion)
	Octreotide (reduced glucagon secretion)
Protein metabolism[a]	Corticosteroids
•Elevated blood urea nitrogen (BUN) and urinary nitrogen losses, peripheral muscle-wasting	
Fat Metabolism	
•Hypertriglyceridemia	Cyclosporine
	Tacrolimus
	Propofol

[a]Elevated BUN may occur from hypovolemia with diuretics and from renal vasoconstriction with amphotericin B or cyclosporine. (From refs. 21,22.)

if not considered in the nutritional care plan of the patient. Glucose intolerance or overt hyperglycemia is common in cancer patients who present with febrile neutropenia and deserves prompt treatment and consideration in feeding.

Drug-induced GI disorders (nausea, vomiting, diarrhea, or constipation) may influence oral or enteral nutrition support tolerance and administration. Furthermore, most cancer patients with chronic pain often require maintenance bowel regimens to prevent obstipation from their opioid-based treatments. Clinicians should routinely monitor bowel function in the oncology patient as this is frequently problematic given the adverse effects from chemotherapy (e.g., mucositis) and the other extreme of constipation from narcotics and poor oral intake of fluids and/or food. Specific attention should be focused on the remaining GI tract integrity if prior surgery or radiation therapy has been part of the treatment regimen. This becomes a major consideration when selecting drug or nutrition therapy.

Common drug–electrolyte interactions in the cancer patient generally occur 1–3 d after initiation of the drug therapy; however, patients with pre-existing renal dysfunction may develop manifestations immediately (especially tumor lysis syndrome). Tables 3 and 4 list many of the common electrolyte and acid–base disorders seen in cancer patients with the respective drugs. The clinician should attempt electrolyte replacement from a chronic perspective (weeks to months) more than the acute (hours to days) time frame given the durations of treatment many cancer patients receive along with the residual drug effects that can remain for years (e.g., cisplatin).

Table 3
Common Drug–Electrolyte Interactions in Cancer Patients

Disorder	Interfering Drug(s) and Mechanism of Action
Hypernatremia	Amphotericin B–Nephrogenic diabetes insipidus
	Lactulose–Fecal water loss from diarrhea
Hyponatremia	Diuretics (Loop > Thiazide)–Increased renal Na^+ losses
	Cisplatin–Renal tubular defect in Na^+ handling
	Cyclophosphamide, Vincristine–SIADH
Hyperkalemia	Trimethoprim, Triamterene, Amiloride, Pentamidine–Inhibits renal K^+ secretion
	Angiotensin-converting enzyme (ACE) inhibitors–Inhibits ACE and aldosterone
	Heparin, Spironolactone, Cyclosporine, Tacrolimus–Inhibits aldosterone
	Nonsteroidal anti-inflammatory drugs (NSAIDs)–Decreased renal blood flow
	Antineoplastics–Tumor lysis syndrome
Hypokalemia	Diuretics (Loop > Thiazide), Amphotericin B, Ifosfamide–Increased renal K^+ losses
	Corticosteroids (Hydrocortisone)–Aldosterone-induced K^+ losses
	Insulin, Dextrose, β-agonists, and Sodium bicarbonate–Intracellular shift of K^+
	Foscarnet–Unknown mechanism
Hyperphosphatemia	Antineoplastics–Tumor lysis syndrome
	Phosphate-containing laxatives–Increased phosphate intake
Hypophosphatemia	Aluminum-containing antacids, Sucralfate, Ca^{++} supplements–Increased binding of phosphate
	Dextrose–Intracellular shift of phosphate
	Foscarnet–Unknown mechanism
	Corticosteroids, Ifosfamide, Cidofovir–Increased renal PO_4 losses
Hypermagnesemia	Magnesium-containing antacids and laxatives–Increased Mg^{++} intake
Hypomagnesemia	Diuretics (Loop > Thiazide), Amphotericin B, Cisplatin, Carboplatin, Cyclosporine, Tacrolimus, Aminoglycosides–Increased renal Mg^{++} losses
	Foscarnet–Chelation of Mg^{++}
Hypercalcemia	Thiazide diuretics–Decreased renal Ca^{++} losses
	Vitamin D–Increased GI Ca^{++} absorption
Hypocalcemia	Loop diuretics, corticosteroids–Increased renal Ca^{++} losses
	Foscarnet–Chelation of Ca^{++}

SIADH, syndrome of inappropriate antidiuretic hormone. (From refs. *23–26.*)

Table 4
Common Drug-Induced Acid–Base Disorders in Cancer Patients

Disorder	Interfering Drug(s) and Mechanism of Action
Metabolic alkalosis	Corticosteroids–Increased renal hydrogen losses and bicarbonate reabsorption, hypokalemia
	Diuretics (Loop > Thiazide)–Same as above with hypovolemia
	Sodium Bicarbonate, Acetate, and Citrate, Lactated Ringer's– Source of alkali or bicarbonate precursor
Metabolic acidosis	Acetazolamide, Ifosfamide–Increased renal bicarbonate losses
	Amphotericin B, Ifosfamide, Cidofovir–Renal tubular acidosis (distal and proximal)

From refs. *23–26.*

The perceptive clinician can easily appreciate how the development of drug-induced nutritional deficiencies may occur more quickly in the oncology population secondary to their frequent underlying chronic malnutrition. The use of a multidisciplinary approach including a physician, nurse, dietitian and pharmacist can greatly improve the overall care of the cancer patient when considering DNIs.

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22 Drug–Nutrient Interactions in Transplantation

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1. NUTRITION AND TRANSPLANTATION

Although nutrient effects and nutritional status are specific to each type of organ transplant, there are some basic premises that apply to transplantation in general. Those guidelines can be explained in terms of the time period surrounding transplantation.

1.1. Pretransplant

Nutritional status abnormalities are common during the waiting period for transplantation. Malnutrition is manifested by muscle wasting, weight loss (unless edema or ascites is present), and general deconditioning. Causes of malnutrition are multifactorial (Table 1) *(1)*. Malnutrition adversely affects posttransplant hospitalization events (tracheostomies, length of mechanical ventilation, length of stay) as well as survival *(1a–9)*.

At the opposite end of the spectrum, obesity may be a risk factor for transplantation. Two recent studies in kidney transplant recipients characterize the conflicting conclusions on this topic. Howard et al. compared kidney transplant recipients with a normal body mass index (BMI) of less than 25 kg/m^2 ($n = 457$) to overweight (BMI of 25–30, $n = 278$) and obese patients (BMI >30, $n = 98$) *(10)*. They found no difference in rates of delayed graft function, graft survival, or patient survival. On the other hand, Meier-Kriesche categorized 51,927 kidney transplant recipients according to BMI *(8)*. Significant increases in relative risk for death with functioning graft (1.1 to 1.3) were identified in the lower weight (BMI <22) and higher weight (BMI >34) groups. Studies evaluating obesity as a risk factor for liver transplantation suggest wound infection may be increased in obese patients; however, graft and patient survival are not adversely affected *(11–13)*.

1.2. Perioperative

Although there are no published studies proving benefits of pretransplant nutrition support, one could theorize that maximizing a patient's nutritional status prior to transplantation would help improve posttransplant recovery and outcomes. Postoperative

Table 1
Factors Contributing to Malnutrition in Organ Transplant Candidates

Organ Transplanted	Factors Contributing to Malnutrition
All solid organs	• Anorexia • Nausea, vomiting • Difficulty chewing or swallowing • Limited access to food • Depression • Fatigue • Restricted diets • Hypermetabolic state due to disease and/or surgery • Drug–nutrient interactions

Heart	• Poor nutrient delivery to tissue owing to impaired waste removal secondary to ↓ circulatory function
	• Cardiac cachexia
	   — ↓ nutrient intake
	   — ↓ gastrointestinal absorption
	   — ↑ stool and urine loss
	   — ↑ cardiac and pulmonary energy expenditure
	   — Ascites and early satiety (when hepatic congestion occurs)

Intestine	• Complications of total parenteral nutrition (PN)
	   — Metabolic bone disease
	   — Trace mineral deficiencies
	   — Cholestasis
	   — Cholelithiasis
	   — Hepatic dysfunction
	   — Portal hypertension
	   — Splenomegaly
	   — Urolithiasis

Kidney	• Glucose intolerance • Hypertriglyceridemia • Abnormal metabolism of calcium, phosphorus, vitamin D, and aluminum • Urea causes insulin-stimulated protein synthesis and ↑ protein degradation
Liver	• Protein, fluid, electrolyte abnormalities • Nutrient malabsorption and steatorrhea • Esophageal strictures and dysphagia • Mental alteration • Early satiety because of ascites • ↑ intestinal losses of protein • Impaired hepatic protein synthesis • Altered intermediary metabolism • ↑ energy expenditure • Malabsorption owing to ↓ bile salt levels • Small bowel dysfunction resulting from portal hypertension or lymphostasis • Pancreatic insufficiency

Table 1 (continued)

Organ Transplanted	Factors Contributing to Malnutrition
Lung	• ↑ work of breathing and resting energy expenditure
	• Hyperinflation resulting in early satiety
	• ↑ energy expenditure owing to chronic infections (cystic fibrosis)
Pancreas	• Nephropathy
	• Gastroparesis
	• Cardiovascular disease

From ref. *1* with permission.

nutrition support is indicated when patients are unable to meet nutrient needs via an oral diet within a few days after transplantation. Small bowel transplant recipients initially require parenteral nutrition (PN) until the graft functions. Other indications for PN for transplant recipients include prolonged ileus, high-output fistulas, and gastrointestinal (GI) bleeding. Enteral nutrition (EN) is indicated for patients who do not have adequate oral intake but have intact GI function. Hasse et al. reported improved nitrogen balance and decreased viral infections in liver transplant patients who received immediate posttransplant EN *(14)*.

General nutrient requirements are summarized in Table 2 *(14a)*. Common post-transplant complications such as rejection, infection, impaired wound healing, renal insufficiency, hyperglycemia, and surgical complications may require changes in nutrient requirements or nutrient route *(15)*.

1.3. Chronic Posttransplant

Several chronic complications following transplantation are the result of drug–nutrient complications. Excessive weight gain, hyperlipidemia, hyperglycemia, hypertension, and osteoporosis are linked to side effects of immunosuppressive drugs. An appropriate diet with optimal calories, limited saturated fat and sodium, balanced carbohydrate, and adequate micronutrients is encouraged to prevent and/or treat these comorbid conditions. An expanded discussion of these complications appear later in this chapter.

2. SIDE EFFECTS OF IMMUNOSUPPRESSANT MEDICATIONS

Because the normal immune system will recognize a transplanted organ as nonself, it will attempt to reject the organ. To prevent rejection, lifelong immunosuppression via drugs is necessary. There are several immunosuppressive drugs that are used in combinations to prevent and treat rejection. These agents include the corticosteroids (e.g., prednisone, methylprednisolone), antiproliferative agents (e.g., azathioprine, mycophenolate mofetil), monoclonal (e.g., basiliximab, daclizumab) and polyclonal antibodies (e.g. antithymocyte globulins), calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and rapamycin derivatives (e.g., sirolimus). Common side effects of these drugs include GI symptoms, hyperlipidemia, obesity, hypertension, and osteoporosis.

Table 2
Nutrient Requirements During the Acute Posttransplant Recovery Phase

Nutrient	Condition	Requirements
Calories	Patient is stable after transplant	$1.3 \times$ BEE[a]
	Patient is underweight and weight gain is desired	$1.5 \times$ BEE[a]
Protein	During the immediate posttransplant phase and during administration of additional corticosteroids for rejection	1.5–2.0 g/kg[a]
	Patient has renal insufficiency requiring dialysis	1.2 g/kg[a]
Carbohydrate	Patient is stable after transplant	70% Nonprotein calories
	Patient has diabetes	Meal plan for diabetes
Fat	Patient is stable after transplant	30% nonprotein calories
	Patient is malabsorbing long-chain fatty acids (as in immediate post-small bowel transplant)	Limit long-chain fatty acids; supplement with medium-chain triglycerides for additional calories
	Patient has pancreatitis	Nothing by mouth or minimal fat intake
Fluid	Patient is stable after transplant	30–35 mL/kg dry weight
	Patient has increased losses via drains, urine output, diarrhea, nasogastric tube output, pancreatic exocrine drainage (pancreas transplant)	Increase intake to match output unless diuresis is desired
	Patient has decreased urine output	Minimize fluid intake
Electrolytes	Patient has hyponatremia	Restrict fluid intake (1000–1500 mL/d)
	Patient has hypernatremia	Increase fluid intake
	Patient has severe ascites, edema	Restrict sodium intake to 2–4 g/d
	Patient has hypokalemia	Increase intake of high-potassium foods or supplement with potassium
	Patient has hyperkalemia	Restrict intake of potassium
	Patient has hypophosphatemia	Increase intake of high-phosphorus foods or supplement with phosphorus
	Patient has hyperphosphatemia	Consider use of phosphate binders
	Patient has hypomagnesemia	Supplement with magnesium

[a]use estimated dry body weight in calculation.
BEE, basal energy expenditure (using Harris Benedict equation). From ref. *14a* with permission.

2.1. Gastrointestinal Complications

One of the most common side effects of immunosuppressive medications is GI disturbance such as nausea, vomiting, anorexia, and diarrhea. A number of agents can cause these symptoms. The result is decreased food intake and malabsorption. Diarrhea can lead to dehydration, weight loss and, if severe, excessive loss of electrolytes and nutrients. Vomiting can decrease the amount of medication being absorbed by the patient, thus risking rejection. Patients should be encouraged to eat several smaller meals a day and consume dietary supplements to fulfill nutritional requirements. The use of antiemetics and antidiarrheals may also be necessary. In some patients, discontinuation of the offending agent and substitution of another immunosuppressive is necessary. For example, a major side effect of mycophenolate mofetil is diarrhea; the effect may be dose-dependent. If a patient is experiencing severe diarrhea, a reduction of the dose or elimination of mycophenolate mofetil may improve the diarrhea.

2.2. Hyperlipidemia

The risk of cardiovascular disease is significantly increased in kidney and liver recipients and is the leading cause of morbidity in kidney transplant patients [16–19]. The development of hyperlipidemia in recipients is commonly caused by immunosuppressive medications including cyclosporine, corticosteroids, and sirolimus. Cyclosporine decreases lipoprotein lipase activity and decreases bile-acid synthesis from cholesterol [20]. Corticosteroids reduce lipoprotein lipase activity, increase very low-density lipoprotein synthesis in the liver, inhibit bile acid synthesis and decrease low-density lipoprotein receptor activity [21]. Sirolimus reduces the catabolism of apoB-100 containing lipoproteins and consequently increases lipid levels [22]. Lipoprotein abnormalities have been demonstrated to increase the risk of cardiovascular related death in the posttransplant period [23]. As a result of hypercholesterolemia-induced vasculopathy, it has been suggested that heart recipients may develop coronary artery disease, liver recipients may develop vanishing bile duct syndrome, and kidney recipients may develop chronic rejection of their organs [23].

One option to reduce serum lipid levels is to reduce the dose of the offending drug or to switch medications altogether. Additionally, a low-fat, low-cholesterol diet should be employed. Regular exercise should be encouraged in these patients. If needed, lipid-lowering drugs such as bile-acid sequestrants, nicotinic acid, and hydroxy-methyglutaryl-coenzyme A (HMG-CoA) reductase inhibitors can be used. However, patients must be closely monitored for drug interactions. Serum liver function tests should be monitored in patients taking lipid-lowering drugs. The safety and efficacy of low doses of HMG-CoA reductase inhibitors following kidney, liver and heart transplants has been demonstrated [24–29]. However, there are concerns that the use of statins with calcineurin inhibitors may increase myotoxicity and thus has limited the use of higher doses of statins thus far in transplant recipients. The use of omega-3 fatty acids to decrease triglyceride levels, blood pressure, and platelet aggregation needs further study.

Cyclosporine has been demonstrated to increase blood homocysteine levels in kidney transplant recipients [30,31]. Hyperhomocysteinemia is another contributing factor to the development of atherosclerosis in transplant recipients. It has been suggested that supplementation with folate and vitamins B_6 and B_{12} may be effective for treatment of hyperhomocysteinemia in transplant recipients [32].

2.3. Obesity

As previously discussed, the consequential risks of preoperative obesity in transplant recipients is controversial. The cause of obesity is clearly multifactorial and has been documented in kidney, liver, pancreas/kidney, and heart transplant recipients *(33–38)*. Most clinicians would argue that attempts at weight reduction should be attempted prior to transplantation. Posttransplant obesity is associated with hypertension and hyperlipidemia *(12,39)*. Postoperative weight gain can be caused by a number of factors including increased food intake, improved nutrient digestion, improved quality of life, and lack of exercise. Additionally, corticosteroids may increase dietary intake because of hyperphagia. The majority of the weight gain in liver recipients occurs in the first 2 yr following the transplant *(35)*. The best approach to preventing weight gain in posttransplant patients is to encourage exercise, provide psychological support and educate the patient about nutrition. If weight loss is required, it should be slow and steady to avoid depleting muscle stores.

2.4. Hypertension

Renal transplant recipients frequently develop hypertension postoperatively, which may have a significant impact on graft survival *(40–42)*. The development of hypertension is clearly multifactorial, with underlying chronic disease, drug exposure, uncontrolled renin secretion of recipient kidneys, impaired sodium excretion, and stenosis of the transplant vascular anastamosis all contributing *(43)*. Additionally, recipients of cardiac, lung, and liver transplants have been reported to develop hypertension at an increased rate emphasizing the causal role of immunosuppressive therapy.

Calcineurin inhibitors (CNIs) are well known to cause hypertension and the most common offending agents are cyclosporine and tacrolimus. These drugs appear to cause hypertension through the inhibition of calcineurin, which causes systemic hypertension and decreased renal blood flow *(44–47)*. Therefore, the hypertensive side effect is inseparable from the therapeutic suppression of the immune system. Interestingly, although tacrolimus is a more potent immunosuppressive, the rate of hypertension is higher with patients on cyclosporine than those on tacrolimus *(48)*.

Treatment options for posttransplant hypertension should first include sodium restriction, weight control, and regular exercise. If high blood pressures continue, reducing the dose of drug or possibly switching agents, and initiating antihypertensive medications may be necessary. The substitution of mycophenolate mofetil and sirolimus to reduce hypertension is promising, but requires further study with long-term follow up *(49)*. Most standard antihypertensive medications have been demonstrated to be safe in transplant recipients. Because sodium retention and graft vasoconstriction are mechanisms of posttransplant hypertension, diuretics and calcium channel blockers are frequently employed. However, drug monitoring is necessary because patients on diltiazem, but not verapamil or nifedipine, have decreased renal clearance of cyclosporine and tacrolimus *(50)*. The use of angiotensin-converting enzyme inhibitors is controversial and may cause decreased renal function, graft thrombosis, and acute tubular necrosis *(51,52)*.

2.5. Diabetes

The development of posttransplant diabetes is an independent cardiovascular risk factor for transplant recipients and is associated with the same vascular complications that affect diabetics at large. The actual incidence of diabetes in transplant recipients is complicated by differences in the criteria used to diagnose diabetes, differences in the types of organs transplanted, and variations among immunosuppressive protocols employed. The most common immunosuppressive agents to cause diabetes are corticosteroids, cyclosporine, and tacrolimus. Steroids induce insulin resistance, whereas cyclosporine and tacrolimus inhibit pancreatic islet cell function. Transplant recipients treated with tacrolimus showed a significantly increased risk of developing diabetes compared to those treated with cyclosporine (53–55). Hyperglycemia has been reported to increase the risk of infectious complications in the immediate postoperative setting (56).

Most cases of posttransplant diabetes occur in the first few months after transplant. Risk factors for a recipient developing diabetes include age, ethnicity, increased body weight, and family history (39,57–61). The treatment options include reduction of steroid dose, switching agents from tacrolimus to cyclosporine, or using lower doses of CNIs while adding sirolimus or mycophenolate mofetil. As with any diabetic patient, weight control, carbohydrate-controlled diet, and regular exercise should be encouraged. Oral hypoglycemics and insulin-sensitizing agents should be used as needed. The administration of insulin may be needed to control hyperglycemia.

2.6. Osteoporosis

Many patients awaiting transplantation already have some degree of bone loss secondary to poor nutritional status, inactivity, age, and chronic disease states. Bone mineral density changes have been demonstrated postoperatively in liver, kidney, heart, and lung transplant recipients (62,63). Small bowel recipients frequently have bone disease and mineral deficiencies prior to transplantation as a result of malabsorption. The first 6 mo after transplantation represent the most rapid rate of bone decline, corresponding to highest levels of immunosuppressive medications (62,64). The most common agents for bone pathology following transplantation are steroids. Corticosteroids reduce intestinal absorption of calcium, increase renal excretion of calcium, and reduce the secretion of sex hormones. Corticosteroids also are believed to have direct osteoblast toxicity. Cyclosporine and tacrolimus contribute to bone loss by altering the ratio of osteoclast to osteoblast activity, favoring bone resorption.

The nondrug-related risk factors for posttransplant osteoporosis include chronic disease states, alcohol abuse, diuretic use, low estrogen levels, female gender, coexisting diabetes mellitus, hyperparathyroidism, and cigarette smoking (65–70). Calcium supplementation and vitamin D are both options to prevent bone loss. Hormone replacement therapy in postmenopausal women is also useful. If possible, the dose of corticosteroids should be reduced. Exercise should be encouraged, as should cessation of smoking. The utility of bisphosphonates in preventing bone loss following renal transplantation was recently reported (71). Further studies are needed to determine the best therapy and duration of treatment to prevent the bone loss of patients on immunosuppressive drugs.

3. TRANSPLANT NUTRITION GUIDELINES

General nutrient recommendations are reviewed in Table 2. Specific considerations based on the transplant type and immunosuppression protocol are discussed here.

3.1. Kidney Transplantation

For the patient with chronic kidney disease (CKD), there are three therapeutic options: hemodialysis, peritoneal dialysis, and kidney transplantation. Transplantation provides the only opportunity for a life free of dialysis, infectious risks, and restrictions. The most common causes of CKD are diabetes, hypertension, glomerulonephritis, systemic lupus erythematosus, interstitial nephritis, renal stones, chronic pyelonephritis, and polycystic kidney disease *(72)*. As a result of their underlying chronic disease, many patients will already be malnourished and have vitamin and mineral deficiencies. Renal failure disrupts normal calcium, phosphorus, vitamin D, and aluminum homeostasis. Many patients are on restricted diets while on dialysis and may experience nausea and vomiting as a consequence of uremia, which also stimulates protein synthesis and degradation.

In the immediate postoperative setting, malnutrition increases the patient's risks of infection, inhibits wound healing, and prolongs rehabilitation. Although recipients' diets are frequently advanced quite rapidly, nutrient requirements need to be determined on an individual basis. As in any surgical patient, the decision to start EN is decided on a case-by-case basis.

The long-term immunosuppression options for kidney recipients usually consist of both corticosteroids and a CNI (cyclosporine or tacrolimus) combined with either a purine antagonist (azathioprine or mycophenolate mofetil) or sirolimus *(73)*. Steroid withdrawal is frequently attempted. As discussed, kidney recipients are at an increased risk for obesity, diabetes, hypertension, hyperlipidemia, and osteoporosis.

3.2. Liver Transplantation

Liver transplantation is indicated for end-stage liver disease (ESLD). There are numerous causes of ESLD requiring transplantation, but the majority of patients requiring the procedure are significantly malnourished and depleted of muscle and fat stores *(74–76)*. The most common cause of malnutrition in the liver failure patient is insufficient caloric intake secondary to loss of appetite and an increase in the patient's protein requirements. Patients often have depleted glycogen stores and are in a metabolic state resembling prolonged starvation, increased lipid oxidation, and decreased carbohydrate utilization *(77)*. The increased oxidative stress on the liver becomes additionally important because antioxidant deficiencies frequently co-exist *(78)*. Another contributing factor may be intestinal malabsorption secondary to luminal bile-acid deficiency.

Adequate pretransplant nutritional status correlates with favorable posttransplant outcomes in liver recipients *(3,6)*. Efforts should be made to supply adequate protein because of the high protein breakdown rate in these patients. EN is necessary for patients under significant stress with inadequate intake, whereas PN is reserved for patients without a functioning GI tract.

In the perioperative setting, an oral diet can usually be started once bowel recovery has begun. The use of postoperative EN is controversial. PN is reserved for prolonged impairment of intestinal function, such as ileus. For the first two postoperative weeks with a

well-functioning graft, increased protein breakdown continues and repletion of this protein is likely beneficial at promoting wound healing and preventing complications *(79)*. This protein degradation rate slows but does not fully normalize 12 mo after transplantation *(80)*. However, some of the nutrient abnormalities that existed prior to transplantation will return to normal within days of the procedure. Vitamin A and zinc levels will normalize rapidly *(81,82)*. In order to maximize dietary intake, small frequent meals can be used with supplements. Also, nausea, vomiting, diarrhea, and constipation can be treated pharmacologically as needed.

In the long-term outpatient setting, patients may gain excessive weight or develop high serum cholesterol levels. As previously discussed, the use of immunosuppressive drugs to prevent graft rejection significantly increases the prevalence of cardiovascular risk factors. Liver transplant recipients are usually placed on dual therapy of corticosteroids, and CNIs. Because corticosteroids can cause hypertension, obesity, diabetes, and hyperlipidemia, a steroid taper is usually attempted *(83)*. In a well-functioning graft without evidence of rejection, the gradual withdrawal of prednisolone has been shown to reduce the rate of these risk factors *(84)*. Recent studies have shown that tacrolimus has more significantly reduced prevalences of cardiovascular risk factors than cyclosporine *(48)*.

In addition to determining the optimal therapeutic combination, nutritional assessments and dietary modification are helpful in reducing cardiovascular risks. As in the general population, exercise and a low-fat, calorie-controlled diet is recommended. The use of antihyperlipidemics, antihypertensives, and diabetic medications may be necessary. This is particularly important because as the field of transplantation expands, older recipients with pre-existing cardiovascular risk factors will certainly become more common.

3.3. Pancreas Transplantation

Pancreas transplantation is performed on patients with type 1 diabetes mellitus. Although islet cell transplantation is an area of increasing research interest, the majority of pancreas transplants are performed in conjunction with renal transplants for nephropathy secondary to long-standing type 1 diabetes mellitus. Simultaneous pancreas kidney transplants (SPKs) have increased graft survival rates over isolated pancreas and kidney after pancreas transplants *(85)*. SPKs were historically performed with exocrine drainage provided via the bladder. However, an increased rate of urinary complications and bicarbonate losses has led to the increasing use of enteric drainage, which is more physiologic.

As a result of their diabetes, patients awaiting SPKs frequently have renal failure, gastroparesis, cardiovascular disease, and retinopathy. Therefore, their preoperative nutritional status should be evaluated. Hyperglycemia should return to normal with a well-functioning pancreatic graft. Glycosylated hemoglobin levels should reflect this change 2 mo postoperatively. Fluid and electrolyte disturbances require close attention in the immediate postoperative setting. Patients are at an increased risk of hyperglycemia, hypokalemia, hypocalcemia, and metabolic acidosis secondary to bicarbonate losses. If exocrine drainage is provided via the bladder, high levels of urine and bicarbonate losses are frequent and must be replenished. Additionally, pancreatitis is a complication of transplantation and may require fluid resuscitation. If the patient had gastroparesis preoperatively, prolonged decompression with a nasogastric tube and nasoenteric feeding may be beneficial.

The immunosuppressive protocol depends on the center. The most frequently employed medications are steroids, cyclosporine, tacrolimus, sirolimus, mycophenolate mofetil, muronomab-CD3, and other monoclonal and polyclonal antibodies or antilymphocyte antibodies. Recipients of pancreas transplants that are placed on the lifelong immunosuppression are at risk for fluid and electrolyte disturbances, fistulas, gastroparesis, pancreatitis, hyperglycemia, obesity, hyperlipidemia, hypertension, and osteoporosis *(86)*. These conditions should be treated as in other transplantation patients with diet therapy, exercise, vitamin supplementation, and hydration. Gastroparesis requires frequent small meals and may require the placement of a jejunostomy tube for enteric feeding. As in any patient with gastroparesis, the use of motility agents may be beneficial.

3.4. Heart and Lung Transplantation

Depending on the etiology and severity of their disease, patients may undergo transplantation of the heart, single lung, double lung, or heart and lung simultaneously. Heart transplantation is indicated for chronic heart failure. The most common causes of heart failure requiring transplantation are ischemic heart disease and cardiomyopathy. Patients awaiting lung transplants frequently suffer from chronic obstructive lung disease, cystic fibrosis (CF), bronchiectasis, or pulmonary hypertension *(87)*.

The preoperative nutritional status is dependent on the etiology of the patient's underlying disease. In the patient with chronic heart failure awaiting heart transplantation, malnutrition is common *(88,89)*. As a result of decreased cardiac output and decreased peripheral blood flow, the body responds by releasing catecholamines that vasoconstrict splanchnic arterioles. The result is decreased circulation to the gut. Additionally, venous congestion can result in renal and hepatic dysfunction, which can lead to GI disturbances. This release of sympathomimetic agents also increases the patient's metabolic rate, which increases the patient's nutritional demands *(90)*.

In chronic lung disease, the etiology of malnutrition is different. There is increased energy expenditure from the work of breathing and patients with hyperinflated lungs can have decreased oral intake secondary to a feeling of fullness. Patients with CF and bronchiectasis frequently suffer from infections that result in the production of cachectin and increased energy expenditure. Patients with CF may also have malabsorption from pancreatic insufficiency. Determination of nutritional status is essential because preoperative nutritional support is effective at reducing postoperative morbidity and mortality in lung transplant recipients *(91)*.

Cardiac recipients can be on dual, triple, or quadruple long-term therapy using a combination of CNIs, corticosteroids, and purine antagonists. Dual therapy could be cyclosporine and azathioprine. Triple therapy is most frequently employed and consists of cyclosporine or tacrolimus, corticosteroids, and either mycophenolate mofetil or azathioprine *(92)*. Quadruple therapy is triple therapy plus a 1-wk course of an antilymphocyte agent *(93)*. Many centers will attempt to reduce or withdraw the steroid to reduce associated morbidities.

In the immediate preoperative setting, it is not uncommon for lung recipients to receive a calcineurin inhibitor and/or azathioprine *(94)*. Long-term immunosuppression in lung

recipients usually consists of three agents: steroids, cyclosporine or tacrolimus, and azathioprine or mycophenolate mofetil. Steroid withdrawal is not frequently tolerated in lung recipients *(94)*. The transplanted lung is at a particular high risk for infection because the native defense mechanisms of the lung have been disrupted and patients require high levels of immunosuppression.

3.5. Small Bowel Transplantation

One of the most rapidly advancing areas of transplantation is that of the intestines. Small bowel transplantation is indicated for chronic intestinal failure that results in the inability to maintain adequate nutrition on an enteral diet. Although PN is an option for these patients, it may become impossible secondary to limited venous access or PN-induced liver dysfunction. Additionally, transplantation may improve quality of life *(95–97)*. The most common conditions resulting in the need for transplantation are short bowel syndrome, malabsorption syndrome, motility disorders, neoplastic disease, and primary or secondary transplant failure *(98)*. Intestinal transplantation can be isolated intestinal, combined intestinal and liver or multivisceral.

Because of their underlying disease, patients will be malnourished and depleted of vitamins and minerals while awaiting transplantation unless maintained on preoperative PN. Fat-soluble vitamins should be replenished prior to transplant with particular attention given to vitamin K because of dependence on this vitamin in the coagulation cascade.

In the immediate postoperative setting, diarrhea is a common problem that requires fluid repletion. Fluid status must be closely monitored because recipients may have high levels of enteric fluid losses. There are numerous possible causes for the diarrhea, but changes in the graft's neural modulatory pathway, malabsorption, loss of the ileocecal valve, bacterial overgrowth, graft ischemia, and immunosuppression may all play a role *(99)*. Patients may have hyponatremia, hypokalemia, hypomagnesemia, and metabolic acidosis. Parenteral nutrition is frequently continued for several weeks postoperatively and EN should be started when the graft and recipient remnant intestines appear to have motility.

The discovery of tacrolimus was a key event in the development of small bowel transplantation. Immunosuppression protocols, as in other solid organ transplants, vary among centers *(100)*. Corticosteroids and tacrolimus are the primary drugs and the addition of adjunctive therapy is frequent *(101)*. Abu-Elmagd and colleagues reported promising results using bone marrow augmentation in recipients and ex vivo irradiation of grafts *(102)*. It is possible that future management protocols for small bowel transplantation will rely more heavily on these protocols than the addition of more potent immunosuppressive medications.

The studies of long-term health risks following intestinal transplantation are still immature for this relatively new procedure. Obesity does not appear to be a problem with these recipients because of decreased absorption rates and the reliance on tacrolimus, but limited data exists. The frequent use of corticosteroids and tacrolimus probably causes hyperlipidemia in these patients, but these studies have not been performed. Hypertension is a risk because of tacrolimus and corticosteroid use. Additionally, these patients frequently have fluid imbalances. Hypertension should be treated pharmacologically because sodium restriction may discourage adequate oral intake.

4. CONCLUSION

The field of solid organ transplantation has expanded dramatically since the 1950s. Crucial to advancements within the field, has been the development of newer immunosuppressive medications. These medications are lifesaving for transplant recipients. However, these drugs have risks. The benefits of tissue tolerance far outweigh the risks associated with these drugs at the present time. The search continues for newer medications that will selectively inhibit the immune system while reducing unwanted side effects. In the meantime, the metabolic disturbances of lifelong immunosuppression will need to be minimized and treated in order to maximize graft and recipient survival.

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23 Drug–Nutrient Interactions and Immune Function

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1. INTRODUCTION

The overall objectives of this chapter are to provide a brief overview of the immune system, the numbers of individuals affected by immune-related diseases and infections, examine the classes of drugs used to treat the most prevalent diseases of the immune system, and review the data on certain nutrients that have been shown to enhance immune responses in clinical studies.

Nutritional status greatly affects the ability to mount an effective immune response. However, the effects of nutrients differ with the age of the individual, as well as with lifestyle factors. Because seniors are the greatest consumers of prescription drugs, often using multiple agents, we review the data from clinical studies that examine the effects of nutrients and/or drugs on immune responses in this age group. Immune-mediated diseases and immune responses also can affect nutritional status and are affected by dietary habits. In this area, we examine the effects of acute infection and the importance of vaccines especially in childhood and also in the elderly. The use of antibiotics and other drugs to treat chronic infections such as tuberculosis and human immunodeficiency virus (HIV) infection and anti-inflammatory drugs for treatment of autoimmune diseases including diabetes, systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are also included. The drugs used to treat acute and chronic infections as well as autoimmune diseases all have some negative impact on certain aspects of nutritional status. Thus, the interactions between nutrition and immune function, drug–immune-related response or disease, and drug–nutrient interactions (DNIs) are complex. We review the data from the most prevalent conditions and those where there are data available about these interactions. It must also be noted that certain lifestyle habits, such as cigarette smoking and alcohol consumption, may also affect dietary intake, immune function, and drug disposition. In 2000, 25% of men and 21% of women were cigarette smokers in the United States *(1)*. Multiple interactions add to the complexity of predicting the effects of nutritional status and concomitant drug use on the immune responses of individuals.

For the majority of chronic diseases, whether immune-related or not, there are cardinal features of disease that impact nutritional status. Usually, during the course of disease, there is an increase in metabolic rate that is often associated with fever; gastrointestinal (GI) tract impairment resulting in decreased intake and/or absorption, increased excretion, and pain. Often, prolonged drug therapy affects the liver and its capacity to enhance fat absorption (and fat-soluble vitamin absorption), production of nutrient carrier proteins, and increase gut motility. Similarly, many drugs affect pancreatic function causing alterations in protein breakdown, glucose utilization, and gastric emptying. Many chronic diseases (and a number of drugs used to treat the diseases) result in tissue destruction possibly resulting from increases in oxidative damage; it is often difficult to determine which is the first event and which is the consequence (2).

2. THE HUMAN IMMUNE SYSTEM

The human immune system is comprised of cells, tissues, and organs that interact with each other for the primary purpose of maintaining the internal integrity of the body. In order to protect from external pathogens, immune cells are located at all orifices as well as in the lungs, along the GI tract, and in the liver. Immune cells are also found in the central nervous system, in the walls of blood vessels, and can move to any area within the body that is the site of a challenge. The primary organs of the immune system include the thymus, bone marrow, and the spleen; lymph nodes and mucosal-associated lymphoid tissues comprise the secondary organs. The primary function of the thymus is the maturation of certain lymphocytes. Within the bone marrow, there are pluripotential cells or stem cells. The bone marrow stem cell-derived white blood cells include granulocytes (most numerous are the neutrophils), lymphocytes, and macrophages that circulate in the blood and lymph and can move throughout the body (3–5).

There are two major categories of lymphocytes, T cells and B cells. T cells, associated with immunosurveillance, and cell-mediated immunity, are involved with the killing of pathogens that live within human cells, such as viruses and intracellular pathogenic organisms. The two major types of T cells include T helper (Th) cells that help generate most of the body's immune responses, and T cytotoxic cells that modulate the helper response to maintain immune balance. B cells produce antibodies, in response to Th cell signals. Antibodies adhere to extracellular pathogens such as bacteria and contribute to their demise. The cells of the immune system synthesize and secrete numerous cytokines that can bind to receptors on cells of the immune system or other cells to initiate responses. The cytokines include interleukins, interferons, and tumor necrosis factors (TNFs); prostaglandins, formed from long-chain fatty acids, also modulate immune responses and are synthesized by cells of the immune system. T and B cells are unique in that they have memory functions and are rapidly activated when exposed to a pathogen for the second or subsequent times. The memory function is the basis of vaccination responses. Under normal circumstances, during the development of the immune system in the early months of life, the immune system "learns" to recognize the antigens on its own cells and develops tolerance for self-antigens.

Tolerance is particularly important during pregnancy, as the fetus is not self, yet must not be destroyed by the maternal immune system. Likewise, the developing fetal immune system cannot be vigorous enough to destroy the immune or other maternal cells and tissues. This one example provides a glimpse into the complexity of the immune system.

The neonatal immune system is not fully developed and exposure to external antigens is critical for the "education" of immune cells. Many childhood infections occur only once because the immune system remembers and destroys these pathogens if challenged for a second time.

Although it may appear that the immune system has the capacity to defend against pathogens, this is obviously not the case in many instances as there have been epidemics throughout human history. A critical factor in host defense is nutritional status. Millions of white blood cells are formed each day and usually a corresponding number are destroyed. Significant nutritional resources are expended to maintain the immune system at its optimal and if the required nutrients are not consumed, the result is a less than optimal immune response to infection. As discussed later, we still have many examples of undernutrition associated with childhood pathogens such as measles and diarrheal disease. Acute infections can also affect nutritional status. High fever is often accompanied by a lack of appetite, nausea, and/or diarrhea. Chronic inflammation from infection or autoimmune diseases also often adversely impacts nutritional status.

Antibiotic use by humans in the United States is estimated at 4.5 million pounds annually *(6)*. Antibiotic exposure, however, is considered to be much higher owing to inadvertent exposure to foods that contain antibiotics, such as beef, chicken, and certain root vegetables. Estimates of antibiotic use in the veterinary industry and as growth promoters in the animal feed industry approach 30 million pounds per year. Antibiotic-resistant strains of pathogens are a growing problem and results in the use of multiple antibiotics and stronger drugs that can further adversely affect nutritional status via nutrient absorption, elimination, and/or utilization.

There are several new infectious agents that have been seen in human populations in the past decades. These include Ebola and West Nile viruses and bacterial infections such as Lyme disease. There has also been a significant increase in antibiotic-resistant strains of bacteria and other pathogens. Thus, there is a great deal of interest in nutrients–drugs–biologicals that can boost immune responses and modulators of immune responses for different age groups (Tables 1, 2).

Vaccines against childhood infections have been responsible for saving millions of lives annually. The World Health Organization (WHO) has an active program of immunization in developing countries. Developed nations also immunize their children against diseases that were common in the 20th century and now have been almost eradicated. Common vaccines include tetanus, diphtheria, pertussis, tuberculosis, polio, measles, mumps, rubella, hepatitis B, and chicken pox. As with seniors, childhood malnutrition can compromise the efficacy of vaccinations *(7,8)*.

3. IMMUNE-RELATED DISEASE AND DRUG-USE PREVALENCE

In the United States, immune-related conditions altogether are the third leading cause of death, surpassed only by heart disease and cancer *(1)*. Of the 10 leading causes of death, 5 have links to the immune system directly: chronic lower respiratory disease, diabetes, pneumonia/influenza, nephritis, and septicemia. The percentage of US individuals reporting fair to poor health is about 10% in those 45–54 yr of age and jumps to 33% in those 75 yr of age or older. In 2000, the Medicare program for individuals 65 yr of age or older in the US had 40 million enrollees and expenditures of $222 billion *(1)*. In 1998 in the US, 88% of the noninstitutionalized elderly had a prescribed medical expense *(1)*.

Table 1
Infections With Global Consequences

Ebola virus	Malaria
West Nile virus	Rabies
Small pox	Salmonella
Tuberculosis	Yellow Fever
Rotavirus	Diptheria
Respiratory syncytial virus	Pertussis
Shigella	Tetanus
Syphilis	Staphylococcus
Candida	Streptococcus
Chlamydia	*E. coli*
Measles	Hemophilus
Rubella	Meningococcal meningitis
Gonorrhea	Plague
Chicken pox	Cholera
Meningitis	Hepatitis A, B, and C
Hemmorhagic fever	Anthrax

From refs. *8,22,23*.

Table 2
Global Disease Incidence/Mortality

Disease	*Incidence/ Mortality*
Tuberculosis	2 billion infected globally; 3 million deaths per year
HIV	37 million infected globally; 730,000 cases of AIDS in US since 1985—one-third in females
Autoimmune diseases	8 million deaths per year in US
Acute respiratory tract infections	3.7 million cases; cause of 30% of all childhood deaths in underdeveloped countries
Diarrheal diseases	3.5 million deaths per year globally

From refs. *1*,7,8.

The major chronic diseases of the immune system are caused by an inappropriate response of the immune system to self-antigens resulting in autoimmune diseases. Autoimmune diseases are noncontagious, although these may be triggered by an infectious agent. On the cellular level, the T cells no longer recognize self-antigens and stimulate either the production of antibodies to the self-antigens, autoantibodies, or there is destruction of self-cells by the immune system. There is a strong genetic predisposition to autoimmune diseases, however, the triggering event is considered to be environmental. Pathogens, pollutants, drugs, and even nutritional factors have been implicated as the initiating factors in autoimmune diseases. Certain autoimmune diseases are organ-specific (thyroid, pancreas) and others are systemic, such as SLE and RA. In the majority of autoimmune diseases, there is a much greater incidence in women than in men; for example, the incidence of SLE is 10-fold higher in women *(3)*.

Chronic illnesses, such as diabetes, arthritis, and other immune-related diseases, as well as cardiovascular disease affect about 45% of the adult US population *(1)*. With regard to nutritional status, it must be noted that about 30% of the US population over 65 yr of age have experienced total tooth loss *(1)*. Tooth loss is often associated with decreased total food consumption and especially decreased consumption of nutrient-rich foods such as meats and raw fruits and vegetables that are hard to chew.

Serious infections, allergies, and several immune-related diseases are often diagnosed in mid-life; these illnesses may not occur independent of other chronic conditions *(9–12)*. A recent study in US Medicare beneficiaries aged 65 and over found that 82% suffered from one or more chronic conditions, and 65% had multiple chronic conditions *(13)*. In this population, the most prevalent cause of hospitalization was for bronchopneumonia; 48% of hospitalizations had this diagnosis. Another cause of serious illness in the elderly is postoperative infection, which was found to be the cause of 13% of hospitalizations in the Medicare population. About 85% of adults over age 65 were taking some prescription drug prior to the diagnosis of a new disease such as diabetes *(14)*.

4. AGING OF THE IMMUNE SYSTEM

The aging of the immune system results in greater occurrence of infection in seniors *(3,4,15)*. Bogden et al. *(16)* documented a significant decline in delayed hypersensitivity responses to previously encountered antigens (a clinically relevant in vivo measure of immune function) in individuals 60 yr old and older. They found about 40% of this apparently healthy population were anergic, and thus did not have a skin-test response to the seven test antigens; another 30% had partial responses. Merrie et al. *(17)* documented the progressive decline in both number and diameter of skin-test responses to seven test antigens in individuals aged 66–82 compared to those aged 25–40; of those aged 25–40, 35% had positive responses to five of seven antigens, whereas none of the matched group aged 66–82 had five responses. At the same time, only 1.5% of the younger group was anergic (no responses to the seven antigens); 18% of the older group had no responses. In addition to responding to fewer antigens, the older group also had approximately half the induration response as seen in the younger group.

Clinical studies have shown that delayed-type hypersensitivity (DTH) can be used as a predictor of morbidity and mortality in the elderly; that is, elderly with anergy had twice the risk of death from all causes as elderly who responded to the antigens *(18)*. Moreover, in hospitalized elderly who had undergone surgery for any reason, anergy was associated with a greater than 10-fold increased risk of mortality and a 5-fold increased risk of sepsis *(19)*. DTH responses are also indicative of morbidity within an age-matched elderly population; those who lived at home and were self-sufficient averaged positive responses to two antigens and indurations of about 8 mm compared to those in nursing homes who were self-sufficient (1.1 response and 4 mm induration) and nursing home residents who were not self-sufficient (0.5 response and 4 mm induration) *(17)*. Thus, if micronutrient supplements could improve DTH responses in the elderly, the health effects could be very great *(20)*.

In addition to declines in responses to antigens the body has already seen, the aging immune system also has declines in response to new antigens, often presented in the form of vaccines. Vaccines are important drugs used to "educate" the immune system to very small quantities of an antigen so that it can respond vigorously when challenged directly

by the pathogen. Several vaccinations are important in preventing infection-related morbidity and mortality especially in seniors. However, even when seniors are vaccinated, there is not a 100% response rate to the vaccines, and this may be in part owing to the nutritional status of the senior (see the multivitamin section). Two infections are associated with high rates of morbidity and mortality in the aging population. Influenza has caused approx 20,000 deaths per year in US seniors during epidemic years. In 2001, about 65% of seniors reported taking the flu vaccine. Pneumococcal disease killed about 3400 seniors in 1998. About 60% of seniors took the pneumococcal vaccine in 2001. Most seniors who took one of these vaccines, took both vaccines *(21)*. In addition to improving vaccination rates, optimization of immune responses to vaccines such as these can significantly reduce the risk of disease in the elderly.

5. MAJOR IMMUNE-RELATED DISEASES: DRUG AND NUTRIENT EFFECTS

5.1. Acute Respiratory Tract Infection

Acute respiratory tract (ART) infections are major killers of young children and the major killer of infants in developing countries accounting for more than 3.7 million deaths, or more than 30% of all deaths in young children in underdeveloped countries *(22)*. Influenza and pneumonia, as well as ART infections following measles and HIV infections are the major causes of morbidity and mortality. Malnutrition is a serious risk factor in the progression of ART infections. Both zinc and vitamin A deficiencies have been associated with increased risk of ART infections and zinc supplementation has been shown to reduce the incidence of infection in poor children. Low selenium status has also been identified as a risk factor for poor recovery. Prior viral infections especially respiratory syncytial virus (RSV)-associated pneumonia, often linked to malnutrition, also appears to reduce immune responses to bacterial pathogens that infect the airways. Aside from malnutrition that may be present prior to ART infections, the infections can cause a further 10–20% reduction in food intake. Thus, nutritional intervention is critical in the care of infected children.

ART infections are also the major killers of frail elderly. As indicated earlier, bronchopneumonia is the most prevalent cause of hospitalizations in the US Medicare population. The decline in immune function combined with the loss of appetite, reduced mobility, and increased use of several drugs to treat the multiple chronic conditions that affect the aging population, also contribute to the rise in ART infections. Wolff et al. *(13)* reported that the prevalence of chronic conditions in enrollees in the US Medicare program increased with age from 74% in those aged 65–69—with an average of 2.3 conditions—to 88% in individuals aged 85 and older—with 2.7 conditions.

5.2. Diarrheal Diseases

Diarrheal diseases are the leading cause of childhood morbidity and mortality in underdeveloped countries. The major causes are pathogenic viruses, bacteria, or gut parasites that infect undernourished children. Diarrheal diseases are responsible for about 3.5 million deaths per year, with most of the deaths occurring in children under 2 yr old. Associated with diarrheal disease are dehydration, fever, anorexia, convulsions, measles, micronutrient deficiencies, and severe protein energy malnutrition *(23)*.

Immune suppression linked to undernutrition has been documented in children suffering from diarrheal disease. DTH responses to recall antigens are significantly depressed, indicating suppression in cell-mediated systemic immune responses. Children with no responses to recall antigens (anergy) have significantly increased risk of diarrheal disease. Vitamin A deficiency is also predictive of diarrheal disease and the disease also reduces vitamin A status, leading to a viscous circle of sickness. Zinc deficiency is also associated with diarrheal disease and supplementation has been shown to reduce incidence in children in underdeveloped countries.

5.3. Tuberculosis

About one-third of the world's population (almost 2 billion people) is infected with the tuberculosis (TB) bacterium. Annually, there are about 10 million new active cases per year, with about 3 million resultant deaths (Table 2). Thus, TB is the greatest cause of infection-related mortality worldwide, surpassing acquired immunodeficiency syndrome (AIDS). In the developed world, TB is often seen in individuals infected with HIV or other chronic diseases that reduce immune responses to bacterial infections. The most common type of TB is pulmonary and infants, children, the elderly, those with diabetes or other immunodeficiency diseases or immunodepression as a result of cancer chemotherapy or organ transplant medications are most at risk. The pulmonary form is spread via contact with infected sputum. Malnutrition is also a major risk factor for TB infection. Specifically, protein-calorie malnutrition is well documented. Low intakes of vitamin A and C as well as reduced exposure to the sun and/or low vitamin D intake have all been seen in individuals infected with TB *(24)*.

TB is normally treated with up to four antibiotics simultaneously in order to reduce the potential of forming drug-resistant strains of the bacteria. TB treatment is long term and the drugs have adverse effects on food consumption, may cause vomiting, diarrhea, and loss of appetite (Table 3). Following acute infection, there is often a latent period where the bacteria are not reproducing and the infected patient recovers strength. There are few well-controlled studies that indicate that nutritional interventions can affect the progression of TB once contracted. There are also few studies that show success in reducing the progression from latent to reactivated disease with nutritional measures. However, there are very few studies and it is difficult to separate the nutritional intervention effects from the antibiotic therapy's effects. In summary, poor nutritional status increases the risk of contracting TB and continued malnutrition cannot improve prognosis. Long-term, beneficial nutritional interventions have yet to be identified for TB patients *(24)*.

5.4. HIV Infection and AIDS

HIV was first identified in 1984 following the recognition in 1981 of an unusually high number of infections caused by the pathogenic microorganism, *Pneumocystis carinii*, and the appearance of a rare form of cancer, Kaposi's sarcoma, in homosexual men in San Francisco and New York *(25)*. HIV infection was shown to be caused by one of two retroviral species designated HIV-1 and HIV-2. The virus infects cells of the immune system resulting in severe immunosuppression that has been termed AIDS *(26–28)*.

Since its discovery, HIV infection has spread throughout the world and has become a major threat to populations especially in underdeveloped nations. Currently, the WHO estimates that about 37 million people worldwide are infected with the HIV virus; half

Table 3
Select Antibiotic Drug Classes and Nutrient/Food Interactions

Drug Family	Drug Name	Administration Instructions	Nutritional Effects	Adverse Reactions
Penicillins	Amoxicillin	Can take with water, fruit juice, milk, or carbonated beverages (150)		Diarrhea (151)
	Ampicillin	Take with water on an empty stomach 1 h before or 2–3 h after meals (152,153)		
	Penicillin	Take with water on an empty stomach 1 h before or 2–3 h after meals (152,153)		
Tetracyclines	Tetracycline HCL	Take with water on an empty stomach 1 h before or 2–3 h after meals (150,153,154)	Avoid calcium (milk and dairy products) and iron-containing foods, antacids, or supplements for 2–3 h after taking drug (150,151, 155). Tetracyclines can interfere with the activity of folic acid, potassium and vitamins B_2, B_6, B_{12}, C, and K (151)	Anorexia, nausea, vomiting, diarrhea (48)
Macrolides	Erythromycin stearate	Take with water on an empty stomach 1 h before or 2–3 h after meals (154, 155)	Erythromycin may interfere with the absorption and /or activity of calcium, folic acid, magnesium, and vitamins B_6 and B_{12} (151)	May upset stomach (154) GI side effects including nausea, vomiting, abdominal pain, diarrhea and anorexia (48)
	Azithromycin (capsules)	Take with water on an empty stomach 1 h before or 2–3 h after meals (155). When taken with food, its absorption is reduced by 50% (156)	Avoid aluminum and magnesium-containing antacids (151,154)	GI side effects including dyspepsia, flatulence, vomiting (48)

(continued)

Table 3 (continued)

Drug Family	Drug Name	Administration Instructions	Nutritional Effects	Adverse Reactions
	Dirithromycin	Take with food or within 1 h of eating a meal *(154)*		
Rifampin	Rifampicin	Take with water on an empty stomach 1 h before or 2–3 hr after meals *(152)*		
	Rifampin	Take on an empty stomach *(155)*	Cause vitamin D deficiency. Give vitamin D if patient cannot tolerate milk *(155)*	
Quinolones	Ciprofloxacin; Norfloxacin	Can be taken with meals but best when taken 2–3 h after meals *(154)*	Avoid calcium (dairy products), aluminum, zinc, iron, and magnesium-containing antacids or supplements *(106,156)* Give with increased fluids *(155)*	Nausea, diarrhea, vomiting *(48)*

of those infected are women *(8)*. The number of infections from this pandemic surpasses those of any war in the history of humankind. During 2001, more than 5 million people worldwide were newly infected with the virus. It is estimated that over the next 10 yr, if there are no effective, low-cost, and available treatments, there will be more than 20 million people worldwide who have died as a result of this epidemic *(8)*.

During the last 20 yr, HIV disease has been extensively studied, including the relationship between HIV infection and nutrition. Nutritional status has been demonstrated to affect the course of the infection from the onset, during latency and progression to AIDS, as well as throughout the course of opportunistic infections *(29–46)*. Nutritional therapy is especially important where antiretroviral drugs are not available *(31)*, and is also required when patients are treated with one or more antiretroviral and/or other drugs.

5.4.1. Drugs Used to Treat HIV Infection and Their Effects on Nutritional Status

The primary objective of drug therapy is to halt viral replication. Most drugs target the enzymes that either permit the virus to enter the host cell's DNA or decrease the potential for the virus to replicate within the host's cells. Drug treatment usually involves the simultaneous administration of at least two drugs; in developed countries, these are given to infected individuals from the onset of symptoms and continue indefinitely. Resistance to HIV drugs is common and thus throughout the course of the disease there are multiple adjustments in drug combinations (Table 4) *(25,47,48)*.

Even when patients are asymptomatic, there are many relevant nutritional consequences owing to the advance of the disease *(25)*. Continuing production of pro-inflammatory cytokines and a general state of increased metabolic activity contribute to the weight loss seen as disease progresses. Reduced dietary intake and nutrient malabsorption also contribute to the deteriorating nutritional status. Finally, most drugs used to treat HIV and AIDS have similar adverse effects on the GI tract, resulting in nausea and diarrhea, loss of appetite, dyspepsia and anorexia, loss of sensation in the mouth, and changes in taste perception. Consequently, patients suffer from decreased food intake. There is also an acceleration of loss of nutrients because of the persistent diarrhea seen with the disease as well as in response to drug therapy. Both macro- and micronutrients, including sodium, potassium, proteins, fat, and fat- and water-soluble vitamins, are lost in diarrhea. More serious adverse effects to drugs include pancreatitis and liver dysfunction *(28,49)*.

There appears to be an increased requirement for macronutrients and several of the micronutrients in HIV-infected individuals. When clinical studies are undertaken, these patients are almost always treated with a multiple of the drugs noted in Table 4. HIV-infected patients often have elevated triglycerides and may have higher circulating fatty acids. Arginine and glutamine, amino acids that have been shown to be immunomodulatory, have been given to HIV-infected patients with consequent beneficial effects such as increases in lymphocyte counts and decreases in infections *(50)*.

With regard to micronutrients, there are consistent reports of significantly lower circulating levels of riboflavin, niacin, folate, vitamins B_6 and B_{12}; vitamin B_6 and folate are important for optimal immune responses. Low serum vitamin A levels are predictive of poor long-term outcomes. Indicators of increased oxidative stress are well documented and selenium, vitamins C and E circulating levels are often reduced *(10,25–27,51–53)*.

Low zinc status is associated with depressed immune responses in non-HIV-infected adults and children. The mechanisms involved in zinc immunosuppression include its requirement for the synthesis of thymulin needed for the maturation of T cells in the thymus. Zinc is also required for the activation of several enzymes associated with immune-cell replication. With regard to the HIV, in vitro studies have shown that zinc can block the activity of the HIV-protease that is required for the synthesis of new viral particles. Also, other zinc-containing proteins can inactivate HIV replication in vitro. As already mentioned, reactive oxygen-containing radicals can initiate HIV replication and zinc is the mineral found in the antioxidant metallothionein and copper–zinc superoxide dismutase. Thus, it is not surprising that low zinc status in HIV-infected patients and AIDS patients is predictive of poorer immune status than if zinc status is normal *(25)*. Several small studies have examined the effects of zinc status in HIV and AIDS and have also examined the effect of zinc supplementation (intravenous and oral administration) on drug therapy. Specifically, zinc supplements enhanced the zidovuline efficacy as measured by reduction in secondary infections *(53)*. In contrast, there are also cross-sectional epidemiological data that suggest that zinc supplementation is associated with decreased survival in patients supplemented with more than the current recommended daily intake level of 15 mg/d *(45)*.

5.5. *Autoimmune Diseases*

As indicated previously, the immune system can react to self-antigens and attack specific organs or multiple, systemic sites within the body, resulting in inflammation and cellular destruction. One clear example of how the immune system can influence one's nutritional status is seen in the autoimmune disease, pernicious anemia. In autoimmune-related pernicious anemia, the body synthesizes antibodies against gastric parietal cells responsible for the secretion of intrinsic factor that is required for the absorption of vitamin B_{12}. The autoimmune disease also results in a significant drop in the production of acid in the stomach, as parietal cells are also the source of stomach acid. Thus, both the intrinsic factor associated absorption as well as the acidic pH required for B_{12} release from foods are adversely affected *(54)*. Vitamin B_{12} (cobalamin) is a cofactor in the synthesis of DNA and is required for the development of all new cells. Because red blood cells are one of the major cell types that are produced at high rates daily, a deficiency of vitamin B_{12} is seen in a malformation of the nucleus of the immature red blood cell. This larger than normal or megaloblastic red cell is characteristic of the anemia seen with B_{12} deficiency. Other major targets are epithelial cells and the myelin-producing cells lining nerves; these cells are actually of immune-cell origin. Injections of vitamin B_{12} overcome the requirement for both intrinsic factor and stomach acid. High oral doses of B_{12} (1000 times the recommended intake level) can also reduce the signs of B_{12} deficiency *(55)*.

There are more than 50 autoimmune diseases that have been identified in the past decades. Examples of organ-specific autoimmune diseases include Type 1 or juvenile diabetes (pancreas), Grave's disease of the thyroid, and Meniere's disease of the ear. Systemic diseases include SLE, multiple sclerosis (MS), RA, and other arthrides. A recent important epidemiological study identified 24 of the most commonly occurring autoimmune diseases in the United States and found that more than 8 million adults, which is about 1 in 31 individuals or about 3% of the adult population, has an autoimmune disease *(56)*. For the 24 types of autoimmune diseases, women were at 2.7 times greater

Table 4
Drugs Used to Treat HIV and Possible Nutritional Effects

Drug Class	Specific Drug (Drug Common Name)	General Effects Related to Nutritional Status	Administration Instruction/ Specific Nutritional Effects
Nucleoside analogs reverse transcriptase inhibitors (NRTIs)	Zidovudine (Retrovir, formerly AZT)	• Nausea • Diarrhea • Constipation • Loss of sensation in the mouth • Oral ulcers • Changes in taste perception • Loss of appetite • Other GI tract reactions that result in decreased food intake • More serious adverse effects include pancreatitis and liver dysfunction (28,48,49)	The effect of food on the absorption from tablet is unknown (48). Reduction in copper and zinc blood levels. If low B_{12}, more likely to develop blood-related side effects (anemia) (151).
	Dianosine (Videx)		Should be taken on an empty stomach 30 min before or 2 h after eating food (48,151).
	Zalcitabine (HIVID)		Absorption is reduced when drug is administered with food (48).
	Stavidine (Zerit)		Zerit should be taken every 12 h without regards to meals (48).
	Lamivudine (Epivir)		Epivir (liquid or tablets) can be administered with or without food (48).
Protease inhibitors (PI)	Saquinavir (Fortovase)	• PIs are known to cause dyspepsia and anorexia • Redistribution and accumulation of body fat • Increase in triglycerides • Increase cholesterol	Increased (about eight times higher) single dose absorption under fasting conditions was reported (48).

(continued)

Table 4 (continued)

Drug Class	Specific Drug (Drug Common Name)	General Effects Related to Nutritional Status	Administration Instruction/ Specific Nutritional Effects
	Saquinavir (Invirase)	• Onset of new diabetes and exacerbation of preexisting conditions • Diarrhea • Nausea *(48)*	Patients should be advised to take drug within 2 h of a full meal. When drug is taken without food, concentrations of drug in the blood is very low and may result in much reduced (approximately eight times less) antiviral activity *(48)*.
	Ritonavir (Norvir)		Drug should be taken with food if possible. Drug may cause a reduction in copper and zinc blood levels. If patients have low B_{12}, they are more likely to develop blood related side effects like anemia *(151)*.
	Amprenavir (Agenerase)		May be taken with or without food. Should not be taken with a high fat meal (reduce its effectiveness) *(48)*.
	Indinavir (Crixivan)		Take each dose (every 8 h) without food but with water at least 1 h before or 2 h after a meal. May be taken with a light meal (that contains no fat). Can cause kidney stones and should be taken with water or other liquids *(48)*.
Non-nucleoside reverse transcriptase inhibitor (NNRTI) *(48)*	Nevirapine (Viramune)		Drug is readily absorbed and the bioavailability is not affected by ingestion of foods including high-fat meals *(48)*.

Table 4 (continued)

Drug Class	Specific Drug (Drug Common Name)	General Effects Related to Nutritional Status	Administration Instruction/ Specific Nutritional Effects
	Delaviridine (Rescriptor)		May be administered with or without food, however, there is a significant reduction in the amount of the drug in the plasma when taken with a high fat meal. Drug should be taken apart from antacids (at least 1 h) *(48)*.
	Efavirenz (Sustiva)		It may be taken with or without food, however, high-fat meals should be avoided as it may increase absorption significantly *(48)*.
Sulfonamides	Trimethoprim and sulfamethoxazole (Bactrim)	Most common adverse effects are GI-related including nausea, vomiting, and anorexia. Caution when given to patients with folate deficiency *(48)*.	Should be taken with plenty of fluids. The incidence of hyperkalemia appears to be higher with AIDS patients receiving Bactrim *(48)*.
Macrolides	Clarithromycin (Biaxin)	Most frequent effects were diarrhea, abnormal taste and nausea *(48)*.	Biaxin can be taken with or without food. The drug is rapidly absorbed, with about 50% bioavailability. Food slightly delays absorption with increased plasma concentration but without increased bioavail-ability *(48)*.
Antiprotozoal	Atovaquone (Mepron)		Administration with food enhances drug's absorption (twofold). The bioavailability is highly dependent on the formulation and the diet *(48)*.

Table 4 (continued)

Drug Class	Specific Drug (Drug Common Name)	General Effects Related to Nutritional Status	Administration Instruction/ Specific Nutritional Effects
Orexigenics	Megestrol (Megace)		The effect of food on absorption has not been evaluated *(48)*.
	Dronabinol (Marinol)	Effective against anorexia associated with AIDS *(48)*.	Drug should be taken prior to lunch and dinner *(48)*.

risk than men of suffering from an autoimmune disease. The most prevalent diseases were Grave's disease of the thyroid, type 1 diabetes, pernicious anemia, and RA. For comparison, the prevalence of type 1 diabetes is 192/100,000 US adults, whereas lupus is seen in about 24/100,000 people (mainly women). Jacobson et al. *(56)*, indicate that the incidence of RA and type 1 diabetes and three other autoimmune diseases will increase over time, based on past analyses. These authors also point out the need for better demographic information about the prevalence and incidence of autoimmune diseases. The economic impact is considerable because the majority is afflicted during their most productive years, and the conditions are chronic, with no cures currently available.

5.5.1. Rheumatoid Arthritis

RA is a chronic, progressive autoimmune disease of unknown origin that is associated with a genetic predisposition and an environmental trigger *(57–59)*. RA causes a deterioration of articular joints, causing pain, stiffness, swelling, and deformity that over time results in severe disability. The autoantibodies in RA are sometimes referred to as rheumatoid factor and titers are used diagnostically. The autoantibodies are found in the joint fluids and are probably the initiators of the symmetrical inflammation seen in peripheral joints. The age of onset may be in youth or young adulthood resulting in juvenile RA. About 1% of the population suffers from adult-onset RA; more than 2 million US adults are affected and 75% are women. Oxidative damage to the joints and increased production of inflammatory cytokines are hallmarks of RA. Patients with RA may also have symptoms of anemia that is unrelated to a lack of dietary intake of iron. Anemia of chronic disease (ACD) is associated with a reduction in red blood cell (RBC) iron. There appears to be a redistribution of iron from inside the RBC to within the synovial fluid. The RBCs have receptors for the rheumatoid factor. Binding of rheumatoid factor to the receptor on the RBC triggers autoimmune destruction of the RBC and release of iron into the synovial fluid. RA-associated ACD causes an increase in oxidative damage in the joints exposed to free iron *(57,60)*.

5.5.2. Systemic Lupus Erythematosus

SLE mainly affects women of childbearing age; only 10% of lupus patients are male. Worldwide, the incidence in white women is 1 in 1000, but is 1 in 250 in Black women. In the United States, the disease affects about 1.4 million women. About one-third of patients have more than one autoimmune disease; about half have a relative who is also affected by autoimmune disease. There are few data associating nutritional status and risk of lupus. A prospective epidemiological study noted that low vitamin E status preceded diagnosis of SLE and RA in a well-characterized population *(61)*. There are suggestions from a limited number of studies that certain food components and nutrients may affect the course of the disease. The data, however, are from small studies over relatively short periods of time.

5.5.3. Drugs Used to Treat Autoimmune Diseases and Their Effects on Nutritional Status

Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) are usually the first medications given to reduce the inflammation. However, their efficacy is often inadequate. Corticosteroids are potent anti-inflammatory drugs but do not stop the joint

erosion and their efficacy decreases with use. Disease-modifying drugs, such as gold compounds, cause potential adverse reactions that include GI tract disturbances. Cytotoxic drugs (such as methotrexate, an antifolate) are the next group of drugs given when RA continues to cause pain and joint. These drugs reduce pain but do not affect disease progression. The progressive nature of RA results in the successive use of more toxic drugs that have serious side effects on overall health and nutritional status *(51,62,63)*. Additionally, as discussed later, the potential for the development of drug-induced osteoporosis is significantly increased by both corticosteroids and cytotoxic drugs (Table 5; *48,51,58,62,64–68*). Newer drugs used to treat RA include etanercept (Enbrel) and infliximab (Remicade). These two drugs show indications of actually stopping the disease progression. Both drugs target TNF, an inflammatory cytokine produced by immune cells. The drugs bind to TNF before it can trigger inflammatory responses. Neither drug is given orally; entanercept is given by injection and infliximab is given by intravenous infusion *(51,68)*.

Liver dysfunction and GI tract discomforts are common with NSAIDs, cytotoxic drugs, and corticosteroids. Newer NSAIDs that target only the type 2 cyclooxygenase enzyme (COX-2), may not cause as many GI tract problems as older drugs that targeted both COX-1 and COX-2. Most of the cytotoxic drugs, such as methotrexate, are folate antagonists and therefore will decrease folate status and increase homocysteine levels. Increasing folate intake can overcome some of these effects; however, there may be a decrease in drug efficacy *(66)*. Methotrexate also can cause mouth ulcers that can affect overall consumption of food. Cyclosporine, another cytotoxic drug, reduces the activity of T cells and is a potent immunosuppressive agent used for transplantation and RA therapy *(65)*. However, side effects include hyperglycemia, hypercholesterolemia, electrolyte disturbances, and renal insufficiency *(69)*. The TNF-targeted drugs can result in increased infections, as TNF is a normal immune cytokine involved in destruction of pathogens *(57)*.

5.5.4. Nutrients That May Affect Autoimmune Diseases

Several dietary components have been shown to inhibit COX-2 and/or reduce the formation of inflammatory prostaglandins—the products of COX-2 enzyme activity *(70,71)*. These include vitamin E and long-chain omega-3 and omega-6 fatty acids. Supplementation has resulted in pain reduction in some studies and reduction in pain medication use in others. In one study involving 49 RA patients, supplementation with γ-linolenic acid (omega-6) and eicosapentaenoic acid (omega-3) for 1 yr resulted in decreased pain and tapering of NSAID use in 80% of patients compared to 33% in the placebo group. A number of studies have examined the effects of supplementation with omega-3 fatty acids and have shown consistent reductions in tender joints and morning stiffness *(72)*.

5.5.5. Diabetes

There are two classes of diabetes (Table 6): type 1, an autoimmune disease, and the more common clinical presentation type 2, associated with metabolic syndrome and obesity, of unknown cause. Regardless of the initial cause, the long-term consequences of these chronic conditions are similar. Numerous and cumulative debilities to many tissues and organs of the body are the consequences of diabetes *(73–78)*. Atherosclerotic

Table 5
Drugs Used to Treat RA and Possible Nutritional Effects

Drug Class/Mode of Action	Specific Drug (Drug Common Name)	Administration Instructions	Nutritional Effects and Other Indications
Nonsteroidal anti-inflammatory drugs (NSAIDs) *(48)*	Indomethacin (Indocin)	Should be taken with food to prevent stomach irritation, however high-protein and high-fat foods have been reported to interfere with the drug absorption *(151)*.	Cause GI irritation, bleeding, and iron loss. Drug may increase potassium levels. Decreased absorption of folic acid and vitamin C. Calcium and phosphate levels may be reduced *(151)*. Sodium and water may be retained *(48,106)*.
	Ibuprofen (Advil, Motrin, Nuprin)	Should be taken with food to prevent GI upset *(151)*.	Cause GI irritation, bleeding, and iron loss. Drug may increase potassium levels. Sodium and water may be retained *(151)*.
	Naproxen (Ec-Naprosyn, Naprosyn)	Should be taken with food to prevent upset stomach *(151)*.	Cause GI irritation, bleeding, and iron loss. Drug may increase potassium levels. Sodium and water may be retained *(151)*.
Corticosteroids *(48)*	Cortone (Cortisone) Prelone (Prednisolone) Depo-Medrol (Methylprednisolone) Decadron (Dexamethasone) Celestone (Betamethasone)	Drugs can cause stomach upset and should be taken after eating a meal, before 9AM for best results. Drugs can cause protein wasting and for some diseases high-protein diets should be recommended (perhaps not SLE) *(151)*.	Drugs may increase loss of magnesium and increase loss of potassium in the urine. Drug may increase loss of vitamin B_6. Sodium retention may be a problem. Drugs reduce the body's ability to activate vitamin D, increasing the risk of bone loss *(151)*.

(continued)

Table 5 (continued)

Drug Class/Mode of Action	Specific Drug (Drug Common Name)	Administration Instructions	Nutritional Effects and Other Indications
Disease modifying antirheumatic drugs (DMARDs). Anti-inflammatory effects as well as immunomodulatory properties.	Gold compounds (Myochrysine injection)		Predominant action appears to be a suppressive effect on the synovitis of active rheumatoid disease *(48)*. Reduce number of monocytes and cytokine production.
	Antimalarial agents (Plaquenil)		GI complaints (diarrhea, anorexia, nausea) may occur *(48)*.
	Penicillamine (Cuprimine, Depen)	Food decreases drug absorption, thus should be taken 1 h before or 2 h after any food to avoid this interaction. When taken with iron, its absorption is decreased *(151)*.	This is a chelating agent; it chelated copper, iron and zinc *(106,151)*. Therapy with this drug has been associated with sodium depletion *(151)*. It also reduces excess of cystine. Drug may cause a vitamin B_6 deficiency *(48,106)*.
Cytotoxic immunosuppressive drugs. Use is based on the premise that the drugs down regulate immune functions; however there is lack of evidence that the	Cyclophosphamide (Cytoxan, Neosar)	Take on an empty stomach unless severe GI upset. May cause nausea, mouth sores, and food aversions *(151)*.	Active alkylating metabolites interfere with the growth of rapidly dividing cells. The mechanism is thought to be through cross-linking to DNA.
	Methotrexate (Folex, Rheumatrex)	Food can interfere with the drug absorption, and it can cause	Decrease leukocyte trafficking. Considered effective as an

Table 5 (continued)

Drug Class/Mode of Action	Specific Drug (Drug Common Name)	Administration Instructions	Nutritional Effects and OtherIndications
suppression of the immune system accounts for clinical effects. Cytotoxic drugs suppress both cellular and humoral host defenses.		upset stomach. May cause nausea, mouth sores, and food aversions *(151)*.	antiinflammatory as well as an immune suppressive agent, thus decrease folate status and increase homocysteine *(48,150,151)*. It is recommended that for RA people should supplement with folic acid *(151)*, however, drug efficacy may be decreased *(66)*.
	Azathioprine (Imuran)	May cause nausea, mouth sores, and food aversions *(151)*.	Immunosuppressive anti-metabolite. Mechanism in which it affects autoimmune disease is unknown. Inhibit the proliferation of T lymphocytes and antibody formation *(48)*.
	6-mercaptopurine (Purinethol)	May cause nausea, mouth sores, and food aversions *(151)*.	Purine analogue that interferes with nucleic acid biosyn-thesis *(48)*.
	Cholrambucil (Leukeran)	May cause nausea, mouth sores, and food aversions *(151)*.	Bifunctional alkylating agent that has been found active against selected neoplastic disease *(48)*.

(continued)

Table 5 (continued)

Drug Class/Mode of Action	Specific Drug (Drug Common Name)	Administration Instructions	Nutritional Effects and OtherIndications
Novel drugs	Infliximab (Remicade, intravenous infusion)		This compound is a mono-clonal antibody containing regions that binds to TNF.
Tumor necrosis factor (TNF) antagonist	Etanercept (Enbrel, injection)		This compound binds to TNF and blocks its interaction with cell surface TNF receptors, thus preventing the biological activity of TNF *(68)*.

Table 6
Nutritional Consequences of Diabetes (Types 1 and 2)

Short-Term Consequences	Long-Term Consequences
• Low level of vitamin C in the blood.	• Diabetic gastroenteropathy include dysphagia, nausea, vomiting, diarrhea, constipation, and fecal incontinence.
• Elevated triglycerides.	• The incidence of liver diseases is higher with frequent viral hepatitis.
• Hypertension, hypertriglyceridemia, decreased HDL and increased risk of atherosclerosis and cardiovascular diseases.	• Formation of advanced glycosylation products, activation of protein kinase C, increasing growth factor, and production of cytokines.
• Hypertriglyceridemia, probably owing to a decrease in lipoprotein lipase activity. Consequently, the plasma levels of VLDL are elevated, and increased deposition of lipids possibly accelerate the atherosclerotic process.	• Once infected, the ability of diabetics to tolerate the infection is reduced. • Morbidity as a result of infection. • Cardiovascular diseases including acceleration of atherosclerosis of coronary and peripheral arteries, cardiomyopathy, and cardiac neuropathy.
• Injury to the endothelial cells as a result of hyperglycemia, insulin resistance, increased plasma LDL, decreased HDL, abnormal platelet aggregation, and coagulation.	• Monckeberg sclerosis resulting from calcification of the media of large arteries. • More frequent ischemic heart disease relative to general population.
• Increased production of oxidants by the endothelial cells as a result of hyperglycemia via two mechanisms: nonenzymatic glycation of proteins and increased production of H_2O_2.	• More frequent myocardial infraction with an increased lethal ventricular arrhythmias possibly induced by more fibrosis complicated by reduced response to antiarrhythmic drugs. • Autonomic neuropathy causes the alteration in the vagus nerve function and sympathetic activity leading to cardiac arrhythmia.
• Increased level of lipid peroxidation products as well as antioxidant enzymes.	• Increased stiffness of diabetic ventricle may lead to congestive heart failure. • Peripheral neuropathy: increased incidence of peripheral vascular disease. Chronic foot ulcers involving both micro- and macrovessels. • Blindness and vision disability that develops in both types 1 and 2 diabetes (although the onset and the rate may be different in the two types of diabetes). • Cataract is considered an important ocular manifestation of diabetes. • Increased levels of glaucoma. • Diabetic nephropathy in type 1 (30–40%) and type 2 (5–10%). Clinical signs include hypertension, renal insufficiency, heavy albuminurea, and edema. • Noninfectious complications of diabetes include several abnormalities including xanthomas, sclerederma, and necrobiosis.

HDL, high-density lipoprotein; VLDL, very low-density lipoprotein; LDL, low-density lipoprotein. (From refs. *73–78*.)

cardiovascular disease, hypertriglyceridemia, and increased low-density lipoprotein (LDL) with reduced high-density lipoprotein (HDL), and increased bacterial and fungal infections are some of the common secondary consequences of diabetes.

The major cause of death in diabetics is atherosclerotic cardiovascular disease *(79)*. As diabetes progresses, there is an overall decrease in antioxidant status with decreased levels of vitamin C, glutathione, superoxide dismutase, and other antioxidants in the blood of diabetics compared to nondiabetics that are age, sex, and dietary intake-matched *(80)*. Reduced antioxidant status may be a major factor in the increased damage to both the micro- and macrovasculature in diabetics.

Hyperglycemia is associated with depressed cellular immune responses and that results in increased prevalence of bacterial and fungal infections; infections are often persistent, with the formation of ulcers and deep infections in the joints *(81–83)*. Increased oxidative stress and free radical damage could be the cause of many of the pathologies seen in diabetes *(84)*.

There is an increase in the procoagulant factors in the blood along with hypertriglyceridemia, increased LDL , and reduced HDL levels are common. Advanced glycation endproducts (AGEs), that result from glucose binding inappropriately with the body's proteins, are triggers for many immune cells to produce inflammatory cytokines. AGE receptors are also found on endothelial and renal cells where the binding of AGE results in the production of inflammatory cytokines such as interleukin (IL)-1, TNF, and insulin-like growth factor-1. Consequently, there is an increase in inflammation in the blood vessels throughout the body and loss of renal function *(85)*.

5.5.5.1. Type 1 Diabetes and Drugs Used to Treat. Type 1 diabetes, an autoimmune disease, is caused by the self-destruction of the majority of the insulin-secreting cells of the pancreas *(86,87)*. Genetic predisposition and a triggering factor that initiates the inappropriate recognition of the insulin-secreting pancreatic islet cell as non-self by T cells are two major factors that are thought to be essential in the development of type 1 diabetes *(88)*. Inappropriate destruction of islet cells results in an increased oxidative stress on the pancreas, and continued adverse effects, owing to the lack of insulin, further increases the potential for oxidative damage *(89–91)*. The potential for beneficial effects of antioxidant supplementation in patients with type 1 diabetes were examined by Jain et al. *(89–91)*. They have found a marked decrease in glycosylated hemoglobin and reduction in triglyceride levels following supplementation with vitamin E *(89)*.

The initial major drug requirement difference between the two diabetes is the need for insulin immediately once there is a diagnosis of type 1 diabetes as the autoimmune destruction of the islet cells of the pancreas that produce insulin has proceeded to the point of clinical recognition of the disease. The precipitous rise in circulating glucose levels is often the defining feature of the diagnosis; glucose is also excreted at high levels in the urine. Moreover, glucose does not enter the tissues appropriately resulting in a lack of energy source in critical tissues and organs such as the brain and retina *(76,77)*. Without the administration of insulin, the type 1 diabetic would succumb in a few weeks or months. Thus, insulin is the drug that is administered daily to type 1 diabetics. Type 1 diabetes often develops during childhood before the age of 10. Even with the use of insulin, the nutritional management of the patient (who is usually young) is critical for optimal long-term survival *(92,93)*.

5.5.5.2. Type 2 Diabetes and Drugs Used to Treat. Type 2 diabetes develops most frequently in mid-life, although the incidence is increasing in the young. Approximately 50% of individuals with type 2 diabetes are 65 yr old or older. The disease is characterized by a depressed response of target tissues to insulin, resulting in a higher than normal circulating level of glucose, and a lower than normal level of glucose in tissues *(75,81,84,94)*. Additionally, type 2 diabetics often have hyperlipidemia and hypertension, and are also often obese. Increased body mass index (BMI), used to define obesity, is related to decreased insulin sensitivity in type 2 diabetics *(73)*. There is an increased risk of type 2 diabetes in both men and women with increased central or visceral obesity *(95)*. Long-term effects of type 2 diabetes include nephropathy, neuropathy, retinopathy, impaired cellular immunity, osteoporosis, and multiple adverse effects on the cardiovascular system *(74,79,96–104)*. Diet changes are often the first line of defense against the insulin resistance seen in type 2 diabetes. However, only about 10% of adults can control their circulating glucose levels with lifestyle changes alone *(105)*.

There are a number of drugs used to treat type 2 diabetes, although these patients often require additional insulin as well *(47,106,107)*. Metformin, which is frequently the first drug used in the treatment of type 2 diabetes in adults, is the only oral hypoglycemic drug that is currently approved for the treatment of type 2 diabetes in children. Combination therapies are frequently prescribed. These include the addition of α-glucosidase inhibitors or thiazolidinediones, sulfonylurea agents in combination with the oral hypoglycemic drugs (Table 7; *107,108*).

5.5.5.3. Drug–Disease Effects on Nutritional Status. Insulin, which is the most commonly used drug for treatment of both types of diabetes, has a well-recognized side effect of increasing weight gain. Thus, it is especially difficult for the overweight or obese patient to lose or even maintain weight during insulin therapy. Currently, obese diabetics are also often given antiobesity drugs including sibutramine or orlistat. The latter agent can reduce fat-soluble vitamin status and can also reduce long-chain fatty acid levels that are important immunomodulators. The effects of weight-reduction interventions on nutritional as well as immunological status can be numerous and particularly serious for the diabetic *(14,109)*.

Sulfonylureas have also been associated with causing increased weight gain and hypoglycemia *(110)*. α-Glucosidase inhibitors compete with the native enzyme and slow the breakdown of starches, thereby slowing the rise in blood glucose following a meal. However, there are GI side effects such as diarrhea, cramping, abdominal pain, and flatulence that can affect compliance and also result in loss of fluids and micronutrients. Lowered serum levels of vitamins B_6, B_{12}, and folic acid are associated with increased serum homocysteine, a risk factor for cardiovascular and cerebrovascular diseases and diabetic neuropathy *(111–116)*. Although there has not been a clear association between serum homocysteine levels and drugs to treat diabetes, metformin may induce vitamin B_{12} malabsorption, and this may result in higher homocysteine levels *(117)*.

Oxidative stress is increased in diabetics *(80,118)* and antioxidant nutrient status is often lower than optimal *(119)*. Ascorbic acid (vitamin C) and glucose enter cells through the glucose transporter and elevated glucose levels competitively inhibit the movement of vitamin C into cells. Consequences of lower than optimal antioxidant status have been documented in the cardiovascular tissues and lipoproteins of diabetics *(120)*. Supple-

mentation with vitamins E and C has been shown to have beneficial effects on several immune parameters in diabetics *(121)*. Vitamin E supplementation reduced protein glycosylation and platelet aggregation in type 1 diabetics and improved glycemic control and insulin action in type 2 diabetics *(122)*. Several studies have shown that vitamin E supplementation reduced the potential for LDL oxidation ex vivo. Recent data suggest that vitamin E reduces the synthesis and secretion of inflammatory cytokines from macrophages taken from diabetics *(85)*.

Chromium supplementation in some studies in diabetics has been shown to decrease blood glucose by potentiating the action of insulin. However, there are data indicating that chromium absorption is decreased in diabetics *(123,124)*.

6. NUTRITIONAL COMPONENTS THAT ENHANCE IMMUNE RESPONSES

6.1. Vitamins

Vitamin A has been called the anti-infective vitamin for almost a century. Vitamin A deficiency has been associated with significantly increased risk of infection especially in young children in underdeveloped countries and also in poorly nourished children in developed countries *(125)*. Vitamin A deficiency affects an estimated 253 million preschool children worldwide. The consequences of vitamin A deficiency include growth failure, depressed immunity, higher risk of xerophthalmia and blindness, anemia, and increased morbidity and mortality from some infectious diseases *(126–128)*. Decades of clinical studies have shown that vitamin A status significantly affects morbidity and mortality associated with measles infections in children. Vitamin A supplementation studies have also shown that supplemented children have better outcomes, especially if their vitamin A status was low at the time of infection/hospitalization. Recently, these data were confirmed and extended to show that vitamin A supplementation also reduced the number of children with measles-related pneumonia and reduced the time to recovery *(129)*. β-carotene is the major carotenoid precursor of vitamin A and it too has immunoenhancing properties that may be additional to its role as a source of vitamin A *(130)*. β-carotene supplementation in both young and senior men reduced the immunosuppressive effects of ultraviolet (UV) light in well-controlled studies. Because many seniors move to sunnier environments where exposure to UV light is increased, these data suggest that β-carotene may protect from any depressions in immune responses as a result of sun exposure *(131)*.

Vitamin E supplementation in healthy, well-nourished seniors has resulted in significant enhancements in multiple aspects of immune function including delayed hypersensitivity responses, responses to the hepatitis B vaccine, lymphocyte proliferation, and reduction in the formation of immunosuppressive prostaglandins. There is also the suggestion that vitamin E supplementation may reduce the incidence of respiratory tract infections in healthy seniors. Low serum vitamin E levels have been seen in individuals with impaired immune responses associated with viral infection. Von Herbay et al. *(132)* reported that serum vitamin E levels were significantly lower in patients with severe viral hepatitis compared to controls and returned to control levels when the hepatitis subsided. These data suggest that hepatitis involved oxidative reactions that consumed vitamin E and may consequently decrease potential immune responses to the disease. Comstock et al. *(61)* found that lower than average serum vitamin E levels preceded the diagnosis

Table 7
Drugs Used to Treat Diabetes Type 2 and Possible Nutritional Effects

Drug Class/Mode of Action	Specific Drug (Drug Common Name)	Administration Instructions	Nutritional Effects and Other Indications
Sulfonylureas Insulinotropic, increases circulating insulin. Insulin secretion from the islet is stimulated perhaps by increasing β cell sensitivity to glucose *(48)*.	Glipizide (Glucotrol) Gilmepiride (Amaryl) Glyburide (Diabeta) Chlorpropamide (Diabinese)	Drug should be administered 30 min before a meal *(48)*. Drug should be administrated with meals *(48)*. Drug should be administrated with breakfast or a main meal. One or two doses are usually sufficient *(48)*. The drug is absorbed rapidly and within 2–4 hr reaches maximum levels in the blood *(48)*.	Numerous drugs (niacin, thiazide diuretics, β-blockers, corticosteroids) reduce insulin sensitivity thus decrease efficacy. Newer drugs (Glipizide) control blood glucose w/o deleterious changes in the plasma lipoprotein levels. Some sulfonylureas cause adverse GI effects like diarrhea (5% for Glipizide).
Meglitinides Insulinotropic, stimulates the release of insulin from the pancreas therefore, it requires functioning β cells *(48)*.	Repaglinide (Prandin)	Drug should be taken before the meal (15 min).	GI effects like nausea (5%) or diarrhea (5%) *(48)*. Effective with Metformin; should not be taken with sulfoylureas.
Biguanides Increases insulin-simulated glucose uptake, reduces hepatic glucose production, and increases insulin-simulated glucose uptake at the periphery *(48)*.	Metformin (Glucophage)		Adverse GI symptoms including diarrhea, nausea, and anorexia are approx 30% higher than with a placebo, especially initially. Food decreases the extent and slightly delays the absorption. A decrease of B_{12} levels is observed in 7% of the patients, perhaps owing to interference

(continued)

Table 7 **(continued)**

Drug Class/Mode of Action	*Specific Drug (Drug Common Name)*	*Administration Instructions*	*Nutritional Effects and Other Indications*
			with B_{12} absorption. Stabilization or decreased body weight. Tendency to improve lipid profile, particularly when baseline is elevated *(48)*. Used effectively with sulfonylureaes. Slightly anorectic. May reduce triglycerides.
Carbohydrate Inhibitors Inhibition of alpha-glucosidase in the intestinal brush border, leading to delay in carbohydrate absorption.	Acarbose (Precose), Miglitol (Glyset)	Should be taken with the first bite of the meal, for every meal.	GI symptoms of diarrhea in approx 20% of cases over control. Low serum calcium and low plasma vitamin B_6 were associated with the drug. May be used in combination with sulfonylurea; metformin or insulin. Because of its different mechanism of action, the effects of the combined drugs is additive *(48)*.
Thiazolidinediones Enhances insulin sensitivity. Lower blood glucose levels and decrease insulin level. Increased the insulin content of pancreatic islets.	Rosiglitazone (Avandia) Pioglitazone (Actos)	May be administered with or without food.	Increase weight has been observed when used as a single treatment. High-density lipoprotein increased over time, whereas low-denisty lipoprotein only increased in the first couple of months of therapy *(48)*. Has been approved to be used in combination with sulfonylureas or metformin.

From refs. *107,108*.

of two autoimmune diseases, RA and SLE. Low vitamin E status has been associated with the conversion of an avirulent viral strain to a virulent one in an animal model *(61,133)*. As mentioned previously, several studies have noted the beneficial effects of vitamin E in diabetes. However, not all intervention studies have found an immunoenhancing effect of vitamin E supplementation. Graat et al. *(134)*, in a study involving more than 650 individuals over age 60, gave one-fourth of the population a supplement of 200 mg of vitamin E for about 14 mo. They found no decrease in the incidence of ART infection and an increase in the duration and symptoms compared to placebo. The infections were self-reported. The same study included a multivitamin/mineral supplement arm and also showed no significant decreased risk of infection—however there was no increase in duration or symptoms in this arm of the study. The group given both actives responded similarly to the individuals getting each active alone.

Vitamin C supplementation, following depletion in a controlled, metabolic ward study, restored the DTH responses that were severely depressed following the depletion phase of the study. The level of supplementation required was several-fold higher than the current recommended intake level. Vitamin C also regenerates the antioxidant form of vitamin E and therefore may be particularly important to see the full benefit of vitamin E supplementation. Vitamin C is also critically important in the killing of bacterial pathogens by neutrophils, the most abundant population of white blood cells. Neutrophils contain very high concentrations of vitamin C, and the vitamin protects these cells from self-destruction by the oxidants produced to kill the pathogens *(135)*.

Vitamin B_6 (pyridoxine) supplementation with relatively low doses of the vitamin (about 3 mg/d) has recently been shown to enhance lymphocyte proliferation and IL-2 levels in young women *(136)*. Further research with this nutrient is needed to determine if there are clinical benefits to the supplementation.

6.2. Minerals

Zinc is a critical nutrient for immune function. The mineral is a component of the thymic hormone, thymulin required for the maturation of T lymphocytes. Zinc is required for the functioning of more than 200 enzymes necessary for virtually all cell functions including cellular proliferation that is critical to the production of the millions of new white blood cells per day. Zinc deficiency is associated with severe immune dysfunctions. Zinc deficiency also results in a loss of appetite, and thus further deficiencies resulting from decreased food intake. Studies in senior men and women have found that zinc supplementation in populations with initially low zinc status results in increased serum thymulin levels, enhanced appetite, improved antibody responses to influenza vaccine, improved delayed hypersensitivity responses, and decreases in respiratory infections *(137)*.

Zinc deficiency is common in underdeveloped countries and infant and toddler morbidity and mortality has been directly associated with zinc intake and status. Recently, Osendarp et al. *(138)* completed a well-controlled study in infants (about 1 mo old) in Bangladesh. The infants were given 5 mg/d zinc or placebo for about 2 yr. In the infants

with low initial zinc serum levels, the supplementation resulted in significantly enhanced growth and significant reduction in ART infections. These researchers have also reported that zinc supplementation during pregnancy significantly reduced infant diarrheal disease morbidity *(138)*.

In many underdeveloped countries worldwide, toddlers, young children, and pregnant women are at a high risk of vitamin A, zinc, and iron deficiency *(128)*. Zinc deficiency, as with iron deficiency, is associated with diets low in meat protein sources *(22,23)*. Zinc deficiency has been associated with growth retardation and immune suppression. Iron deficiency is a major problem among preschool children worldwide, and consequences of iron deficiency include retarded psychomotor development, impaired cognitive function, and anemia *(139,140)*. The link between iron deficiency and increased risk of infection is not as clear as it is for vitamin A and zinc. However, vitamin A supplementation often also concomitantly increases iron status and therefore it is difficult to separate the effects of any single nutrient from the effects of others that change during a single nutrient supplementation program.

Within the past decade there have been a series of experiments in mice that indicated that the nutritional status of the host could affect the virulence of a viral strain. Beck and Levander *(133,141)* discovered that the avirulent strain of coxsackievirus B3 became virulent in selenium and/or vitamin E-deficient mice. This critical finding may have relevance in humans and the emergence of new virulent pathogens, such as HIV.

6.3. Multivitamin Supplements

Several investigators have examined the effects of different combinations of vitamins and minerals on immune responses, mainly in healthy seniors *(142)*. There are consistent findings of enhancement in DTH responses, proliferative responses, and enhancement of responses to certain vaccines important for the health of the elderly. In some cases, there were also reductions in the rates of infections and decreased morbidity if infections did occur. These results are quite promising and require further study in senior populations that are at increased risk for immunosuppression, such as seen with diabetes and cancer.

6.4. Omega-3 Fatty Acids

Simopoulos *(143)* and Belluzzi *(72,144)* recently reviewed the clinical data on the anti-inflammatory properties of the longest-chain omega-3 polyunsaturated fatty acids, eicosapentaenoic acid and docosahexaenoic acid. These oils, usually in the form of either algal or fish oil have been shown to reduce the inflammation associated with several types of autoimmune diseases including RA, inflammatory bowel disease, lupus, MS and psoriasis. In addition to clinical benefits, supplementation appears to be safe at the levels given in most clinical studies. In many of the studies in patients with RA, there was also a decreased need for NSAIDs and/or corticosteroid drugs.

Anderson and Fritsche *(145)*, in a comprehensive review, examined the divergent database on the effects of omega-3 fatty acid supplementation during infectious disease. Because omega-3 fatty acids can reduce inflammatory responses in part by down-regulating macrophage and lymphocyte functions, there is still a question about the efficacy of supplementation during infection. This extensive review concluded that omega-3 fatty

acids can have beneficial effects in some instances, but not in all, and that further research is warranted.

6.5. Protein, Amino Acids, and Nucleotides

It is well accepted that protein deprivation results in significant immunodepression. In addition to nutritional deprivation, major trauma to the body results in a hypermetabolic state in which muscle tissue proteins are used to provide energy for the traumatized body. In fact, major trauma can result in acute protein malnutrition that can cause serious, life-threatening effects on the heart, liver, and immune system. Recent research has focused on certain individual amino acids and nucleotides that have been shown to individually enhance immune responses, especially during stressful situations such as surgery and other traumas *(146)*. The two amino acids that have been studied the most extensively are arginine and glutamine. Arginine supplementation restores lymphocyte proliferative responses and enhances delayed hypersensitivity responses; enhancement of T-lymphocyte responses is thought to be the major mechanism involved in the immune enhancement *(147)*. Additionally, arginine enhances the formation of collagen and is thus important in wound healing *(50)*. Glutamine serves as a major source of energy for lymphocytes, mucosal cells lining the GI tract, and macrophages. Glutamine is also the precursor of glutathione, a major water-soluble antioxidant. Nucleotides are required for the proliferation of all rapidly dividing cells, including cells of the immune system and the lining of the GI tract. Nucleotide supplementation has been found to enhance immune responses to infectious agents in animal models (*148,149*).

7. CONCLUSIONS

The immune system functions to ensure the internal integrity of the body by constant surveillance of the normal entries to the body, responding to unanticipated breaks in the skin or other body parts, and by monitoring the cells of the body to recognize and destroy cells that have been altered in some way to make them recognizable as "non-self." During fetal development and continuing through the first years of life, the cells of the immune system that are responsible for self-recognition, are educated to tolerate, and not destroy, cells that have self-antigens on their surface. The immune system involves the formation of millions of new cells per day and thus there is a very high requirement for energy and essential nutrients to support this high cellular turnover. The immune system is not fully developed at birth and responses become more vigorous during adulthood, and then, in general, become less strong during the sixth decade and thereafter.

Pathogenic organisms, such as viruses, bacteria, fungi, protozoans, and other life forms, can be destroyed by the immune system, but the immune system can also be overcome by these pathogens. Many of these infectious agents seriously affect nutrient absorption and/or inappropriately increase loss of nutrients. The double effects of infection and loss of nutrients can cause the pathogen to overwhelm the body's capacity to fight off the infection. The discovery of antibiotics has increased survival from infections. But all drugs have negative effects, and many involve the GI tract resulting in lowered nutritional status. Moreover, there are new, highly virulent infectious agents and current antimicrobials may not be effective against these new human pathogens. Multidrug therapies are often used, and these can have additive and/or synergistic negative effects on dietary intake and nutrient losses.

Vaccines are critical drugs that only work if there is an optimal immune response to the vaccine's antigen. Responses to vaccines are also, in many cases, dependent on the nutritional status of the individual being vaccinated. Moreover, in the very early years of life and in the elderly, immune responses are not as vigorous as these are in adulthood. Research has found that certain micronutrient supplementations can improve responses to certain vaccines.

Several serious infections, such as ART infections, diarrheal diseases, HIV, and TB affect billions of lives globally and are responsible for millions of death annually. Numerous drugs are used in the treatment of these infections. Both the disease itself and the treatments can cause additional detriments to the immune system. These interactions are often overlooked and an examination of the detailed tables provided in this chapter document the need for attention to the drug–nutrient effects as well as the potential nutrient–drug effects.

When the immune system is triggered by some unknown agent to recognize certain cells or tissues of the body as non-self, the result is autoimmune disease. There are about 50 characterized autoimmune diseases and virtually all of them are found in a much greater frequency in women compared to men. This chapter reviews the major effects of RA, SLE, and diabetes (types 1 and 2) and the drugs used to treat these diseases as well as the nutritional consequences of the disease, drug, and their interactions. The limited data on the potential for certain nutrients to be of benefit in autoimmune diseases treatment are also reviewed. Additional research is required in this area.

Finally, there are data that suggest that certain vitamins, minerals, multivitamins, omega-3 fatty acids, and certain proteins or amino acids may enhance immune responses to infections, reduce autoimmune responses, improve vaccine responses, and reduce secondary infections. Many of the studies have been done in young children and in the elderly, groups with compromised immune responses. These studies are particularly important in the elderly as it is this population group that has the greatest exposure to drugs, often multidrugs, daily. At present, most of the nutritional studies have included healthy elderly who do not consume drugs. It is critical for future studies to examine the role that nutritional interventions can play in improving immune responses in elderly taking commonly used drugs that could adversely affect their nutritional status. Drug–nutrient interactions can have serious effects on the ability of the body to mount an optimal immune response.

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24 Drug–Nutrient Interactions in Patients With Chronic Infections

Steven P. Gelone and Judith A. O'Donnell

1. INTRODUCTION

Drug–nutrient interactions (DNIs) can result in significant inconvenience to patients that can subsequently cause an increase in patient nonadherence. Unless instructed otherwise, most patients will take their medications along with meals assuming this may minimize gastrointestinal (GI) adverse effects, as well as potentially providing them a trigger to remember to take their medications. A lack of knowledge of potential DNIs may therefore lead to poor clinical outcomes. As the potential impact of these interactions may be of greatest individual and public health consequence in the treatment of chronic infection, this chapter deals specifically with DNIs in patients infected with Mycobacterium tuberculosis, the human immunodeficiency virus (HIV), or chronic viral hepatitis viruses, particularly those occurring between oral dosage regimens and food.

1.1. Mechanisms of DNIs

Although it is often difficult to determine the exact mechanism by which food causes a change in the bioavailability of a drug, several mechanisms may be involved *(1)*:

- a delay in gastric emptying
- stimulation of bile flow
- a change in GI pH
- an increase in splanchnic blood flow
- a change in luminal metabolism of the drug substance
- a physical or chemical interaction with the dosage form or drug substance

Food intake will directly affect GI secretions and gastric pH. In general, GI secretions will increase in response to food intake, resulting in an increase in acid secretion in the stomach and a lowering of stomach pH *(2)*. The impact of this change is that in the presence of a more acidic environment, the dissolution and absorption of basic drugs will be accelerated, whereas acid-labile agents will be degraded more rapidly. The quantity and content of a meal will also affect drug absorption. The intake of a large solid food meal will delay the stomach emptying rate, potentially resulting in increased degradation of acid-labile agents, but may result in increased absorption of agents that have slower

dissolution rates *(2)*. The intake of large fluid volumes tends to increase stomach-emptying rates and can have the opposite effect of a large solid meal *(1)*. The contents of a meal also may play an important role in DNIs. For example, meals containing polyvalent metal ions (calcium, aluminum, magnesium, or iron) may bind to or chelate drug substances, making the drug unavailable for absorption. Examples of this type of interaction include the potential chelation of tetracycline or fluorquinolone derivatives when coadministered with food items that have high quantities of polyvalent ions *(1)*. The content of a meal may also be an important determinant of alterations in drug metabolism *(3)*. Important examples include dietary protein, cruciferous vegetables, grapefruit juice, and the intake of charcoal-broiled meats.

Ultimately, DNIs can have one of three outcomes with regard to drug absorption. Drug absorption may be increased, decreased, or not affected at all. With regard to decreased absorption, it is important to separate delayed absorption (no change in area under the concentration-time curve [AUC] but an increase in the time to reach maximal absorption [tmax]; generally not clinically important) vs reduced absorption (a decrease in the AUC is seen; depending on the magnitude of the reduction in AUC, may be clinically important).

1.2. Studying and Evaluating Food Effect

The US Food and Drug Administration (FDA), through the Center for Drug Evaluation and Research's (CDER) Food-Effect Working Group has published guidelines for food-effect bioavailability and bioequivalence studies for immediate and modified-release drug products *(4)*. This document provides consideration for study design, subject selection, dosage strength, the contents of the test meal, drug administration, sample collection, and data analysis. A randomized, balanced, single-dose, two-treatment (fed vs fasting), two-period, two-sequence crossover design involving a minimum of 12 subjects receiving the highest strength of a drug intended to be marketed is recommended for the study of food effect. In particular, the meal conditions recommended are those that "are expected to provide the greatest effects on GI physiology so that systemic drug availability is maximally affected." Specifically, a high-fat (approx 50% of total caloric content of meal) and high-calorie (approx 800–1000 kcal) meal is recommended as a test meal for food-effect bioavailability and fed bioequivalence studies. This meal should derive 150, 250, and 500–600 kcal from protein, carbohydrate, and fat, respectively. The specifics of the design and test meal should be clearly outlined in the study report and are of great importance in interpreting the results of any food-effect study.

2. DNIS FOR MEDICATIONS USED TO TREAT HIV INFECTION

The treatment of HIV infection has evolved over the last decade to include the use of multiple agents simultaneously *(5)*. Currently, no cure for this infection exists, and therefore patients receiving pharmacological treatments are currently committing to lifelong therapy. The complexity of taking multiple agents, multiple times per day is made that much more troublesome when many of the antiretroviral agents' bioavailability can be significantly impacted on by food. The added burden of needing to administer a drug with or without food can make an already difficult to take regimen nearly impossible for a patient to adhere to over the long term. The clinical ramification of poor adherence in this

setting is not insignificant. The virus is more able to mutate and treatment failure is more likely if a patient is not able to remain adherent to his or her prescribed antiretroviral regimen more than 90% of the time *(5)*.

2.1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (Table 1)

2.1.1. ABACAVIR (ZIAGEN®, TRIZIVIR®)

Abacavir is rapidly and extensively absorbed after oral administration. The mean absolute bioavailability of the tablet formulation is 83% *(6,7)*. The bioavailability of abacavir tablets was assessed in the fed and fasting states *(8)*. After single doses of abacavir taken with food, the maximum drug concentration in blood (Cmax) was reduced by 35% and the AUC by 5%. No significant difference in systemic exposure (AUC) was noted in the fed and fasting states and the tablets may therefore be administered with or without food. No specific food-effect studies have been conducted on the oral solution, but the oral solution provides comparable systemic exposure to the tablet formulation and these products have been deemed interchangeable *(6)*.

Abacavir is eliminated metabolically via alcohol dehydrogenase. Because of their common metabolic fate, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected patients *(6)*. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg of ethanol, and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of abacavir and ethanol resulted in a 41% increase in abacavir AUC and a 26% increase in abacavir half-life (t $\frac{1}{2}$). No effect on ethanol was seen in males.

2.1.2. DIDANOSINE (VIDEX EC®)

Didanosine is currently available as enteric-coated beadlets in a capsule and a buffered formulation. The enteric coating protects didanosine from degradation by stomach acid. Additionally, this formulation has been shown to provide an equivalent AUC to the buffered tablet formulation of didanosine, but the Cmax is reduced by 40% and the tmax is increased by approx 1 $\frac{1}{2}$ h when administered as the enteric-coated formulation *(9)*. The impact of food on the two formulations is quite different. Food reduces the absolute bioavailability of the buffered formulation by approx 50% *(10)*. The presence of food reduces the AUC of the enteric-coated formulation by 19% *(9)*. The timing of food administration has been studied in 10 HIV-infected patients *(11)*. This study showed that the food effect could be minimized if one administers the buffered formulation 30–60 min before or 2 h after a meal. It is recommended that the buffered formulation be administered 30–60 min before or 2 h after a meal and the enteric-coated formulation be administered on an empty stomach.

2.1.3. LAMIVUDINE (EPIVIR®, COMBIVIR®, TRIZIVIR®)

Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability in HIV-infected patients of 86% for the 150 mg tablet and 87% for the oral solution *(12)*. Lamivudine was administered to 12 HIV-infected patients on two occasions, once in the fasted state and once with food (1099 kcal; 75 g fat, 34 g protein, 72 g carbohydrate) *(12,13)*. Absorption was slower in the fed state (tmax 3.2 h vs 0.9 h), Cmax was 40% lower in the fed state than fasted state, but there was no difference in the systemic exposure in the fed and fasted states. Therefore, lamivudine (tablet or oral solution) may be administered with or without food.

Table 1
Nucleoside Reverse Transcriptase Inhibitors:
Manufacturers' Recommendations for Coadministration With Food

Generic Name	Brand Name (US)	Recommendation
Abacavir	Ziagen, Trizivir	Can be given without regard to food
Didanosine	Videx, Videx-EC	Take on an empty stomach, 30–60 min before or 2 h after a meal
Lamivudine	Epivir, Combivir, Trizivir	Can be given without regard to food
Stavudine	Zerit	Can be given without regard to food
Tenofovir	Viread	Administer with food
Zalcitabine	HIVID	Can be given without regard to food
Zidovudine	Retrovir, Combivir, Trizivir	Can be given without regard to food

2.1.4. STAVUDINE (ZERIT®)

Stavudine is rapidly absorbed after oral administration with Cmax achieved within 1 h after dosing of the capsule or oral solution. The administration of stavudine is not affected by food and it can be taken with or without food *(14,15)*.

2.1.5. TENOFOVIR (VIREAD®)

Tenofovir disoproxil fumarate is a water-soluble diester prodrug of the active ingredient tenofovir. Following oral administration, the oral bioavailability of tenofovir is approx 25%. Administration of tenofovir following a high-fat meal (700–1000 kcal containing 40–50% fat) increases the oral bioavailability (to approx 39%), with an increase in the AUC of approx 40%, an increase in the Cmax of 14% and an increase in the tmax by 1 h *(16)*. It is therefore recommended that tenofovir be administered with a meal to enhance its bioavailability.

2.1.6. ZALCITABINE (HIVID®)

Zalcitabine, when administered orally to HIV-infected patients, has a mean absolute bioavailability of more than 80% *(17)*. Coadministration with food in 20 patients resulted in a reduced rate of absorption (tmax of 1.6 h vs 0.8 h in fasted state), a 39% decrease in the Cmax, and a 14% reduction the AUC *(18)*. This has been considered to be clinically insignificant and zalcitabine can be administered with or without food.

Coadministraion of Maalox® (30 mL) with a single dose of 1.5 mg of zalcitabine in 12 HIV-infected patients resulted in a decrease in the mean Cmax by approx 33% and a reduction in the AUC by approx 25% *(17)*. Although the clinical significance of this is not known, it is recommended that zalcitabine not be ingested simultaneously with magnesium/aluminum-containing antacids.

2.1.7. ZIDOVUDINE (RETROVIR®, COMBIVIR®, TRIZIVIR®)

Zidovudine is well absorbed after oral administration with a bioavailability that averages between 60–70% *(19,20)*. Considerable variability between patients does exist, and the bioavailability can range from 40 to 100%. Several studies have evaluated the impact of food on the absorption of zidovudine *(21,22)*. In general, food consumption tends to decrease the rate but not the extent of absorption of zidovudine. This is especially true for

high-fat meals. One study in 13 patients with acquired immunodeficiency syndrome (AIDS) was conducted in the fed (a standard breakfast) and fasting states *(23)*. The mean AUC in the fed state was 24% lower than fasted state and there was more interpatient variability. In general, zidovudine is recommended to be administered without regard to food. Based on the results in patients with AIDS, it may be advisable to administer zidovudine on an empty stomach. If GI adverse events preclude this, coadministration with a low-fat meal is recommended.

Zidovudine is commercially available as a combination dosage form with lamivudine (Combivir) and with lamivudine and abacavir (Trizivir). Combivir has been studied in 24 healthy subjects in the fed and fasted state *(24)*. There was no difference in the AUC regardless of the coadministration with food. Trizivir has been studied in 24 subjects in the fed and fasted state as well *(25)*. The Cmax was 32%, 18%, and 28% lower for zidovudine, lamivudine, and abacavir, respectively when administered with a high-fat meal compared to the fasting state. Food did not alter the extent of absorption (AUC) of any of the components of Trizivir. It is therefore recommended that both Combivir and Trizivir be administered with or without food.

2.2. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Table 2)

2.2.1. DELAVIRDINE (RESCRIPTOR®)

Delavirdine is rapidly absorbed after oral administration, with peak plasma concentrations occurring approx 1 h after administration and a bioavailability of approx 85% *(26)*. The single-dose bioavailability of 100 mg tablets of delavirdine was studied in 16 healthy subjects and has been shown to be increased by approx 20% when the tablets are allowed to dissolve in water and form a slurry before administration *(27)*. The 200 mg tablet has not been evaluated as a slurry for administration as it is not readily dissolved in water.

The effect of food on delavirdine absorption was evaluated in 13 HIV-infected patients in a multiple-dose, crossover study *(26)*. Patients were maintained on their typical diet (meal content was not standardized) and delavirdine was administered every 8 h with food or 1 h before or 2 h after a meal. Although the Cmax was reduced by 25% in the fed state, there was no effect on AUC or minimum drug concentration in blood (Cmin) of coadministering delavirdine with food. It is therefore recommended that delavirdine can be administered with or without food.

The effect of an acidic beverage on the pharmacokinetics of delavirdine has been evaluated in HIV-infected patients. Matched subjects with ($n = 11$) and without ($n = 10$) gastric hypoacidity were given delavirdine 400 mg three times daily. The pharmacokinetics of delavirdine and its *N*-desalkyl metabolite were determined over 8 h after administration for 14 d. Delavirdine exposure (as measured by Cmax, AUC, and Cmin) were lower and the extent of metabolism greater in subjects with gastric hypoacidity. Orange juice increased the absorption of delavirdine by 50–70% in subjects with gastric hypoacidity, but had only a marginal impact on absorption in subjects without gastric hypoacidity *(27a)*.

2.2.2. EFAVIRENZ (SUSTIVA®)

The absolute bioavailability of efavirenz has not been determined after oral administration. In HIV-infected patients, the tmax is reached in 3–5 h and patients achieve steady state concentrations in 6–10 d *(28)*. The administration of efavirenz 600 mg capsules with

Table 2
Non-Nucleoside Reverse Transcriptase Inhibitors: Manufacturers' Recommendations
for Coadministration With Food

Generic Name	Brand Name (US)	Recommendation
Delavirdine	Rescriptor	Can be given without regard to food
Efavirenz	Sustiva	Avoid taking with high-fat meals
Nevirapine	Viramune	Can be given without regard to food

a high-fat/high-caloric meal (894 kcal, 54 g fat, 54% calories from fat) or a reduced-fat/
normal caloric meal (440 kcal, 2 g fat, 4% calories from fat) was associated with a mean
increase of 22% and 17% in efavirenz AUC and a mean increase of 39% and 51% in
efavirenz Cmax, respectively, relative to the exposures achieved when given under fasted
conditions *(28)*.

Administration of efavirenz 600 mg tablets with a high-fat/high-caloric meal (approx
1000 kcal, 500–600 kcal from fat) was associated with a 28% increase in mean AUC of
efavirenz and a 79% increase in mean Cmax of efavirenz relative to the exposures achieved
in the fasted condition *(28)*. It is recommended that coadministration of efavirenz with
a high-fat meal be avoided to minimize the likelihood of adverse events.

2.2.3. NEVIRAPINE (VIRAMUNE®)

Nevirapine is readily absorbed after oral administration with an absolute bioavail-
ability of more than 90% in both healthy subjects as well as HIV-infected patients *(29)*.
Nevirapine 200 mg was studied in 24 healthy adults (12 male, 12 female) with either a
high-fat breakfast (857 kcal, 50 g fat) or an antacid (Maalox®, 30 mL) *(29)*. The extent
(AUC) of nevirapine absorption was comparable to that observed under fasting condi-
tions. In a separate study of six HIV-infected patients, nevirapine was studied when
coadministered with the buffered formulation of didanosine *(29)*. Again, the AUC of
nevirapine was not significantly altered. It is recommended that nevirapine can be admin-
istered with or without food, a magnesium/aluminum-containing antacid, or didanosine.

2.3. Protease Inhibitors (PIs) (Table 3)

2.3.1. AMPRENAVIR (AGENERASE®)

Amprenavir capsules and oral solution are rapidly absorbed after oral administration
in HIV-infected patients with a time to peak serum concentration (tmax) of between 1 and
2 h *(30)*. The absolute oral bioavailability of amprenavir has not been established. It is
important to note that the oral solution is 14% less bioavailable than the capsule and is
therefore not interchangeable on a milligram-per-milligram basis.

The relative bioavailability of amprenavir capsules has been assessed in the fed and
fasting states in healthy subjects *(30)*. Subjects were given a single 1200 mg dose of
amprenavir on an empty stomach or after ingestion of a standardized meal (967 kcal, 67
g fat, 33 g protein, 58 g carbohydrate). In the fed state, Cmax and tmax were reduced by
approx 33%, whereas the AUC was reduced by approx 27%. It is therefore recommended
that amprenavir can be administered with or without food, but that it should not be taken
with a high-fat meal.

Each capsule of amprenavir contains 109 international units (IU) of vitamin E in the
form of d-α tocopheryl polyethylene glycol 1000 succinate. The total amount of vitamin

Table 3
Protease Inhibitors: Manufacturers' Recommendations for Coadministration With Food

Generic Name	Brand Name (US)	Recommendation
Amprenavir	Ziagen	Can be given without regard to food; avoid vitamin E-containing supplements
Indinavir	Crixivan	Administer 1 h before or 2 h after a meal with a sufficient quantity of water
Lopinavir/ Ritonavir	Kaletra	Take with food
Nelfinavir	Viracept	Take with a meal
Ritonavir	Norvir	Can be given without regard to food; take with meals to prevent gastrointestinal upset
Saquinavir	Invirase	Take with a high-fat meal
Saquinavir	Fortovase	Take with food

E in the recommended daily adult dose of amprenavir is 1744 IU. It is therefore recommended that patients receiving amprenavir not take additional vitamin E supplements.

2.3.2. INDINAVIR (CRIXIVAN®)

Indinavir is rapidly absorbed in the fasted state with a time to serum peak concentration of 0.8 h, with an oral bioavailability of approx 65% *(31)*. Indinavir was administered to 10 subjects ingesting a high-fat/high-calorie (784 kcal, 48.6 g fat, 31.3 g protein) *(32)*. In the fed state, the AUC of indinavir was reduced by approx 77% and the Cmax was reduced by 84%. A similar study in 12 subjects was performed to investigate the impact of a "light meal" *(31)*. Subjects ingested a meal including dry toast with jelly, apple juice, and coffee with skim milk, and sugar, or a meal of corn flakes, skim milk and sugar. This meal type had little or no change in the AUC, Cmax, or trough concentrations of indinavir. It is recommended that indinavir be taken 1 h before or 2 h after meals. If GI upset occurs, indinavir may be administered with skim milk or a light/low-fat meal as described earlier.

The impact of grapefruit juice on indinavir pharmacokinetics was also studied *(31)*. A single 400 mg dose of indinavir was administered with or without 8 ounces of grapefruit juice. The addition of grapefruit juice resulted in a reduction of indinavir AUC by approx 26%. It is recommended that patients avoid taking indinavir with grapefruit juice.

Indinavir was studied in eight HIV-negative volunteers to determine the impact of the dietary supplement St. John's wort (*Hypericum perforatum*, standardized to 0.3% hypericin) on indinavir levels *(33)*. Patients received 800 mg of indinavir every 8 h for four doses prior to and at the end of a 14-d course of St. John's wort 300 mg three times per day. Indinavir concentrations were determined following the fourth dose of indinavir prior to and following St. John's wort. Following the course of St. John's wort, the AUC of indinavir was decreased by 57% and the Cmin was decreased by 81%. It is therefore recommended that indinavir not be administered concomitantly with St. John's wort.

A known adverse effect of indinavir is nephrolithiasis. The stones that form in the kidney consist of indinavir crystals that form because indinavir is poorly soluble *(31,32)*. To minimize this adverse effect, it is recommended that indinavir be taken with at least 32 ounces of water daily.

2.3.3. LOPINAVIR/ RITONAVIR (KALETRA®)

The oral bioavailability of Kaletra in humans has not been determined. In HIV-infected patients with no meal restrictions, Kaletra 400 mg/100 mg at steady state had a tmax of approx 4 h *(34)*. Under nonfasting conditions (500 kcal, 25% from fat), lopinavir concentrations were similar following administration of capsules or liquid. Under fasting conditions, the AUC and Cmax of lopinavir were 22% lower for the liquid relative to the capsule formulation.

A single dose of 400 mg/100 mg of Kaletra capsule was studied when given with a moderate fat meal (500–682 kcal, 23–25% from fat) *(34)*. The AUC of lopinavir was increased by 48% and the Cmax was increased by 23% relative to the fasting state. For the oral solution, the corresponding increases in lopinavir AUC and Cmax were 80 and 54%, respectively. Relative to fasting, administration of Kaletra with a high-fat meal (872 kcal, 56% from fat) increased the lopinavir AUC and Cmax by 97 and 43%, respectively for capsules, and 130 and 56%, respectively for the oral solution *(34)*. It is recommended that Kaletra be administered with food to enhance bioavailability and minimize pharma-cokinetic variability.

2.3.4. NELFINAVIR (VIRACEPT®)

After oral administration of 750 mg (three 250 mg tablets) three times daily in 11 HIV-infected patients for 28-d, or 1250 mg twice daily in 10 HIV-infected patients, oral bioavailability has ranged from 20 to 80% *(35)*. The effect of food was evaluated in two studies ($N = 14$ subjects) *(35)*. The meals utilized contained 517 to 759 kcal (153–313 kcal derived from fat). Maximal plasma concentrations and the AUC of nelfinavir were two- to threefold higher under fed conditions compared to fasting.

In healthy volunteers, a newly approved 625 mg tablet was not bioequivalent to the 250 mg tablet. Under fasted conditions in 27 subjects, the AUC and Cmax were 34 and 24% higher, respectively for the 625 mg tablet. In a relative bioavailability study under fed conditions in 28 subjects, the AUC was 24% higher for the 625 mg tablet, whereas the Cmax was comparable for both formulations *(35)*.

It is recommended that nelfinavir should be taken with food to maximize bioavail-ability. Patients unable to swallow the tablets may dissolve the tablets in a small amount of water. Once dissolved, patients should mix the cloudy liquid well and consume it immediately. The glass should be rinsed with water and swallowed to ensure the entire dose has been consumed *(35)*.

2.3.5. RITONAVIR (NORVIR®)

The absolute oral bioavailability of ritonavir in humans has not been determined. After administration of a 600 mg dose of the oral solution under fed (514 kcal, 9% fat, 12% protein, and 79% carbohydrate) and fasting conditions, the tmax was 4 and 2 h, respec-tively. When the oral solution was given under nonfasting conditions, peak ritonavir concentrations were reduced by 23% and the AUC reduced by 7% relative to fasting. A single 600 mg dose of the soft-gelatin capsule ($N = 57$ patients) and oral solution ($N = 18$ patients) under nonfasting conditions (615 kcal, 14.5% fat, 9% protein, and 76% carbo-hydrate), was evaluated in two separate studies *(36)*. Relative to the fasting condition, the extent of absorption (AUC) of the soft-gelatin capsule was 13% higher in the fed state,

whereas it was slightly reduced with the oral solution. These changes have been considered clinically not significant and, therefore, it is recommended that ritonavir can be administered with or without food.

It is important to note that GI adverse reactions are quite common following the administration of ritonavir and that patients can take ritonavir with food to minimize these effects. These adverse effects are in particular troublesome with the oral solution. To remedy this, ritonavir oral solution has been studied when diluted with 240 mL of chocolate milk, or Advera® or Ensure® *(36)*. Dilution occurred within 1 h of administration and did not significantly effect the rate or extent of absorption.

2.3.6. SAQUINAVIR (INVIRASE®, FORTOVASE®)

Saquinavir was originally introduced as a hard-gelatin capsule (Invirase). This formulation has an absolute oral bioavailability of approx 4% following a high-fat breakfast (1006 kcal as 48 g protein, 60 g carbohydrate, 57 g fat) *(37,38)*. Additionally, the administration of grapefruit juice in eight healthy subjects has been shown to increase the bioavailability and the AUC up to twofold *(39)*. Invirase is currently most commonly administered in combination with ritonavir. When done so, it can be administered without regard to food *(5,27)*. If Invirase is administered as the sole PI, it is recommended that it be administered with a high-fat meal to enhance bioavailability.

More recently, a soft-gelatin capsule formulation (Fortovase) has been introduced to improve on the poor bioavailability of the Invirase formulation. The absolute oral bioavailability of saquinavir administered as Fortovase has not been assessed. However, following single 600 mg doses, the relative bioavailability of saquinavir as Fortovase compared to Invirase was estimated to be 331% *(40)*. The effect of food on Fortovase was evaluated in 12 healthy subjects receiving a single 800 mg dose with breakfast (1006 kcal as 48 g protein, 60 g carbohydrate, 57 g fat) *(40)*. The AUC in the fed state was increased approx 6.7-fold. It is recommended that Fortovase be administered with food.

2.4. Alternative Therapies

Complementary and alternative therapies are commonly used by patients with HIV infection. As mentioned previously, St. John's wort has been shown to decrease the AUC of indinavir by 57% and the Cmin by 81% *(33)*. As these decreases are likely to be clinically significant, the use of St. John's wort should be avoided in patients receiving PI therapy *(5)*. Garlic ingestion in two patients on ritonavir has been reported to result in severe GI symptoms *(41)*. The mechanism has not been fully elucidated and no evaluation of this interaction at steady state is currently available. The effect of coadministration of garlic with saquinavir has been evaluated more formally in 10 healthy subjects *(41a)*. Volunteers received 1200 mg of Fortovase three times daily with meals for three, 4-d study periods. During the second 4-d period, subjects received garlic capsules twice daily. In the presence of garlic, the mean saquinavir AUC decreased by 51%, the trough level decreased by 49%, and the mean Cmax decreased by 54%. After a 10-d washout, the AUC, trough, and Cmax values returned to 60–70% of their baseline. The use of ethanol in combination with didanosine can increase the risk of pancreatitis and should be avoided *(5,9)*. Anecdotal reports of recreational drug use in HIV-infected patients and its impact on antiretroviral disease and/or HIV disease progression and adverse events continue to appear. Table 4 summarizes current reports *(42,43)*.

Table 4
Interactions With Substances of Abuse

Agent	Comments
γ-Hydroxy-butyrate (GHB, liquid XTC)	May result in increased levels and prolonged effect; avoid use in patients on non-nucleoside reverse transcriptase or protease inhibitors
Amyl nitrate	Can cause glutathione depletion in the liver; associated with increased disease progression
Ketamine	Use with ritonavir has been associated with an increased incidence of hepatitis
Alcohol	Increased risk of pancreatitis in patients taking didanosine
Methylenedioxymethamphetamine (MDMA, Ecstacy)	Possible increased levels with protease inhibitors; one death reported (ritonavir)

Future studies are needed to address this growing area in greater detail. In the mean time, clinicians must include alternative therapies and recreational drugs as part of a patient's medication history.

2.5. Metabolic Impact of the Treatment of HIV Infection

As new, more effective therapies have been developed for the treatment of HIV infection, patients are living longer lives. As patients' lives have been extended, the use of antiretroviral agents has been prolonged for years and years in many. As a result of this improvement in the care for and outcomes in patients with HIV infection, a variety of new adverse effects associated with both HIV disease and its treatment have been documented. In particular and germane to this text, a variety of metabolic complications have been identified in patients taking long-term antiretroviral therapy. These include fat accumulation, disorders of lipid and glucose metabolism, hyperlactatemia and lactic acidosis, bone disorders, and lipoatrophy.

2.5.1. Fat Accumulation

A variety of syndromes of fat accumulation have been documented in patients with HIV infection *(5)*. These include obesity, enlarged dorsocervical fat pad (buffalo hump), and less commonly, benign symmetric lipomatosis. Additionally, breast enlargement has been reported in women, and gynecomastia in men. Syndromes of fat accumulation have been noted both in the presence and absence of lipoatrophy.

Because recognition of abnormal fat accumulation coincided with the widespread use of PIs, many people initially assumed that these changes were directly related to this class of drugs. It is now widely recognized that these changes occur in PI naïve patients and terms such as "protease paunch" have been removed from the lexicon used to describe these conditions. The specific roles of PIs and NNRTIs in the development of these syndromes has not been defined, and it is evident that host factors such as age, baseline fat content and body mass index, race, gender, and HIV-specific factors also affect the risk for developing these syndromes *(44)*.

Cross-sectional studies in HIV-infected subjects with increased abdominal girth have demonstrated marked accumulation of visceral or intra-abdominal fat tissue (VAT) *(44)*. This is of concern as excess VAT is associated with increased risk of coronary artery disease, type 2 diabetes mellitus, cerebrovascular disease, gallstones, and in women, breast cancer. Additionally, visceral adiposity can be a factor in the development of metabolic syndromes characterized by glucose intolerance, hyperinsulinemia, insulin resistance, dyslipidemia, and hypertension *(44)*.

Although no specific treatment is approved for fat accumulation in HIV-infected patients the following modalities have been studied, with varying degrees of success: antiretroviral therapy switching, diet and exercise, metformin, thiazolidinediones, growth hormone, and liposuction.

2.5.2. Lipid Abnormalities

Elevations of serum triglycerides and low-density lipoprotein cholesterol (LDL-C) and decreases in high-density lipoprotein cholesterol (HDL-C) have been observed in patients with HIV-infection receiving antiretroviral therapy *(5)*. Both HIV-infection (low HDL-C and elevated triglycerides) and PIs (elevated total and LDL-C, and triglycerides) are important underlying causes of dyslipidemia in HIV-infected patients *(45)*. The use of NNRTIs will increase total cholesterol and LDL-C, but this may be offset by increases in HDL-C *(45)*.

It is recommended that a fasting lipid profile be performed prior to initiating antiretroviral therapy. It should consist of total cholesterol, HDL-C, triglycerides, and a calculated LDL-C. A repeat fasting profile should be obtained approx 3 mo after initiating antiretroviral therapy. If this remains normal, yearly repeats are currently recommended.

The decision to intervene for lipid abnormalities is a complex one that must take into account the patient's general condition, prognosis, and the presence or absence of significant cardiovascular risk factors. The following interventions are recommended *(45)*: (a) evaluate for potential exacerbating factors such as hypogonadism, hypothyroidism, liver disease, or alcohol abuse; (b) perform a cardiovascular risk assessment per the Adult Treatment Panel III guidelines; and (c) encourage therapeutic lifestyle modification; and for patients who continue to be at significantly increased risk of cardiovascular disease despite the above, clinicians should consider substituting a non-PI containing regimen and/or instituting a lipid-lowering agent.

2.5.3. Disorders of Glucose Metabolism

Prior to the availability of potent antiretroviral therapy, insulin resistance and diabetes were relatively uncommon in HIV-infected patients. Although fasting glucose levels remain normal in most patients receiving potent antiretroviral therapy, up to 40% of patients on a PI-containing regimen will have impaired glucose tolerance resulting from significant insulin resistance *(5,46)*.

Indinavir may induce insulin resistance by inhibiting cellular glucose uptake by interfering with the cellular glucose transporter GLUT-4, and/or inhibiting peroxisome proliferator-activated receptor γ (PPAR-γ) expression *(46)*. Whether all PIs induce such changes remains uncertain, and the relative tendency of the different PIs to induce insulin resistance is unknown.

Fasting glucose should be obtained prior to and during antiretroviral treatment (3–6 mo after initiating therapy and annually thereafter) with a PI-containing regimen. Because of a paucity of data regarding the treatment of diabetes mellitus during HIV infection, established guidelines for treating diabetes mellitus in the general population should be followed. In specific, when drug therapy of diabetes mellitus is required, consideration should be given to using an insulin-sensitizing agent such as metformin or a thiazolidinedione as first-line therapy *(46)*. Careful monitoring for potential adverse effects such as liver dysfunction and lactic acidemia is recommended.

Consideration should be given to avoiding the use of a PI as initial therapy or to substitute alternatives to the PIs if possible in patients with preexisting abnormalities of glucose metabolism or who have risk factors for diabetes mellitus. Substitution of the PI component of a regimen with nevirapine, efavirenz, or abacavir has been associated with short-term improvements in insulin resistance and may be considered when virologically appropriate *(5)*.

2.5.4. Hyperlactatemia and Lactic Acidosis

Hyperlactatemia and lactic acidosis have been observed in HIV infected patients receiving antiretroviral therapy *(5)*. The spectrum of disease ranges from mild to moderate asymptomatic (subclinical) hyperlactatemia to fulminant and life-threatening lactic acidosis. Fortunately, symptomatic hyperlactatemia is uncommon and life-threatening lactic acidosis is even rarer.

Asymptomatic and subclinical hyperlactatemia has been observed in 10–36% of cohorts of HIV-infected patients examined *(47)*. Evidence suggests that exposure to one or more NRTIs plays a central role through toxic effects on mitochondrial function *(47)*. It remains unclear what other factors may be involved in the pathogenesis of this disorder.

Interventions that should be considered for symptomatic hyperlactatemia and lactic acidosis include *(47)*: (a) discontinuation of current antiretroviral regimen or switching to a NRTI-sparing regimen; (b) addition of any or all of the following: thiamine, riboflavin, L-carnitine, coenzyme-Q-10, vitamin C, E, and/or A. It should be noted that the use of these nutrients is based on case reports.

2.5.5. Bone Disorders

Alterations in bone mineralization and development of avascular necrosis (AVN) have been reported to be more prevalent in HIV-infected persons than in non-HIV-infected persons *(5)*. The specific contributions of antiretroviral agents and HIV infection to osteopenia, osteoporosis, and AVN are not well defined. Patients on potent antiretroviral therapy regardless of drug class, have higher rates of osteopenia and osteoporosis than treatment-naïve patients *(48)*. The link between AVN and anti-retroviral therapy is weaker. AVN has been frequently reported in HIV-infected patients not receiving antiretrovirals and has been associated with low CD4+ cell counts, duration of HIV infection, and prior corticosteroid treatment.

The safety and efficacy of standard therapies used to treat bone demineralization have not been evaluated in HIV-infected patients. The following are recommended based on results obtained in non-HIV-infected individuals *(49)*. Lifestyle modification including weight loss and exercise should be attempted prior to considering drug therapy. The use of specific drug therapy including calcium and vitamin D supplementation, bisphos-

phonates, hormone replacement therapy, calcitonin, and teriparatide may be considered. Currently, no specific recommendation exists regarding changing antiretroviral therapy as no drug or drug class has been specifically associated with alteration in bone metabolism.

2.5.6. LIPOATROPHY

Peripheral fat wasting in patients with HIV infection treated with antiretroviral therapy has emerged as a distressing complication that threatens long-term treatment of the virus. Cross-sectional studies have reported prevalence rates that range from 25 to 60% *(50)*.

The etiology of adipose tissue loss is unclear. Currently available information suggests that the development of lipoatrophy is influenced by both the use of antiretroviral therapy and a variety of host factors including age, race, and degree of immunosuppression *(50)*. Both PIs and NRTIs are likely to play a role in the pathogenesis of lipoatrophy. Interestingly, antiretroviral therapy consisting exclusively of PIs appears to have a minimal tendency toward the development of lipoatrophy *(50)*. The risk of development of lipoatrophy is, however, dramatically increased when NRTIs and PIs are used in combination.

Currently, there are no proven therapies known to reverse or prevent peripheral lipoatrophy associated with HIV infection. Approaches that have been considered include antiretroviral switching, the use of thiazolidinediones, antioxidants, and cosmetic surgery.

3. DNIS FOR MEDICATIONS USED TO TREAT MYCOBACTERIUM TUBERCULOSIS INFECTION

The management of tuberculosis has long been a difficult clinical problem, as the causative agent is a slow-growing organism and effective therapy requires the use of multiple agents for extended periods of time. As with the treatment of HIV infection, alterations in one's lifestyle to accommodate drug therapy for a prolonged period of time adds to the complexity of achieving optimal patient adherence. Given that pulmonary tuberculosis is transmitted via droplet nuclei that are aerosolized when an infected patient coughs, the public health impact of treatment failure, especially owing to a modifiable risk such as a DNI, is unacceptable. Clinicians and patients alike need to be keenly aware of the food effect on the bioavailability of these agents (Table 5).

3.1. Aminosalicylic Acid Granules (Paser Granules)

Aminosalicylic acid is commercially available in a granule formulation. The granules are designed for gradual release so as to avoid high peak levels that may cause toxicity. Aminosalicylic acid is rapidly degraded in acid media. After 2 h in simulated gastric fluid, 10% of unprotected aminosalicylic acid is decarboxylated to form meta-aminophenol, a known hepatotoxin *(51)*. The small granules are designed to escape the usual restriction on gastric emptying of large particles. Under neutral conditions such as those found in the small intestine or in neutral foods, the acid-resistant coating is dissolved within 1 min. The protective acid-resistant outer coating is rapidly dissolved in a neutral media so a mildly acidic food such as orange, apple, or tomato juice, yogurt, or apple sauce should be used to enhance oral bioavailability *(51,52)*. In a single 4 g pharmacokinetic study with food in healthy subjects, the median time to peak serum

Table 5

Medications for the Treatment of Tuberculosis: Recommendations for Coadministration With Food and Antacids

Generic Name	Recommendation
Aminosalicylic acid	Administer with a mildly acidic beverage or food such as orange, apple, or tomato juice, yogurt, or apple sauce; avoid antacids if possible
Cycloserine	Do not administer with food
Ethambutol	May be administered with or without food; avoid administration with antacids
Ethionamide	May be administered with or without food or an antacid; avoid excessive ethanol intake
Isoniazid	Administer on an empty stomach and avoid antacids
Pyrazinamide	May be administered without regard to food
Rifabutin	May be administered with food; avoid antacids
Rifampin	May be administered with food; avoid antacids

levels was 6 h (range 45 min to 24 h) *(51,52)*. Patients who have neutralized gastric acid with antacids will not need to protect the acid-resistant coating with an acidic food, but the administration of an antacid is not necessary to achieve good absorption. It is also important to note that the granules are made of a soft skeleton and these may appear in the stool of patients *(51)*.

3.2. Cycloserine

Cycloserine is well absorbed after oral administration, with a tmax of 2–4 h *(53)*. The coadministration of cycloserine with food results in a 16% reduction in the Cmax but no change in the AUC *(52,54)*. Preliminary data suggest that administration with a high-fat meal reduces the Cmax by 31%, whereas administration with orange juice reduces the Cmax by 20% *(52)*. The impact of antacid administration on cycloserine is also minimal *(52)*. It is recommended that cycloserine administration be without food if possible.

3.3. Ethambutol

Ethambutol is rapidly absorbed following oral administration with a tmax of 2–3 h and an approx bioavailability of 80% *(55)*. Two separate studies have evaluated the impact of food on ethambutol *(52,54)*. The impact of a "standardized breakfast" on the mean AUC in 11 healthy subjects was minimal *(56)*. The coadministration of a high-fat meal in 14 healthy male and female subjects showed a delay in the time to peak serum levels, a decrease in the Cmax by 16%, but little effect on the extent of absorption (AUC) *(57)*. The administration of an antacid (Mylanta) is associated with a 28% decrease in Cmax and a 10% decrease in the AUC of ethambutol *(57)*. It is therefore recommended that ethambutol can be administered with or without food, but that it should not be administered with an antacid.

3.4. Ethionamide

Ethionamide is essentially completely absorbed following oral administration (approx 80%) *(53,58)*. There appears to be no effect of the administration of ethionamide with a high-fat meal or an antacid on Cmax or AUC *(52)*. Ethionamide can be administered without regard to food or an antacid. Excessive ethanol intake should be avoided as psychotic reactions have been reported *(59)*.

3.5. Isoniazid

Isoniazid is well absorbed following oral dosing, with the tmax of between 1 and 2 h *(53)*. There are conflicting data regarding the impact of food on the bioavailability of isoniazid. In one study, the Cmax and AUC of isoniazid were decreased by 70 and 40%, respectively, in the presence of food *(60)*. A more recent study in 14 healthy volunteers evaluated the impact of a high-fat breakfast on the absorption of isoniazid *(61)*. The high-fat meal reduced the Cmax by 51%, increased the tmax twofold, and reduced the AUC by 12%. Additionally, data conflict with regard to antacid administration. A decrease ranging from 0 to 19% in the AUC has been reported *(61)*. The recommendation is that isoniazid be administered on an empty stomach and that whenever possible, coadministration with an antacid should be avoided.

3.6. Pyrazinamide

Pyrazinamide absorption takes place in 1–2 h and appears to be complete *(54)*. The effect of a high-fat meal or an antacid on the bioavailability of pyrazinamide has been evaluated in 14 healthy volunteers *(62)*. Neither the high-fat meal nor the antacid had a significant effect on the extent of absorption. As a result, pyrazinamide may be administered without regard to meals.

3.7. Rifabutin (Mycobutin)

Following a single dose of 300 mg of rifabutin to nine healthy subjects, the drug was readily absorbed, with a tmax of 3.3 h *(63)*. The bioavailability of the capsule formulation, relative to an oral solution was 85% in 12 healthy subjects *(63)*.

The effect of a high-fat meal was studied in 12 healthy male subjects *(64)*. Although the time to maximal peak levels was prolonged from 3 to 5.4 h, relative to the fasting condition, there was no significant impact on the extent of absorption. The effect of an antacid on rifabutin has not been studied. The impact of the buffered didanosine formulation has been evaluated and this has shown no effect on rifabutin absorption *(52)*. Rifabutin may be given with food, but coadministration with an antacid should be avoided until it is specifically studied.

3.8. Rifampin

Rifampin is well absorbed from the GI tract, with a tmax of approx 2 h (range 2–4 h) *(53,65)*. Rifampin is better absorbed in an acidic environment than a neutral or alkaline one. The administration of a high-fat meal with rifampin has been evaluated in 14 healthy subjects *(66)*. The addition of a high-fat meal reduced the Cmax by 36% and the AUC by 6%. The administration of a magnesium/aluminum containing antacid had no effect on the bioavailability of rifampin *(66)*. It is recommended that rifampin be taken on an empty stomach whenever possible to minimize any potential decrease in absorption.

4. MANAGEMENT OF CHRONIC VIRAL HEPATITIS

Chronic viral hepatitis is commonly caused by the hepatitis C virus (most common) or by the hepatitis B virus. Over the past decade or so, major advances in the pharmacological management of these diseases have been introduced. For hepatitis B virus, the introduction of oral therapies including lamivudine (discussed earlier in Subheading 2.1.3.) and adefovir has enabled patients to achieve improved therapeutic outcomes as compared to using interferon therapy. For hepatitis C virus, the use of combination therapy with interferon plus oral ribavirin has dramatically improved the responsiveness of this difficult to treat disease. Given that these advances in therapy are administered orally, the potential for drug–food interactions is discussed.

4.1. Adefovir (Hepsera®)

Adefovir is available as a diester prodrug. Oral bioavailability is approx 59%, with a tmax that ranges from 0.58 to 4 h. When coadminstered with food (a 100 kcal high-fat meal) there was no affect on the pharmacokinetics of adefovir *(67)*. It is therefore recommended that adefovir can be administered without regard to food.

4.2. Ribavirin

Ribavirin when administered orally is quickly absorbed, with a tmax of approx 2 h. When coadministered with a high-fat meal, the absorption was slowed (t_{max} = 4 h), the AUC was increased by 42%, and the C_{max} was increased by 66% *(68)*. As bioavailability is enhanced in the presence of food, it is recommended that ribavirin be administered with food.

5. CONCLUSION

The impact of food on the absorption of drugs significantly complicates the treatment of any chronic disease. Importantly, the impact on those with chronic infections differs from conditions such as hypertension and diabetes. Obviously, infections can be transmitted from one individual to another. A decrease in absorption in treating an infection can lead to the development of a resistant infection. Subsequent spread of a resistant infection has significant public health ramifications.

Although unanswered questions regarding drug–food interactions still exist, the information provided in this chapter should be used to educate health care professionals and patients to optimize patient outcome and minimize the development of drug-resistant infections. Older agents still in use were not subject to the more current, rigorous requirements of labeling and should be investigated for interactions with food. Future studies are also needed to answer remaining questions about interactions between drugs used for chronic infections and food, alternative therapies, or illicit drugs.

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25 Antimicrobial–Nutrient Interactions
An Overview

Allison Wood Wallace

1. INTRODUCTION

The current drug–nutrient interaction (DNI) data on antimicrobials available in the literature are a byproduct of both drug–food interaction and drug–antacid interaction data. Much less is available on the influence of antimicrobials on nutritional status. Drug–food interactions are often described as changes in a drug's bioavailability secondary to the effect of food on the gastrointestinal (GI) tract. These effects include changes in transit time through the GI tract, changes in drug absorption from the GI tract—either as a result of direct reduction of drug absorption through chelation or enhancement of transporters that keep the drug in the GI tract, and changes in drug metabolism due to variances in intrinsic gut metabolism as well as drug delivery to the liver (first-pass metabolism) *(1–3)*. Drug–antacid interaction data may be extrapolated to apply to DNIs or drug–food interactions because antacids represent a standardized, quantifiable delivery method of nutrients (i.e., minerals) to the body. The mechanisms of drug–mineral interactions include chelation, adsorption, alteration in gastric pH, and decreased absorption via otherwise unspecified mechanisms, but may also impact drug elimination by altering urinary pH *(4–7)*. From this information, it becomes apparent that in DNIs—and specifically, antimicrobial–nutrient interactions—nutrients have a greater impact on the disposition and effect of antimicrobials than the reverse.

2. REVIEW OF BASIC SCIENCE

It is important to review the influence of food on the GI tract in order to discuss DNIs involving antimicrobials, because nutrients are acquired in most patients by consuming food and nutritional supplements. Except in cases in which the GI tract has been compromised by disease, injury, or surgical interventions, most nutrients are acquired through consumption of a solid meal. Solid meals have the potential to affect the pharmacokinetics of a drug (i.e., absorption, distribution, metabolism, and elimination) through changing gastric residence time, gastric pH, and splanchnic blood flow, as well as acting as a physical barrier to the gut mucosa and receptors contained therein for active transport and metabolism *(1–3,5,8)*. Gastric residence time of an ingested drug may vary from a few minutes to 2–3 h, depending on the spacing of the drug from food, as well as the temperature of the ingested food *(1,3)*. Increased gastric residence time, or delayed gastric empty-

ing, will increase the absorption of drugs normally absorbed from the stomach, decrease systemic absorption of acid-labile drugs via increased degradation in the stomach, and delay absorption of drugs absorbed from the duodenum *(1,2)*. High-protein meals increase splanchnic blood flow, thereby increasing drug absorption, whereas meals high in carbohydrates may decrease splanchnic circulation *(1,3,9)*. Both solid and liquid meals should be taken into consideration when describing interaction potential. Patients with chronic illnesses or those with recent GI surgery may be consuming a significant number of calories, protein, and fat through liquid supplement formulations taken orally or via tube feedings. Furthermore, medications given via nasogastric or gastrostomy tubes must be scheduled and flushed appropriately to avoid interactions. Tubes used for both feedings and medications should be flushed before and after any nutrient or drug administration.

In addition to creating a physical barrier to drug absorption, mineral content of ingested foods can affect drug absorption because of ionic charge of the mineral. With the current trend of food fortification in US food products, the mineral content of foods may be equivalent to that contained in antacids and other dietary supplements. The ionic charge of minerals contained in large quantities in foods can cause chelation and adsorption interactions in the stomach, can change gastric pH, and can change urinary pH *(2,4,6,7,11)*. Foods that are fortified with iron, calcium, magnesium, aluminum, as well as foods that contain 100% of the US Recommended Daily Value (RDV) of multiple vitamins and minerals have the greatest effect on pharmacokinetic parameters, and specifically the systemic availability, of drugs.

3. REVIEW OF CLINICAL EVIDENCE

All drug-specific data, including type and mechanism of interaction, outcome of the interaction, and general clinical recommendations, are contained within Table 1 *(2–15)*.

3.1. Dosage Formulation-Specific Data and Drug-Specific Data

Enteric-coated formulations are created to decrease the potential of drug degradation in the acidic contents of the stomach in order to deliver the drug to the more alkaline duodenum for drug absorption *(1)*. Delayed gastric emptying caused by ingestion of food and nutrients increases the risk of the breakdown of the enteric coating, thereby increasing the potential for drug degradation in the stomach and decreasing systemic drug availability *(1)*. In some cases, DNIs may be formulation-specific. Suspensions may be more labile in the stomach because tablet disintegration is not a rate-limiting step in absorption.

3.2. Effects of Antimicrobials on Nutrient Status and the Physiologic Consequences

Although data abounds regarding the effects of nutrients on antimicrobial absorption and effectiveness, little information is available on the effects of antimicrobials on nutrient status. Logistically, it may be argued that patients with marginal nutrient status—those with malnutrition, digestive diseases causing nutrient malabsorption, or those under intense physiological stress as a result of surgery, trauma, or sepsis—would be more likely to show clinical signs of nutrient deficiency owing to nutrient–antimicrobial interactions. Therefore, tetracyclines and quinolones that form chelation complexes with multivalent cations may have the ability to create calcium, iron, magnesium, and zinc deficiencies in patients with marginal nutrient status. No data currently exist to

quantitatively describe the decrease in nutrient availability owing to such interactions, or to qualitatively describe the clinical significance of these interactions.

Despite the paucity of data regarding the effect of antimicrobials on minerals, the effect of the antitubercular agents, isoniazid (INH) and rifampin, on vitamin B_6 (pyridoxine) and vitamin D has been more extensively described. The potential neurotoxicity of INH (i.e., peripheral neuropathy) has been related to increased elimination of pyridoxine and possibly competitive inhibition with pyridoxine as a cofactor in synaptic neurotransmitter synthesis *(16)*. Therefore, it is common for clinicians to administer pyridoxine with INH, especially because both prophylactic and treatment regimens of INH can last several months. The potential for this interaction has been recognized in both adults and children *(17)*. Rifampin is thought to increase vitamin D metabolism, causing osteomalacia *(16)*. Brodie et al. found that a short course (14-d) of combination antitubercular therapy (600 mg rifampicin and 300 mg INH daily) in eight healthy subjects significantly reduced 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D concentrations by 34 and 23%, respectively, which related to a 57% increase in parathyroid hormone (PTH) *(18)*. However, these statistically significant changes did not result in a drop in calcium or phosphate concentrations in the 2 wk study period *(18)*. Both single-dose INH and short-course (14-d) INH resulted in statistically significant reductions in 1,25-dihydroxy-vitamin D by nearly 50%, as well as statistically significant reductions in 25-hydroxyvitamin D *(19)*. As a result of the statistically significant drop on serum calcium and phosphate concentrations, PTH concentrations increased by more than one-third, thereby increasing the risk of development of metabolic bone disease *(19)*. However, a 9-mo study in patients with tuberculosis, who were being treated with INH and rifampicin, did not reveal any significant change in biochemical or clinical markers of vitamin D-related bone metabolism *(20)*, although it should be noted that baseline nutritional status, and nutrient intake were not closely assessed.

Probably the best recognized antimicrobial–vitamin interaction is that of broad-spectrum antibiotics and antibiotics with the *N*-methylthiotetrazole (NMTT) side chains with vitamin K. NMTT has been shown to inhibit vitamin K-dependent carboxylation, increasing the risk of hypoprothrombinemia, thus increasing the risk of bleeding *(21)*. It seems that cephalosporins with NMTT side chains—cefamandole, cefotetan, cefoperazone, latamoxef, and cefmenoxime —inhibit hepatic vitamin K epoxide reductase, causing an increase in plasma concentrations of vitamin K 2,3-epoxide and increasing the risk of bleeding *(22)*. Furthermore, patients receiving parenteral nutrition without added vitamin K are at greater risk for developing bleeding episodes due to poor vitamin K intake. A second theorized mechanism of antibiotic–vitamin K interaction is via eradication of endogenous vitamin K-producing gut flora, especially in patients with reduced vitamin K intake or with reduced ability to absorbed vitamin K and other fat-soluble vitamins *(23)*. Because at least four clotting factors (II, VII, IX, and X) are vitamin K-dependent, decreased availability of vitamin K for any reason can increase the risk of bleeding. With the advent of the use of warfarin to treat and prevent many coagulation disorders, the awareness of this mechanism is more greatly appreciated. In patients stabilized on warfarin therapy, the initiation of a broad-spectrum antibiotic may produce a clinically and statistically significant increase in the risk of bleeding, which is directly related to an increase in the prothrombin time/international normalized ratio (PT/INR). Likewise, the end of antibiotic therapy in chronic warfarin patients could cause the INR to fall below the therapeutic range for the treatment of that patient's coagulation disorder.

Table 1
Antimicrobial–Nutrient and Antimicrobial–Ethanol Interactions, Outcomes,
and Recommendations

Drug	Interaction	Clinical Outcome	Recommendation
Albendazole	Food: increased absorption	Improved therapeutic outcome	May be taken with food
Amoxicillin	Food: increased degradation resulting from delayed gastric emptying and acid lability	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Ampicillin	Food: increased degradation from delayed gastric emptying and acid lability	Possible treatment failure if administered in low doses and increased risk of resistance	Take on an empty stomach
Amprenavir (oral solid)	Micronutrient: decreased absorption (otherwise unknown mechanism)	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Amprenavir (oral solution only)	Ethanol: competition for alcohol and aldehyde dehydrogenase pathway	Increased risk of propylene glycol toxicity (seizures, lactic acidosis, renal failure)	Avoid ethanol intake during therapy with oral solution.
Atevirdine	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance calcium, zinc, etc.)	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron,
Atovaquone	Macronutrient: increased drug solubility with high-fat meal	Increased drug absorption and improved therapeutic outcome	Take with a high-fat meal

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Azithromycin capsules	Food: increased degradation due to delayed gastric emptying and acid lability	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Azithromycin tablets and suspension	None	No change	May be taken without regard to food
Balofloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Cefamandole	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Cefdinir	Micronutrient: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Cefmenoxime	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Cefoperazone	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Cefotetan	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Cefpodoxime proxetil	Micronutrient: multivalent cations may increase the gastric pH, causing decreased drug dissolution	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Cefprozil	Food: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Ceftibuten	Food: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Cefuroxime axetil	Micronutrient: multivalent cations may increase gastric pH; solubility is dependent on acidic environment	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Cephalexin	Food: increased risk of degradation due to delayed gastric emptying and acid lability	Low clinical significance	May be taken without regard to food
Chloroquine	Micronutrient: multivalent cations will cause adsorption interaction	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Ciprofloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Clarithromycin	Food: increased absorption	Improved therapeutic outcome	May be taken with food
Delavirdine	Micronutrient: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Demeclocycline	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Didanosine	1) Food: increase risk of degradation due to delayed gastric emptying and acid lability 2) Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Doxycycline	1) Micronutrient: multivalent cations will form insoluble ion-drug chelate 2) Micronutrient: multivalent cations may increase urinary pH, resulting in increased renal clearance	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Enoxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Erythromycin	Food: increased risk of degradation due to delayed gastric emptying and acid lability	Possible treatment failure and increased risk of resistance	Take on an empty stomach. Since erythromycin is a prokinetic agent (increases gut motility), gastro-intestinal upset is expected to occur as a side effect; it is not an adverse reaction
Ethambutol	Food: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Fluconazole	Food: no change	No change	May be taken without regard to food
Furazolidone	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Ganciclovir	Food: increased absorption	Possible increased drug effect	Take with food
Gatifloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Gemifloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Gentamicin, intravenous	Micronutrient: increased loss of potassium and magnesium	Potential for hypokalemia and/or hypomagnesemia	Monitor serum potassium and magnesium concentrations

(continued)

Table 1 (**continued**)

Drug	Interaction	Clinical Outcome	Recommendation
Griseofulvin	1) Food: drug absorption is increased with food due to bile secretion 2) Ethanol: unknown mechanism	1) Food is required to achieve adequate drug absorption 2) Flushing, tachycardia, and possibly disulfiram reaction	Must be taken with food to avoid treatment failure Avoid intake of alcohol during therapy and for several days following therapy
Halofantrine	Food: drug absorption is increased with food because of bile secretion	Increased risk of drug toxicity	Take on an empty stomach
Indinavir	Macronutrient: high-protein meal decreases drug absorption due to increased gastric pH and protein binding in the gut	High risk of treatment failure and resistance	Take on an empty stomach
Isoniazid	1) Food: increased risk of degradation due to delayed gastric emptying and acid lability 2) Micronutrient: isoniazid depletes vitamin B_6 3) Micronutrient: isoniazid inhibits vitamin D hydroxylation in GI mucosa 4) Micronutrient: isoniazid is a monoamine oxidase inhibitor 5) Ethanol: inhibits acetaldehyde metabolism	1) Possible treatment failure and increased risk of resistance 2) Increased risk of peripheral neuropathies 3) Increased risk of developing hypovitaminosis D 4) Tyramine hypertensive reaction 5) Disulfiram-like reaction	1) Take on an empty stomach 2) Administer supplemental vitamin B_6 (pyridoxine) to prevent deficiencies 3) May require administration of activated (hydroxylated) vitamin D 4) Avoid tyramine-containing foods 5) Avoid intake of alcohol during therapy and for several days following therapy

(continued)

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Itraconazole capsules	1) Food: increased drug absorption 2) Micronutrient: multivalent cations may increase gastric pH; solubility is dependent on acidic environment	1) Improved therapeutic outcome 2) Increased risk of treatment failure	Take with food that is not fortifiedwith multivalent cations (i.e., iron, calcium, zinc, etc.). Do not take with antacids
Itraconazole solution	Food: increased splanchnic blood flow resulting in increased first-pass metabolism	Increased risk of treatment failure	Take on an empty stomach
Ketoconazole	1) Micronutrient: decreased absorption 2) Ethanol: inhibits acetaldehyde metabolism	1) Possible treatment failure and increased risk of resistance 2) Disulfiram-like reaction	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.). Avoid intake of alcohol during therapy and for several days following therapy
Levofloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multi-valent cations (iron, calcium, zinc, etc.)
Lincomycin	Food: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Lomefloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with cations multivalent (iron, calcium, zinc, etc.)

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Mefloquine	Macronutrient: increased drug solubility with high-fat meal	Improved therapeutic outcome	Take with a high-fat meal
Metronidazole	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Minocycline	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multi-valent cations (iron, calcium, zinc, etc.)
Moxalactam	Ethanol: inhibits acetaldehyde metabolism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Moxifloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Nelfinavir	Food: increased absorption	Improved therapeutic outcome	May be taken with food
Neomycin	Micronutrient: retards absorption of vitamin A	May result in vitamin A deficiency	May require supplemental administration of vitamin A
Nitrofurantoin	Food: increased absorption	Improved therapeutic outcome and decreased gastric irritation	May be taken with food
Norfloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Ofloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Oxytetracycline	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Pefloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Penicillin V	Food: increased risk of degradation due to delayed gastric emptying and acid lability	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Rifampin	Food: increased splanchnic blood flow resulting in increased first-pass metabolism	Increased risk of treatment failure	Take on an empty stomach
Rufloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Saquinavir	Food: increased drug absorption due to increased drug dissolution	Improved therapeutic outcome	Take with a meal. If taken without food, there is an increased risk of treatment failure
Terbinafine	Food: increased absorption	Improved therapeutic outcome	May be taken with food

Table 1 (continued)

Drug	Interaction	Clinical Outcome	Recommendation
Tetracycline	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance. Potential for development of hypocalcemia and osteoporosis if taken chronically	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.). Monitor serum calcium concentrations
Tiprenavir	Micronutrient: decreased absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Tosufloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Trimethoprim	Ethanol: unknown mechanism	Disulfiram-like reaction	Avoid intake of alcohol during therapy and for several days following therapy
Trovafloxacin	Micronutrient: multivalent cations will form insoluble ion-drug chelate	Possible treatment failure and increased risk of resistance	Take on an empty stomach; avoid taking with antacids and with foods fortified with multivalent cations (iron, calcium, zinc, etc.)
Zalcitabine	Food: decreased drug absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach
Zidovudine	Macronutrient: high-fat and high-protein meals reduce drug absorption	Possible treatment failure and increased risk of resistance	Take on an empty stomach

From refs. *2–15*.

4. LIMITATIONS OF CURRENT DATA AND FUTURE RESEARCH NEEDS

Aside from the fact that little data specifically examines effects of antimicrobials on the status of specific nutrients, the greatest limitation of the current data on drug–nutrient or drug–food interactions lies with the standard research method for determining these interactions. The current meal required by the US Food and Drug Administration (FDA) used to quantify drug–food interactions prior to submitting new drug applications is a high-fat/high-calorie breakfast, which has little other nutritive value. This FDA-standardized breakfast consists of two eggs fried in butter, two strips of bacon, two slices of toast with butter, 4 ounces of hash brown potatoes, and 8 ounces of whole milk *(24)*. The possible interaction of drugs with breakfast foods is particularly important, because it may be argued that patients taking medications on a once-a-day regimen probably take their medication in the morning.

In today's society, the likelihood of patients requiring prescription drugs consuming this "standard" breakfast is low. Many Americans eat foods that require little preparation time. For example, a breakfast might consist of a bowl of cereal with low-fat milk, yogurt, or an instant breakfast bar or shake. These products are often fortified with vitamins and minerals, which pose an additional threat to the bioavailability of drugs taken concomitantly, although these vitamins and minerals are meant to have positive health implications. For instance, one serving of Total Whole Grain™ cereal contains 100% of the RDV of calcium, iron, and zinc, whereas one serving of milk (as contained in the FDA-approved breakfast) contains only 30% of the RDV of calcium.

It is evident from average supermarket products that the food industry is moving toward the marketing of "health-conscious" products. Now product packaging includes terms such as "fortified with vitamins and minerals," "low-sodium," "enriched," "low-fat," "low-cholesterol," and "high fiber." In addition, many traditional meat products are now being made from alternative sources, such as turkey bacon and "veggie" burgers. Therefore, it is plausible that a re-evaluation and revision of the current FDA-standardized meal—a high-fat/high-calorie breakfast—is needed to obtain more applicable drug–food and drug–nutrient interaction data.

5. CONCLUSION AND CLINICAL RECOMMENDATIONS

The primary step in identifying, preventing, and managing antimicrobial–nutrient interactions in patients is to determine the average nutrient content of a given patient's diet. If a given patient takes medications only once daily, this task may be made simple by asking the patient what foods or beverages make up a usual breakfast. From this, the average nutrient content and potential for interaction may be assessed. However, in patients whose antimicrobial medication regimen may be more complex, as in patients on antivirals for HIV, possibly with other antibiotics and antifungals for opportunistic infections, it would be more helpful to have the patient keep a food diary for 1 or 2 wk. The patient or the clinician may use this food diary to determine the nutrient content of the patient's average daily diet via free software on the internet or by more sophisticated software used by nutrition and dietetic consultants. Both pharmacists and dietitians are invaluable resources in planning intricate schedules for drug and food administration.

In general, taking medications with water and allowing for a 2-h space in administration of medications may prevent the vast majority of detrimental DNIs. Explicitly, patients should avoid eating for 2 h before and 2 h after taking oral medications when the medication is recommended to be taken on an empty stomach, based on an average gastric emptying cycle. All clinical recommendations to prevent nutrient-antimicrobial interactions are contained within Table 1.

ACKNOWLEDGMENTS

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26 Drug–Nutrient Interactions in Patients Receiving Enteral Nutrition

Carol J. Rollins

1. INTRODUCTION

Malnourished patients and those at risk of malnutrition are candidates for nutrition intervention. This includes previously well-nourished patients who have been or will be without oral intake for 3 to 5 d (pediatric populations) or 5 to 10 d (adults). Enteral nutrition (EN), which is synonymous with tube feeding, should be considered when a patient cannot, will not, or should not consume appropriate quantities of nutrients by mouth to prevent malnutrition. There are few absolute contraindications to tube feeding other than a bowel obstruction that cannot be bypassed. However, conditions such as diffuse peritonitis, intractable vomiting, intractable diarrhea, and ischemia of the small bowel may be contraindications to EN therapy *(1)*. Most other conditions allow at least some nutrients to be delivered enterally.

Advances in enteral formulas and tube-placement techniques since the 1980s allow full nutrition support via EN today where parenteral nutrition (PN) was previously the norm (e.g., patients with mild to moderate pancreatitis). Some patients tolerate only partial EN support and require both EN and PN to achieve full support. Other patients require EN as a supplement to inadequate oral intake. Once EN is started, it is most often continued until the patient is able to meet his or her nutrient requirements by mouth. Thus, EN therapy is relatively common in the hospital setting, "step-down" facilities for rehabilitation or skilled nursing care, and other patient-care facilities. A large population also receives home enteral nutrition (HEN). In 1992 it was estimated that 152,000 people received HEN therapy *(2)*. The number was estimated to be much greater in 2003, although there is no centralized data collection that allows accurate determination of the number of HEN patients.

As the population of patients receiving EN in various settings grows, the potential for interactions between drugs and EN components and administration techniques increases. Such drug–nutrient interactions (DNIs) have the potential to adversely affect patient outcomes when feeding tubes occlude, inadequate drug is absorbed, or nutrient provision is compromised. To understand the potential for DNIs in patients receiving EN therapy,

it is first necessary to have a basic understanding of EN. This chapter provides a brief overview of EN, then reviews available data, discusses problems in extrapolating available data to current practice, and provides recommendations for managing DNIs in patients receiving EN therapy.

2. REVIEW OF ENTERAL NUTRITION BASICS

2.1. Tube Placement

EN therapy is characterized by both the route of tube placement and the site of feeding. Tubes can be placed through the nares or by ostomy formation. The route of tube placement per se is unlikely to influence DNIs in patients receiving EN therapy. Tube size and length, however, may be influenced by the route of placement and these characteristics can affect the risk of tube occlusion when drugs are administered via the tube. Nasal placement requires that a long, small-bore tube be passed through the nares, pharynx, and esophagus. Tubes used in adults are typically 8 to 10 French (F); pediatric tubes may be as small as 2 F for young children. Polyurethane is the preferred material for nasal tubes. These tubes remain soft and flexible when exposed to gastric acid rather than becoming brittle like polyethylene or polyvinyl chloride tubes. Polyurethane tubes are less likely to collapse when aspiration is attempted and less likely to occlude than silicone tubes because of their larger internal diameter for a given F size. In general, risk of tube occlusion decreases with increasing internal tube diameter regardless of the tube material and with increasing external diameter (i.e., F size) for a specified feeding tube material. Patients expected to require EN for a short duration of time are most appropriate for nasal placement of the tube. Bedside techniques are generally effective for tube placement through the nares, although radiological guidance may be necessary in some patients.

Feeding ostomies (i.e., enterostomies) are reserved for patients requiring long-term EN therapy. The definition of "long-term" ranges from a minimum of 4 wk to at least 6 mo duration for EN therapy, depending on specific patient characteristics, the type of enterostomy, and physician preferences (3). Percutaneous endoscopic techniques and surgical procedures are available for enterostomy formation. Passage of an endoscope into the stomach or small bowel and transillumination to the skin surface are required to perform endoscopic enterostomy techniques. Conditions precluding endoscopic enterostomy include morbid obesity, peritoneal dialysis, hepatomegaly, and portal hypertension (4). Massive ascites, coagulopathy, and a history of Crohn's disease or radiation enteritis (i.e., patients at high risk of enterocutaneous fistula formation) hinder enterostomy formation by any method, percutaneous or surgical. Percutaneous endoscopic enterostomies are generally favored in patients who do not require laparotomy for another purpose because general anesthesia is not required for percutaneous procedures. Tubes used for enterostomies vary from 5 to 28 F, depending on the type of tube and site of placement. Percutaneous endoscopic gastrostomy (PEG) and surgical gastrostomy tubes are the largest; needle catheter jejunostomy tubes and those used in infants are the smallest. Most tubes used today for needle catheter jejunostomies are at least 7 or 8 F to reduce the risk of tube occlusion. To avoid jejunal obstruction, jejunostomy tube size is generally a maximum of 16 F in adults. Tubes used in children vary considerably in size based on the child's weight and the type of tube. Most of the tubes used for young children are quite small and are more prone to occlusion than tubes used for adolescents and adults. Silicone

is the preferred material in tubes designed for feeding ostomies but red rubber tubes and Foley catheters made of latex continue to be popular (although not recommended) for replacement tubes in enterostomies. Ease and safety of tube replacement depends on the exact procedure used for initial tube placement and the time since tube placement. Needle catheter jejunostomy tubes generally require laparotomy for placement and for replacement if an occlusion occurs that cannot be reversed. Gastrostomy tubes placed through a stoma (e.g., Janeway gastrostomy) are easily removed and replaced.

2.2. Site of Feeding

The name of a feeding tube indicates both the route of placement (i.e., nasal or ostomy) and the site of feeding. Location of the tube's distal tip determines the site of feeding—gastric, duodenal, or jejunal. Tube placement into the stomach is easier than into the small bowel with either nasal or enterostomy techniques. Gastric feeding is more physiologic than postpyloric (i.e., duodenal or jejunal) feeding since most normal gastrointestinal (GI) functions, except those of the mouth and esophagus, are utilized. However, postpyloric feeding is generally more appropriate for patients with gastric dysfunction (e.g., gastroparesis, gastric atony) and when minimal pancreatic stimulation is desired (e.g., pancreatitis). Postpyloric tube placement may facilitate early postoperative enteral feeding since the small bowel regains function more quickly after surgery than the stomach. Postpyloric feeding is the standard of practice for patients at risk of aspiration, including those with poor gag reflex, neurological injury, or delayed gastric emptying and those on mechanical ventilation *(5)*. Despite the standard of practice, most studies have failed to show a difference in the incidence of aspiration between gastric and postpyloric feeding *(6,7)*. This is true even when radiolabeling of the EN formula permits formula aspiration to be distinguished from aspiration of other substances (e.g., oropharyngeal secretions) *(8)*. However, studies rarely specify the location of postpyloric tube placement. Formula from nasoduodenal feeding and the tubes themselves can migrate back into the stomach from a position just beyond the pylorus. Formula and tubes placed past the Ligament of Trietz (i.e., jejunal placement) are unlikely to migrate into the stomach. The site of feeding is an important consideration for DNIs in patients receiving EN when the feeding tube is used for drug administration.

2.3. Administration Regimens for Enteral Feeding

The administration regimen selected for EN therapy depends on the site of feeding, patient tolerance to feeding volume, and fluid requirements. The regimen includes the method of administration as well as the flush volume and frequency necessary to provide adequate fluids. Gastric feeding offers more options for formula administration than postpyloric feeding. There are four general administration methods: continuous, cyclic, intermittent, and bolus. Continuous and cyclic administration are used for both gastric and postpyloric feeding, whereas intermittent and bolus regimens are reserved for gastric feeding. Continuous infusion is the most common administration method for hospitalized patients. The consistent rate of infusion over 24 h minimizes the volume of formula per hour and may reduce the risk of feeding intolerance. Patients receiving postpyloric feeding are particularly prone to feeding intolerance with high infusion rates and/or fluctuations in rate or volume of feeding. Intolerance generally manifests as abdominal pain and cramping with or without diarrhea. The small bowel gradually adapts to larger

volumes thereby allowing transition to a cyclic regimen for many HEN patients with postpyloric feeding tubes. Patients receiving gastric feeding can generally transition from continuous administration to a cyclic regimen faster than those receiving postpyloric feeding and with less risk of intolerance. Cyclic regimens are convenient for many HEN patients because formula infuses at a constant rate but for less than 24 h per day. A typical cyclic regimen infuses for 8 to 12 h at night so the patient is not encumbered by feeding during daytime hours when he or she is most likely to be active. Intermittent and bolus administration provide EN formula in a pattern similar to that of meals with a few to several discrete feedings daily depending on tolerance to volume. The volume provided per feeding is considerably higher than the hourly rate for continuous administration or cyclic regimens, therefore, intermittent and bolus regimens are rarely tolerated by patients with postpyloric feeding tubes. The major difference between intermittent and bolus feeding is the rate of administration. Intermittent feedings are infused over 30 to 60 min, whereas bolus feedings typically infuse over 5 to 10 min. The administration method selected for EN induces physiologic responses by the GI tract that can influence DNIs. In addition, the risk of physical interactions between drugs and formula can be influenced by the feeding method.

3. CLASSES OF INTERACTIONS

Interactions between drugs and EN therapy can be defined as direct interactions between drugs and enteral formula or can be defined more broadly as any effect of a drug on EN therapy or EN on a drug that results in altered response to the other therapy. Using the broader definition, interactions can be divided into several categories or classes as listed in Table 1. These categories are not mutually exclusive as one class of interaction could be associated with another class. For example, a physical interaction that results in precipitation of a drug could lead to altered absorption, a pharmacokinetic interaction. Many pharmacokinetic interactions are, in fact, the result of another class of interaction. Factors contributing to the various classes of interactions can be organized into groups based on the moiety of EN therapy involved (Table 2). These groups serve as a logical basis for reviewing DNIs in patients receiving EN therapy although there is considerable overlap between some groups.

3.1. Administration-Related Factors

3.1.1. TUBE CHARACTERISTICS

Tube size and length can affect the risk of tube occlusion when drugs are administered via the tube. Long tubes with small internal diameters are most prone to occlusion. For a given tube material, smaller F size correlates with increased risk of tube occlusion. Formula characteristics such as viscosity and drug characteristics such as dosage form are synergistic with tube size and length in causing tube occlusion, a form of physical interaction.

3.1.2. ADMINISTRATION REGIMEN

DNIs can be affected by the EN administration regimen in several ways. The first is by the presence of enteral formula or lack thereof at the time drugs are administered. Failure to stop a continuous infusion of EN formula and flush the tube prior to drug

Table 1
Categories of Drug–Nutrient Interactions in Patients Receiving Enteral Nutrition

Category of Interaction	Description/Definition
Physical	Changes in physical appearance, viscosity or consistency of a drug and/or enteral formula that result in adverse outcomes such as feeding tube occlusion when the drug and formula are allowed to commingle.
Pharmaceutical	Inappropriate changes in the drug dosage form to allow administration through a feeding tube that causes inadequate drug delivery, toxicity, or irritation of the gastrointestinal tract.
Pharmacological	The expected effects of a drug based on the drug's mechanism of action interferes with nutrient absorption or induces intolerance to enteral feeding.
Physiological	A physiological response to a drug that causes intolerance to EN therapy and is not related to the purpose for which the drug is administered. A physiological response to an enteral formula that is not related to the nutritional content and results in altered efficacy of a drug. Physiological interactions may also be referred to as side effects or adverse effects of the drug or formula.
Pharmacokinetic	Changes in absorption, distribution, metabolism, or elimination of a drug or nutrient owing to another drug or nutrient.
Pathophysiological	Changes in the response to a drug or nutrient as a result of development or alteration of a disease process (e.g., malnutrition) by a drug or nutrient.

administration contributes to physical interactions between formula and drugs that often result in tube occlusion. Second, the choice of flush fluid significantly affects the risk of physical interactions that contribute to tube occlusion. Water is the preferred fluid for flushing feeding tubes. Carbonated beverages are no better than water as a flush solution and have the potential to interact with formula or drugs (9). Acidic fluids such as fruit juice can cause clumping, curdling, and other physical changes in enteral formula; cranberry juice is particularly problematic as a flush solution (10,11). Adequate flush volume must be used to clear the feeding tube of formula or drug and flushing should occur before, after, and between drugs. Table 3 provides general guidelines for drug administration in patients receiving EN therapy, including recommended flush volumes for nasogastric and small bowel tubes in adults (steps 8 and 9).

Starting and stopping continuous infusion EN formula to allow an hour or more separation between formula administration and drug administration can be difficult. The net result of holding formula administration too long is that patients receive less than the prescribed enteral formula volume. Over time, this could result in malnutrition (undernutrition) with concomitant alterations in drug response, a pathophysiological interaction. When formula is not held long enough after administration of specific drugs (e.g., phenytoin) pharmacokinetic interactions that result in reduced efficacy may occur. In this case, it may be easier to assure that drug and formula administration are separated by an appropriate time period and that adequate formula is delivered when the formula is administered periodically (i.e., intermittent or bolus regimen).

Table 2
Factors Contributing to Drug–Nutrient Interactions With Enteral Nutrition

Administration-related factors
    Tube characteristics
        French size, length, material (internal diameter)
    Administration regimen
        Method—continuous, cyclic, intermittent, bolus
        Flush protocol—water vs other fluid, frequency, volume
    Site of feeding
        Gastric, duodenal, jejunal
Drug-related factors
    Dosage forms
        Solidity—solid vs liquid
        Specific dosage forms
          tablet—simple compressed, film-coated, enteric-coated, extended duration,
            sublingual, buccal
          capsule—hard gelatin (contains powder, granules, beads, or pellets), soft gelatin
            (contains liquid)
          elixir—drug is in solution, contains alcohol to solubilize drug
          syrup—drug is in solution, contains high concentration of sugar
          solution—drug is in solution, does not specify liquid carrier or solubilizing agent
            for drug
          suspension—fine particles of solid drug suspended in liquid
        Excipients—sorbitol, alcohol, other solubilizing agents, stabilizers, flavorings
        Osmolality
        Viscosity
    The absorptive environment
        Solubility—acid vs base and hydrophilic vs lipophilic
    Therapeutic index—narrow therapeutic index drugs
Formula-related factors
    Protein content
        Complexity—intact vs hydrolyzed
        Source—caseinate, isolated milk protein, soy, whey
    Components influencing gastrointestinal motility
        Fat content
        Osmolality
        Viscosity—fiber content and caloric density
        Vitamin K content
Disease state-related factors
    Visceral protein status
    Gastrointestinal motility—gastric emptying and small bowel transit time

The feeding regimen can result in physiological interactions mediated by the GI tract's response to feeding. Patterns of GI motility and secretion can be divided into "fed" and "unfed" patterns. The fed pattern is associated with slower transit from the stomach to the small bowel and increased presence of digestive enzymes and GI tract secretions. Based on individual drug and dosage form characteristics, the "fed" state may be better or worse than the "unfed" state for drug absorption; hence, recommendations to take a drug with

or without food. The influences of tube feeding on drug availability are likely to be similar to outcomes with food, at least for intermittent feeding. Interestingly, continuous infusion of enteral formula into the stomach appears to produce an "unfed" (i.e., fasting) pattern within the GI tract for some drugs. A study in which hydralazine was administered to eight healthy subjects with continuous infusion enteral formula via nasogastric tube demonstrated pharmacokinetic parameters similar to those in the fasted state *(12)*. Hydralazine pharmacokinetic parameters with bolus feeding were similar to those observed following a standard breakfast in this study. There is little evidence to document reduced absorption when the majority of drugs to be taken on an empty stomach are administered with continuous tube feeding. Therefore, in deciding to hold tube feeding for a period of time, usually 1 h, before and after drug administration, one must consider the potential for inadequate enteral formula delivery as well as the consequences of inadequate drug absorption. It may be prudent to hold feedings before and after critical medications to be taken on an empty stomach (e.g., ofloxacin for a serious infection). For other drugs, it may be better to continue feeding, monitor response to the drug, and only hold feedings if the patient fails to respond to the drug.

3.1.3. THE SITE OF FEEDING

Substances administered through feeding tubes bypass specific regions of the GI tract and avoid exposure to the environment at those locations. The site of feeding determines the physiological conditions that are avoided and those to which a drug or nutrient are exposed. Table 4 outlines the physiological conditions and functions normally performed relative to drugs and foods at various sites along the GI tract. The absorptive environment is established by the site of feeding and has a major impact on pharmacokinetic interactions of drugs, absorption in particular. Drugs intended for a local effect in the stomach (e.g., antacids, sucralfate) should not be administered through a postpyloric tube as they will not be able to exert their pharmacological effect.

3.2. Drug-Related Factors

3.2.1. DOSAGE FORMS

The term "dosage form" encompasses the drug itself plus all inert ingredients (i.e., excipients) needed to produce a stable, efficacious, nontoxic product for administration to a patient. Common dosage forms include capsules, elixirs, powders, solutions, suspensions, syrups, tablets, aerosols, creams, lozenges, ointments, suppositories, and transdermal systems. Subsets of tablets and capsules designed for specific purposes are also available, as listed in Table 2. Liquid dosage forms that are commonly administered through feeding tubes are included in Table 2 as well. Solid dosage forms must be altered by crushing or otherwise obtaining a fine powder that can be mixed with water to form a slurry for administration through a feeding tube. When changes in the pharmaceutical dosage form result in reduced efficacy, increased toxicity, or increased adverse effects of the drug, a pharmaceutical interaction has occurred. Enteric-coated and extended duration solid dosage forms are most prone to pharmaceutical interactions. Other coatings (e.g., film-coatings) can also be troublesome as they tend to remain intact despite crushing of the tablet. Table 5 lists several accessory terms associated with dosage forms that should not be crushed and provides examples of drugs using these terms. Lists of drugs that should not be crushed or otherwise altered are also available in the literature *(13)*.

Table 3

Guidelines for Drug Administration in Patients Receiving Enteral Nutrition

1. Administer drugs by the oral route whenever possible. Consider alternate routes (e.g., rectal, sublingual, buccal, transdermal) when drugs are available in these forms and the patient cannot swallow the drug. Some oral dosage forms are effective when administered by the sublingual or rectal route (e.g., sustained-release morphine tablets administered rectally). Consider cost to benefit in the selection of alternate dosage forms.

2. Oral liquid dosage forms are generally preferred, if available, when drugs must be administered through the feeding tube. However, other dosage forms may be preferred when the liquid is associated with a high risk of physical incompatibility and/or gastrointestinal intolerance.

   Problematic oral liquids that should generally be *avoided* include
   - syrups with a pH of 4.0 or less.
   - possibly elixirs with a pH of 4.0 or less.
   - oil-based products (e.g., MCT [medium chain triglyceride] oil, cyclosporin).
   - products with a high sorbitol content. Cumulative sorbitol dose should be no more than 5 g/d. Consider an alternative dosage form (e.g., crushed tablet) if sorbitol content cannot be determined and patient has abdominal cramping, bloating, or diarrhea.
   - some specific formulations that the manufacturer states should not be administered through a feeding tube (e.g., clarithromycin suspension is a microgranular formulation and erythromycin suspension is a microcapsular formulation that are not to be administered through feeding tubes because of risk of tube occlusion).

3. Oral liquid dosages must be properly prepared to administer through a feeding tube.
   - dilute viscous products with 30 to 50 mL water (minimum 50:50 volume:volume) prior to administration (e.g., phenytoin suspension and carbamazepine suspension).
   - dilute hypertonic or irritating products prior to administration using a minimum of 30 mL, preferably more, of water. Hypertonic products may require dilution with more than 100 mL of water to reach an osmolality of approximately 300 mOsm/kg, the goal osmolality if possible.
   - divide doses of hypertonic or irritating products into two to four smaller doses administered at least 1 h apart when this does not alter therapeutic efficacy (e.g., divide 60 mEq liquid potassium chloride into three doses of 20 mEq each).

4. Select appropriate solid dosage forms for administration through the feeding tube, including most
   - immediate release, compressed tablets.
   - capsules that contain powdered drug.
   - capsules containing beads or pellets that are an immediate release form of drug that can be crushed.
   - coated tablets or capsules designed to protect the oral mucosa from dyes, irritants, or bad taste.

   The dosing schedule must be adjusted if the dosage form is changed from one with a prolonged duration of action to an immediate release form.

5. Oral solid dosage forms that should NOT be administered through a feeding tube include
   - sublingual products.
   - buccal products.
   - enteric-coated products.*

Table 3 (continued)

   - dosage forms designed for a prolonged duration of action.*
   - any product that cannot be dissolved or adequately crushed to form a slurry that can pass through the feeding tube without occluding the tube.

   * It may be possible to administer coated pellets, beads, or granules contained in hard-gelatin capsules by opening the capsule and delivering the pieces via a feeding tube with an internal diameter and distal ports of adequate size to allow the pieces to pass through. An acidic fruit juice should be used to flush the tube immediately after administering an enteric-coated product, then follow this with the usual flush of water.

6. Prepare solid dosage forms properly for administration through a feeding tube.
   - tablets—crush to a fine powder and mix with 30 to 50 mL of warm water (15 mL minimum) for administration.
   - capsules—open hard-gelatin capsules containing powder and mix the powder with 30 to 50 mL of warm water (10 mL minimum) before administration through the tube. Hard-gelatin capsules containing beads or pellets are usually long-acting dosage forms that should not be crushed. These products can be administered only through large bore tubes that have openings large enough to permit intact beads to pass through (i.e., 14 F or larger gastrostomy and PEG tubes, possibly jejunostomies).
   - capsules—dissolve soft-gelatin capsules in warm water using adequate volume (suggest 30 mL minimum) to keep the gelatin dissolved during administration. Liquid contents can also be aspirated from these capsules and mixed with 10 to 15 mL water for administration although some of the drug may remain in the capsule when the aspiration method is used.

7. Use only water for mixing and flushing.
   - tap water is generally acceptable if it meets municipal water quality standards, including adequate microbial quality.
   - immunocompromised patients may require water of high microbial quality (i.e., sterile water).
   - do not mix drugs directly with enteral formula. Exceptions to this rule include sodium chloride as table salt and some electrolyte injections.

8. Administer each drug separately with a minimum 5 mL flush of water between each sequentially administered drug. Do not mix drugs together before administration as this increases the risk of interactions and incompatibility.

9. Flush the tube adequately with water before and after administering drugs.
   - nasogastric tubes require a minimum of 15 mL for flushes with 30 mL recommended.
   - tubes in the small bowel require a minimum of 20 mL for flushes with 30 to 50 mL recommended.
   - use the recommended flush volume whenever possible, especially to clear the tube after drug administration.

10. Administer the dissolved drug or drug–water slurry using a 30 to 60 mL syringe and allowing gravity flow to empty the syringe. Use only a gentle push on the syringe plunger when necessary to aid flow. Excessive pressure on the syringe can damage the feeding tube.

11. Hold feedings for the recommended time period before and after administration of specific drugs.
   - carbamazepine—hold formula administration for 2 h before and 2 h after drug administration.

Table 3 (continued)
Guidelines for Drug Administration in Patients Receiving Enteral Nutrition

- ciprofloxacin—hold formula for at least 1 h before and 2 h after drug administration.
- penicillin V potassium—hold formula for at least 1 h before and 2 h after drug administration.
- phenytoin—hold formula administration for 1 to 2 h before and 1 to 2 h after drug administration.
- warfarin—hold formula for at least 1 h before and 1 h after drug administration.

12. Assess response to drugs using clinical parameters and therapeutic drug monitoring as appropriate.
13. Assess response to enteral nutrition therapy.

Note: Volumes for dilution and flushing are for adult patients. Reduce dilution volumes for pediatric doses to a minimum of 50:50 volume:volume; use at least 5 mL for dilution when fluid restriction is not required. Flush volume must be adequate to clear drug from the tube and will depend on the tube length and internal diameter. Follow the manufacturer's recommendation for flush volume to maintain tube patency.

Enteric coating is designed to resist gastric acid and dissolve in the higher pH of the small bowel. Enteric coating is used when the drug is acid labile, causes mucosal or gastric irritation, stains teeth or mucosa, or when exposure to acid results in toxic metabolites. Tablets are the most common enteric-coated dosage form. Additionally, microencapsulated dosage forms consisting of enteric-coated pellets, beads, or granules enclosed in hard gelatin capsules are available. Crushing enteric-coated tablets or microencapsulated dosages removes the protection afforded by the coating, thereby exposing the drug to gastric acid or the body to irritants or toxins when the crushed product is administered by mouth or into the stomach by tube.

For products delivered into the jejunum through a feeding tube, the enteric coating is not necessary. However, crushing enteric-coated dosage forms is still problematic for what might be considered a physical interaction. Enteric coatings are troublesome to crush, tending to form fragments that clump together when mixed with water and occluding the tube if administration through the tube is attempted. Whenever possible, alternative routes or dosage forms should be used rather than attempting to administer an enteric-coated drug through a feeding tube. Nonetheless, when the dosage form is small and the internal diameter and distal ports of the feeding tube are of adequate size (i.e., 14 F or larger gastrostomy or jejunostomy tubes), it may be possible to administer the dosage form through the tube *(14)*. Some microencapsulated dosages can be removed from their outer capsule and delivered through the feeding tube. Table 5 notes some of these products. Pouring the pieces from the capsule down the tube has been suggested *(15)*; however, some pieces may adhere to the inside of the tube with this method unless a vigorous flush with an acidic juice follows the pieces. Another suggestion is to suspend the pieces in an acidic fruit juice for administration. This method also poses some risk of tube clogging. Neither method should be attempted with small diameter tubes, especially tubes that require surgical replacement (i.e., needle catheter jejunostomies). For some drugs to be administered through a jejunostomy tube, it may be possible to dissolve the enteric coating using bicarbonate solution, then crush or dissolve the drug to form a slurry.

Table 4
Physiologic Conditions and Functions at Sites Within the Gastrointestinal Tract

Site	Major Secretions	Activity Related to Drugs	Activity Related to Foods
Mouth	Saliva salivary amylase	Disintegration of solid forms started	Maceration; carbohydrate digestion started
Esophagus	None	Transport to stomach; disintegration continues	Transport to stomach; continue carbohydrate digestion
Stomach	Gastrin Gastric acid (HCl) Pepsinogen (pepsin) Gastric lipase Intrinsic factor	Disintegration; dissolution of acid soluble drugs; some absorption of small, lipophilic molecules and nonpolar weak acids that are soluble in low pH	Mixing; chyme formation; carbohydrate digestion; begin protein digestion; release nutrients from food; reduction of iron (Fe^{+3}); few nutrients absorbed
Duodenum	Gut hormones[a] Pancreatic enzymes[b] Bile	Disintegration of enteric coated drugs; dissolution of drugs soluble at pH 5.0 to 7.0; passive absorption of drugs in solution	Osmolality and pH of chyme; control gastric emptying; carbohydrate, protein and fat digestion; absorption of protein, fats, and many micronutrients
Jejunum	VIP[c] Aminopeptidases Dipeptidases Disaccharidases	Dissolution of drugs soluble at pH 5.0 to 7.0; passive absorption of most drugs occurs to some extent	Absorption of carbohydrate, protein, fat, and many micronutrients
Ileum	Aminopeptidases Dipeptidases Disaccharidases	Continued dissolution of drugs soluble at pH 5.0 to 7.0; passive absorption of most drugs occurs to some extent	Absorption of carbohydrate, protein, fat, and many micronutrients; site of active absorption for vitamin B_{12}; reabsorption of bile acids

[a]gastrin, gastric inhibitory polypeptide (GIP), motilin, glucagon, pancreatic polypeptide, secretin, cholecystokinin.

[b]trypsinogen (trypsin), chymotrypsinogen (chymotrypsin), procarboxypeptidase (carboxypeptidase A and B), elastase, collagenase, ribonuclease, deoxyribonuclease, alpha-amylase, lipase, cholesterol esterase

[c]vasoactive intestinal polypeptide.

Dosage forms designed to provide an extended duration of action should not be crushed or otherwise altered for administration via a feeding tube. These dosage forms contain several doses of drug in one tablet or capsule. Drug is released in the GI tract over several hours, thus reducing the number of times a drug must be administered to once or twice daily. Crushing or dissolving an extended duration dosage form delivers all the drug as an immediate release, consequently causing an "overdose" initially and no drug activity several hours later. Side effects or toxicity of the drug may be increased and disease control may be erratic. As with enteric-coated drugs, it may be possible to administer certain extended-release dosage forms through large-bore feeding tubes. Pellets, beads,

Table 5
Terms Associated With Dosage Forms That Should Not Be Crushed

Accessory Term	Meaning of Term	Examples
CD	Controlled dosing/delivery	Cardizem CD[a]
CR	Controlled release	DynaCirc CR, Norpace CR, Sinemet CR
ER	Extended release	Depakote ER, Flagyl ER
Extentab	Slow release	Dimetane Extentab
LA	Long acting	Entex LA, Inderal LA
Repetab	Slow release	Proventil Repetab
SA	Sustained action	Choledyl SA
Sequel	Slow release	Tedral SA
Spansule	Slow release	Feosol Spansule
Sprinkle	Slow release	Theo-Dur Sprinkle[a]
SR	Sustained release	Calan SR, Cardizem SR[a], Isoptin SR, Pronestyl SR, Wellbutrin SR
TD	Time delay	
Timecaps	Slow release	Nitrocine Timecaps
TR	Time release	Rondec TR, Triaminic TR
XL	Extended release	Ditropan XL, Glucotrol XL, Procardia XL, Ritalin XL
XR	Extended release	Dilacor XR, Tegretol XR
Enteric-coated	Enteric-coated	Creon[a], Pancrease[a], Pancrease MT[a], Prevacid[a], Prilosec[a], Prozac[a], Verelan[a]

[a]These drugs are microencapsulated dosage forms with pellets, beads, or granules in a hard-gelatin capsule. The capsule can be opened and the pieces administered via a feeding tube with adequate diameter and distal port size to allow the pieces to pass through. For enteric-coated products, the tube should be flushed with an acidic juice before the usual flush with water.

or granules that are coated to create an extended release of drug and enclosed in a hard-gelatin capsule can often be removed from their outer capsule and delivered through a feeding tube with an internal diameter and distal ports of adequate size. However, the consequences of possible tube occlusion should be considered before administering these dosage forms that are more a convenience than a necessity.

Administration through a feeding tube of dosage forms not intended to be swallowed often results in a pharmaceutical interaction with altered bioavailability of the drug. Sublingual and buccal dosages are designed for absorption through tissues in the mouth where exposure to gastric acid and hepatic metabolism prior to systemic circulation are not a concern. As such, the amount of drug in most of these dosage forms can be relatively small compared to dosage forms that are swallowed. Likewise, intravenous dosage forms are not designed to withstand gastric acid, digestive enzymes, or other conditions within the GI tract and substantial loss of drug can occur with administration through a feeding tube. Certain intravenous products such as electrolyte solutions are acceptable to administer through a feeding tube; however, less expensive alternatives may be available.

Excipients are additional ingredients in a dosage form that are intended to solubilize, stabilize, bind, dilute, flavor, sweeten, or otherwise allow drugs to be converted to usable dosage forms. Although not intended to produce a response by the body, some excipients

can cause undesirable physiologic responses (e.g., diarrhea). Such unintended responses to a drug administered through a feeding tube that occur in people with a wide range of conditions requiring EN therapy are classified as physiological interactions. When these unintended responses are the result of exacerbating a disease process, the interactions are considered to be pathophysiologic. Wheat or cornstarch used as a binder in tablets, for example, could result in bloating, abdominal pain, and diarrhea for a patient with gluten-induced enteropathy (i.e., Celiac sprue) but would cause no symptoms in most people. The excipient of most concern for people receiving EN therapy is sorbitol. Alcohol, lactose, carbohydrates, and dyes are other excipients of concern for some patient populations.

Sorbitol is a sugar alcohol used as a solubilizing agent, to prevent crystallization of sucrose, and as a "sugar free" sweetener in liquid dosage forms. However, sorbitol doses of 20 to 50 g are used as a purgative agent and cause severe cramping and diarrhea in most people. Doses of only 5 to 10 g cause GI symptoms such as bloating and flatulence in a sizable share of the population (16). Several case reports of GI intolerance secondary to cumulative sorbitol doses can be found in the literature. Thus, care must be taken to avoid excessive cumulative sorbitol intake from multiple drugs (17–19). All dosage forms and doses of a given drug should be evaluated because there can be clinically significant differences in sorbitol content, as shown in Table 6. For example, use of furosemide solution 10 mg/5 mL to administer 40 mg furosemide daily would give 9.6 g sorbitol, whereas furosemide solution 40 mg/5 mL from the same manufacturer would result in 2.4 g sorbitol daily. Therapeutic equivalents for the drug should be considered if necessary. A patient receiving 1200 mg cimetidine daily for erosive esophagitis would receive 11.2 g sorbitol using the 300 mg/5 mL Tagamet liquid. Changing to the therapeutic equivalent ranitidine at an equivalent dose of 600 mg daily, the patient would receive 4 g sorbitol from 150 mg/5 mL Zantac syrup. A therapeutically equivalent dose of famotidine as Pepcid oral suspension would provide no sorbitol.

Most drugs available without prescription now include a list of inert ingredients without quantities on the label, however, a large percentage of prescription medications do not. Excipients may be classified as proprietary information by the manufacturer although often the medical information department will answer whether a specific excipient is present in a specific product. The amount of an excipient present may be more difficult to obtain. Table 6 contains the sorbitol content of a few selected drugs based on information provided by the manufacturer. In recent years, the trend has been toward elimination of sorbitol in some classes of drugs, especially pediatric antibiotics. Table 7 lists several liquid antibiotic preparations that contain no sorbitol. However, published information listing quantities of specific excipients such as dyes and sweeteners (20), carbohydrate (21), or sorbitol (22,23), or statements that none of a particular excipient is present in specific products must be interpreted with caution. Excipients are often manufacturer-specific and may change frequently depending on market availability and cost. The best method to determine whether a product currently on the market contains a particular excipient is to contact the manufacturer and request the information for the care of a specific patient.

Osmolality of liquid dosage forms is somewhat related to the drug itself but more to the number and types of excipients. Hyperosmolar drugs can cause symptoms including nausea, vomiting, diarrhea, bloating, cramping, and abdominal pain that are attributed to

Table 6
Sorbitol Content of Selected Liquid Dosage Forms

Classification Generic Name	Brand and Dosage Form	Concentration per 5 mL	Manufacturer	Sorbitol (g/mL) [a]
Analgesics				
Acetaminophen	Tylenol Infant's drops (100 mg/mL)	500 mg	McNeil	None
	Tylenol Children's elixir	160 mg	McNeil	0.2
	Tylenol Children's suspension	160 mg	McNeil	0.2
	Tylenol Extra Strength liquid	167 mg	McNeil	0.2
Ibuprofen	Pedia-Profen suspension	100 mg	McNeil	0.3
Naproxen	Naprosyn suspension	125 mg	Roche	0.1
Antibiotics				
Nitrofurantoin	Furadantin suspension	25 mg	PG	0.14
Tetracycline	Sumycin suspension	125 mg	Apothecon	0.3
Trimethoprim/ Sulfameth- oxazole (TMP/SMZ)	Bactrim pediatric suspension	[40 mg TMP + 200 mg SMZ]	Roche	0.07
	Septra suspension		GW	0.45
	TMP/SMZ		Biocraft	0.07
Anticonvulsants				
Carbamazepine	Tegretol suspension	100 mg	Novartis	0.12
Phenobarbital	Phenobarbital elixir	15 mg and 20 mg	Lilly	None
Phenytoin	Dilantin-30 suspension	30 mg	Parke-Davis	None
	Dilantin-125 suspension	125 mg	Parke-Davis	None
Primidone	Mysoline suspension	250 mg	WA	None
Valproic acid	Depakene syrup	250 mg	Abbott	0.15
Antidiarrheals				
Loperamide	Imodium A-D	1 mg	McNeil	None
	Loperamide oral solution	1 mg	Roxane	None
Bronchodilators				
Aminophylline	Aminophylline oral liquid	105 mg	Roxane	0.14
Theophylline	Elixophylline elixir (80 mg/15 mL)	27 mg	Forest	None
	Slo-Phyllin 80 syrup (80 mg/15 mL)	27 mg	RPR	0.58

(continued)

Table 6 (continued)

Classification Generic Name	Brand and Dosage Form	Concentration per 5 mL	Manufacturer	Sorbitol (g/mL) [a]
	Theoclear-80 syrup (80 mg/15 mL)	27 mg	Central	0.8
	Theolair liquid (80 mg/15 mL)	27 mg	3M Pharma	0.1
	Theophylline solution (80 mg/15 mL)	27 mg	Roxane	0.46
Theophylline/ Guaifenesin	Elixophylline GG elixir Slo-Phyllin GG syrup	[27 mg theoph. + 100 mg guaifen.]	Forest RPR	0.46 0.12
Diuretics				
Chlorothiazide	Diuril oral suspension	250 mg	Merck	None
Furosemide	Furosemide solution	10 mg	Roxane	0.48
	Furosemide solution	40 mg	Roxane	0.48
	Lasix oral solution	10 mg	HMR	None
Hydrochloro- thiazide	Hydrochlorothiazide solution	50 mg	Roxane	None
GI Stimulants				
Metoclopramide	Metoclopramide syrup	5 mg	Biocraft	0.4
	Metoclopramide oral solution	5 mg	Roxane	0.25
	Metoclopramide Intensol	10 mg	Roxane	0.25
Histamine H_2 Antagonist				
Cimetidine	Tagamet liquid	300 mg	SKB	0.56
Famotidine	Pepcid oral suspension	40 mg	Merck	None
Ranitidine	Zantac syrup (15 mg/mL)	75 mg	GW	0.1
Sedatives/ Hypnotics	Diazepam oral solution	5 mg	Roxane	None
Diazepam	Diazepam Intensol (2 mg/mL)	10 mg	Roxane	None
Diphen- hydramine	Benadryl elixir (cherry)	12.5 mg	Warner Lambert	None
	Benadryl elixir, diet	12.5 mg	Warner Lambert	0.45
Lorazepam	Lorazepam Intensol (2 mg/mL)	10 mg	Roxane	None

[a]Determine daily sorbitol dose by calculating the total milliliter per day of drug, then multiply by the grams of sorbitol per milliliter. For example, the calculation for a patient receiving 320 mg acetaminophen four times daily using Tylenol Children's suspension (160 mg/5 mL concentration) is as follows: 10 mL/dose × 4 doses/d × 0.2 g/mL = 8 g/d.

GW, Glaxo Wellcome; HMR, Hoechst-Marion Roussel; PG, Procter & Gamble; RPR, Rhone-Poulenc Rorer; SKB, SmithKlein Beecham; WA, Wyeth-Ayerst. (Used with permission, Pharmacy Services, Nutrition Support Team, University Medical Center, Tucson, AZ. Data obtained from manufacturers between 1999 and 2003.)

Table 7
Liquid Antibiotic Preparations Reported Not to Contain Sorbitol

Generic Name	Brand and Dosage Form	Concentration (per 5 mL)	Manufacturer
Amoxicillin	Various brands of suspension	125 mg and 250 mg	Apothecon, Biocraft, Lederle, SKB, WA
Amoxicillin	Amoxil and Trimox pediatric drops	250 mg (50 mg/mL)	SKB, Apothecon
Ampicillin	Various brands of suspension	125 mg and 250 mg	Apohecon, Biocraft, Lederle
Azithromycin	Zithromax 100 suspension	100 mg	Pfizer
	Zithromax 100 suspension	200 mg	Pfizer
Cefaclor	Ceclor suspension	125 mg, 187 mg, 250 mg	Lilly
Cefadroxil	Duricef suspension	125 mg and 250 mg	BMS
Cefuroxime	Ceftin suspension	125 mg and 250 mg	GW
Cephalexin	Cephalexin suspension	125 mg and 250 mg	Lederle, Biocraft
	Keflex oral suspension	125 mg and 250 mg	Dista
Cephradine	Velosef suspension	125 mg and 250 mg	BMS
Ciprofloxacin	Cipro oral suspension	250 mg and 500 mg	Bayer
Clarithromycin	Biaxin suspension	125 mg and 250 mg	Abbott
Clindamycin	Cleocin pediatric oral solution	75 mg	Upjohn
Dicloxacillin	Dynapen and Pathocil	62.5 mg	Apothecon, WA
Doxycycline	Vibramycin mono- hydrate suspension	25 mg	Pfizer
	Vibramycin calcium syrup	50 mg	Pfizer
Erythromycin ethylsuccinate	EES 200	200 mg	Abbott
	EES 400	400 mg	Abbott
	EryPed suspension drops	200 mg and 400 mg	Abbott
Erythromycin/ sulfisoxazole	EES/sulfisoxazole suspension	200 mg /600 mg	Lederle
	Pediazole	200 mg /600 mg	Ross
Loracarbef	Lorabid suspension	100 mg and 200 mg	Lilly
Penicllin VK	Various brands of suspension	125 mg	Biocraft, SKB, WA
	Veetids oral suspension	125 mg and 250 mg	Apothacon
Sulfisoxazole	Gantrisin pediatric suspension	500 mg	Roche
Vancomycin	Vancocin oral solution	1 g bottle	Lilly

BMS, Bristol-Myers Squibb; GW, Glaxo Wellcome; SKB, SmithKlein Beecham; WA, Wyeth-Ayerst. (Used with permission, Pharmacy Services, Nutrition Support Team, University Medical Center, Tucson, AZ. Data obtained from manufacturers between 1999 and 2003.)

EN intolerance, thereby resulting in a physiological interaction *(24–26)*. Liquid dosage forms often have an osmolality of 3000 mOsm/kg or higher *(24,27)*. Small amounts of hyperosmolar liquid delivered to the stomach are diluted by gastric fluid prior to being emptied into the duodenum and the rate of delivery is controlled by osmoregulators in the duodenum. Hyperosmolar liquid delivered directly into the small bowel, however, must be diluted by an influx of water. The greater the volume of hyperosmolar liquid and the higher the osmolality, the greater the risk that cramping and diarrhea will result. Diluting the hyperosmolar liquid prior to administration reduces the risk of cramping and diarrhea. For small bowel administration, the desired osmolality is approx 300 mOsm/kg. The volume of water needed for dilution can be calculated by dividing the drug osmolality by 300 then multiplying by the drug volume in milliliters (mL). The drug volume in mL is then subtracted from the first number to arrive at the mL of water for dilution. For example, a 500 mg dose of acetaminophen elixir (65 mg/mL) with an osmolality of 5400 mOsm/kg requires dilution with 131 mL of water to have an osmolality of about 300 mOsm/kg [(5400/300 × 500 mg/65 mg per mL) –7.7 mL] *(27)*. Using the minimum dose of drug necessary to achieve the desired response minimizes the amount of water needed as a diluent. Dividing the ordered dose into two to four doses spread over a few hours can also reduce the impact of hyperosmolar drugs on GI intolerance but this approach should only be considered if drug efficacy will not be adversely affected. For example, an 80 mEq dose of potassium chloride can be divided into four doses of 20 mEq each spread over several hours with little impact on overall effectiveness. Most once daily doses can be divided into two half doses administered 2 to 3 h apart with minimal change in effectiveness.

Certain dosage forms appear to be troublesome with respect to physical interactions between drugs and enteral formulas. About one-third of all drugs tested have demonstrated some degree of physical interaction with enteral formulas *(28–33)*. Syrups, elixirs, and oil-base liquid dosage forms are most often reported to cause physical changes such as curdling, clumping, gelling, emulsion separation, precipitation, increased viscosity, and reduced viscosity. The drug itself is probably of minimal importance except to define the pH and/or solubilizing agent (e.g., alcohol) required for a stable, soluble liquid dosage form. In studies where pH was determined, an association between low pH and physical interaction with intact protein formulas was noted with 9 of 11 incompatible products at pH 4 or below *(28,29)*. Acidic syrups were more likely to interact than acidic elixirs (3/4 syrups vs 2/5 elixirs). Of the 25 drugs reported as incompatible with enteral formula, pH was available for 18 and only 2 of these products had a pH above 6.0; both were antacids (Riopan and Mylanta II at pH 7.5) *(28–31)*. Another in vitro study that evaluated drug vehicles (water, simple syrup, 9% alcohol elixir, 25% alcohol elixir) buffered to pH 2.0, 7.0, or 11.0 and formulas containing single protein sources (caseinates, soy, whey) found that syrups were problematic at both acidic and neutral pH, whereas elixirs caused undesirable physical changes only at an acidic pH *(34)*. This suggests that pharmaceutical syrups, regardless of the drug or pH, must be used with caution when administered through a feeding tube.

Methods of avoiding physical interactions between drugs and enteral formula are summarized in Table 8. One of the most effective methods is to prevent physical contact between the drug and formula. This can be accomplished by flushing feeding tubes appropriately (*see* Table 3) and by using routes of drug administration other than the

feeding tube whenever feasible. Oral drug administration can be used when there is no contraindication to fluids by mouth. Instant dissolving tablets that do not require water may be another option for drugs that are available in this form, such as the antiemetic ondansetron (Zofran) and some nonprescription analgesics. Other routes that are available for some drugs include transdermal, sublingual, and rectal. Parenteral drug administration is the least desirable alternative to drug administration via the feeding tube because of increased cost and venous access issues. Likewise, cost of certain other alternative dosage forms (e.g., transdermal systems) can be prohibitive for some patients. When the drug ordered does not have alternative routes and/or dosage forms that are available and cost effective, a therapeutically equivalent drug may be available in more desirable dosage forms. Properly prepared compressed tablets, hard-gelatin capsules, or soft-gelatin capsules are preferable to "high-risk" liquid dosage forms in many cases and often are the most cost effective means of providing a drug via the feeding tube. When drugs must be administered through a feeding tube, flushing with water before and after drug administration is essential to prevent tube occlusion. Liquids such as fruit juices should never be used as the flush solution, although a drug might be mixed in an acidic juice for administration.

Viscous liquid dosage forms (e.g., suspensions) have a tendency to coat the inside of feeding tubes and drug may remain in the tube after flushing with water. The net result is reduced drug delivery and absorption, a pharmacokinetic interaction. Separate in vitro studies using simulated administration of phenytoin and carbamazepine suspensions through feeding tubes found better drug recovery with diluted suspensions than with undiluted suspensions *(35,36)*. Carbamazepine suspension diluted 50:50 with water, saline, or 5% dextrose solution did not appear to coat the tubes either before or after flushing with water, saline, or dextrose solution *(35)*. Undiluted suspension clung to the tube before flushing but was no longer visible after the tubes were flushed. However, significantly less carbamazepine was recovered in the effluents when undiluted suspension was administered, suggesting that drug remained in the polyvinyl chloride tubes. Polyvinyl chloride nasogastric tubes and silicone PEG tubes used in studies with phenytoin produced essentially the same results *(36,37)*. However, when diluted phenytoin was administered through a PEG tube with latex coating, phenytoin recovery was decreased perhaps because of increased solubility and concomitantly increased binding to the latex *(38)*. Thus, tube material may be an important factor in reduced drug recovery although polyurethane, the most common material for nasal tubes, has not been evaluated but polyurethane is generally not associated with significant adsorption of drugs to the tube. Diluting suspensions 50:50 with water prior to administering viscous liquid dosage forms through a nonlatex feeding tube is unlikely to cause any harm and may prevent erratic serum drug concentrations; therefore, at least a 50:50 dilution of viscous dosage forms with water should be the standard of practice. Further investigation is necessary to determine if this is an appropriate practice for a latex tube.

3.2.2. The Absorptive Environment

The environment to which a drug is exposed has a significant impact on pharmacokinetic interactions of drugs and the amount of drug ultimately available to the body. Drugs typically must be in solution for passive absorption to occur and most drugs are absorbed by this method. Before absorption can occur, solid dosage forms generally undergo a two-

Table 8
Methods to Avoid or Minimize Drug–Nutrient Interactions in Patients Receiving Enteral Nutrition

Method	Type of Drug–Nutrient Interaction				
	Physical	*Pharmaceutical*	*Pharmacologic*	*Physiologic*	*Pharmacokinetic*
Avoid mixing drug and formula	+/+	0	0	0	+/+
Change route of administration to:					
oral	+/+	+/+	0	?	+/+
parenteral	+/0	+/0	0	+/0	+/0
transdermal patch	+/–	+/–	0	+/–	+/–
rectal suppository	+/+	+/+	0	+/+	+/+
other	+/?	+/?	0	+/?	+/?
Change dosage form	+/?	+/?	0	+/?	+/?
Change to therapeutic equivalent	+/?	+/?	+/?	+/?	+/?
Change enteral formula	+/0	0	0	+/?	+/?
Use minimum dose necessary	?	0	+/+	+/+	+/+
Dilute the drug	0	0	0	+/+	0
Treat with adjunct therapy	0	0	+/?	+/?	0

+/+ effective in preventing interaction and minimal change in cost; first-line method.

+/? effective in preventing interaction; cost may be higher, lower, or equivalent.

+/- effective in preventing interaction; usually significantly more expensive.

+/0 effective in preventing interaction; typically the last option because of significant increase in cost and other potential issues.

? possibly effective in some instances.

0 not effective in preventing this type of interaction.

step process consisting of disintegration and dissolution. Disintegration entails break up of the dosage form into granules that then separate further into fine particles, exposing a large surface area to the environment. Drugs formulated as powders and those crushed to a fine powder by mechanical action prior to administration through a feeding tube require dissolution but not disintegration. The large surface area of powders and fine particles aids in dissolution. Liquid dosage forms may already be in solution (e.g., elixirs, syrups) or may require dissolution but not disintegration (e.g., suspensions). Soft-gelatin capsules contain a drug in solution or in an oil albeit the capsule itself must be dissolved in warm water or the liquid contents extracted for administration through a feeding tube.

Drugs and formula delivered via feeding tube bypass the mouth and esophagus where the processes of disintegration and digestion begin, as noted in Table 4. This is of little consequence because drugs are a slurry of fine particles in water or in liquid dosage forms that do not require disintegration. Enteral formulas are liquid products that do not require maceration. Minimal digestion of carbohydrates occurs in the mouth and esophagus. Drugs and nutrients administered through duodenal or jejunal tubes, however, circum-

vent the stomach and are exposed to a very different environment than those that pass through the stomach. Depending on chemical characteristics of the drug or nutrient, bypassing the stomach may alter pharmacokinetic parameters and ultimately increase or decrease the quantity of the substance that can be absorbed.

Substances that enter the stomach are mixed with gastric acid and digestive enzymes. Oral drugs in solid dosage forms that have not disintegrated during passage through the esophagus generally complete that process in the stomach and some drugs undergo dissolution. Drugs that are not soluble in an acidic environment must enter the small bowel before dissolution begins. Weak to moderately acidic drugs (e.g., acetazolamide, tolbutamide, warfarin) that are soluble at the pH of gastric acid are largely in a nonionized form that can be absorbed by passive diffusion. Those that are poorly soluble at the gastric pH (e.g., phenobarbital) are unlikely to be absorbed to any measurable extent from the stomach. Drugs that are weak bases (e.g., meperidine, procainamide, reserpine) are mostly in an ionized form in a low pH environment and are typically not absorbed although they may be relatively soluble in acid. Lipid-soluble, small nonelectrolyte substances (e.g., alcohol) are absorbed from the stomach. However, the stomach provides a relatively small contribution to overall absorption of any substance due to the small surface area and limited blood flow here compared to the small bowel.

Absorption from the small bowel requires that materials first enter the small bowel and that disintegration and dissolution of drugs be completed if this has not already occurred. In most cases, disintegration is complete when drugs enter the small bowel; the notable exception being enteric-coated drugs. In contrast, dissolution is complete only for drugs that are freely soluble in acid. Many drugs have undergone only partial dissolution or are not dissolved at all when they enter the small bowel. For readily absorbed drugs and nutrients delivered through gastric feeding tubes or by the oral route, gastric emptying controls the rate at which substances enter the small bowel and, therefore, is the rate-limiting step for absorption. Gastric emptying is highly variable and influenced by a number of factors *(39–41)*. Table 9 lists several drugs, enteral formula characteristics, and disease states that can influence gastric emptying rate and GI motility. Anything that alters the gastric emptying rate is expected to alter the rate of absorption for most drugs and nutrients in a similar manner; slowed gastric emptying slows the rate of absorption, whereas rapid gastric emptying increases the rate of absorption.

Effects of altered gastric emptying rate on extent of absorption (i.e., percent absorbed or bioavailability) are more variable and may be more difficult to predict than effects on rate of absorption. Extent of absorption may be increased, decreased, or unchanged for either slow or rapid gastric emptying depending on drug or nutrient characteristics and absorption mechanisms. Table 10 shows expected effects of various factors on extent of absorption when gastric emptying rate is decreased. Effects of rapid gastric emptying are much more difficult to predict and may depend on the drug dosage form as well as on small bowel transit time. Dosage forms that require time for disintegration have the least opportunity for absorption when both gastric emptying and GI motility are rapid. With normal small bowel motility, rapid gastric emptying is expected to reduce absorption to the greatest extent when an acidic medium is required for dissolution or is otherwise necessary for absorption (e.g., ketoconazole, itraconazole, tetracycline). More than one factor may influence the extent of absorption for a given drug or nutrient. For example, slow gastric emptying increases the extent of riboflavin absorption by at least two mecha-

Table 9
Factors Influencing GI Motility

Factor	Gastric Emptying Delayed	Gastric Emptying Increased	Small Bowel Motility Decreased	Small Bowel Motility Increased
<u>Formula Characteristics</u>				
High fat (long chain triglycerides)	X			
High protein	X (< fat)			
High viscosity (e.g., fiber)	X			
Liquid consistency		X		
Large particles or tablets	X			
Large volume	X			X
Hypotonic osmolarity (<250 mOsm/L)	X			
Osmolarity over 800 mOsm/L	X			X
Low pH	X			X
<u>Drugs</u>				
Anticholinergic agents	X		X	
atropine, belladonna, benztropine,				
biperiden, ethopropazine,				
hyoscyamine, procyclidine,				
scopolamine, trihexphenidyl				
Cholinergic agonists		X		
bethanechol, cisapride[a]				
Dopamine agonists		X		X
levodopa, metoclopramide				
Motilin agonist		X		X
erythromycin				
Mucosal irritants		X		X
salicylic acid				
Narcotic agents	X		X	
morphine, others				
Octreotide	X		X	
<u>Disease States and Conditions</u>				
Autonomic neuropathy	X			
Diabetic gastropathy	X			
Dumping syndrome		X		X
Duodenal ulcers		X		
Gastric surgery		X		
Billroth I and II				
Irritable bowel syndrome				
• diarrhea predominant				X
• constipation predominant			X	
Partial gastrectomy		X		X
Peptic ulcer disease	X			
Pyloric obstruction	X			
stenosis, gastric cancer				
Scleroderma	X		X	
Vagotomy	X			

[a]Cisapride has only been available under a limited access investigational protocol from the manufacturer since July 14, 2001, due to cardiac toxicity.

Table 10
Change in Extent of Absorption With Decreased Gastric Emptying Rate

	Example
Increased Extent of Absorption	
Active absorption in upper gastrointestinal tract	Riboflavin
Significant absorption in upper gastrointestinal tract	Ciprofloxacin
Poor solubility in stomach and small bowel, acid stable	Griseofulvin, Carbamazepine
Release from food, binding to another substance in the stomach is required	Cobalamin
Soluble in gastric pH but not small bowel (pH 5-7)	Ketoconazole, Tetracycline
Absorption from the stomach (weak acid; small nonelectrolyte)	Alcohol
No Effect on Extent of Absorption	
Enteric-coated tablet or granules	Multiple products
Decreased Extent of Absorption	
Acid-labile	Ampicillin
Poor solubility in stomach and small bowel, acid-labile	Digoxin

nisms. Riboflavin is released from foods in the stomach and absorbed by a saturable transport process in the upper GI tract (i.e., duodenum and jejunum). Slow gastric emptying allows more time to free riboflavin from foods, thereby making more riboflavin available to absorption sites. Additionally, riboflavin enters the region containing transport sites at a reduced rate and over an extended time period. The net effect is that a larger percentage of riboflavin is absorbed because fewer transport sites are "occupied" or saturated when the "free" riboflavin reaches these sites. In general, slow gastric emptying allows more complete release of vitamins from the food matrix while food is in the stomach. Release of vitamins from the food matrix continues in the small bowel as digestion progresses. The majority of vitamins are absorbed by passive transport throughout much of the small bowel; thus incomplete release from the food matrix prior to entering the small bowel is of limited clinical significance to overall absorption. In fact, jejunal feeding with nonhydrolyzed formulas is routine and has not resulted in vitamin deficiencies.

Gastric emptying rate is most likely to influence drug absorption through effects on solubility. Slow gastric emptying increases the extent of dissolution for drugs that are only soluble in an acidic environment (e.g., tetracycline) and for relatively insoluble drugs (e.g., carbamazepine, digoxin, griseofulvin, spironolactone). The extent of absorption increases when these drugs are acid stable (e.g., carbamazepine, griseofulvin) but decreases when the drug is acid labile (e.g., digoxin). In general, exposure to gastric acid increases destruction of acid-labile drugs (e.g., ampicillin, digoxin, omeprazole) and bioavailability is reduced when gastric emptying is slow unless the drug is protected by enteric coating. Substances that can be absorbed from the stomach (i.e., weak acids in solution and small lipid-soluble nonelectrolytes) will be absorbed to a greater extent with longer exposure to the gastric mucosa although this rarely has clinical significance since the majority of absorption still occurs in the small bowel.

Administration of drugs through postpyloric tubes, either duodenal or jejunal, bypasses conditions in the stomach and eliminates the effect of gastric emptying on rate of absorption. A major consequence of bypassing the stomach is reduced exposure to acid. The pH in the proximal duodenum is approx 4.0 to 5.0 and increases to near neutral in the distal duodenum as gastric acids are neutralized by bile salts and pancreatic secretions entering the duodenum. The jejunum is neutral to slightly alkaline. With increasing pH, most basic drugs transform from an ionized, nonabsorbable state to a primarily nonionized state that can be absorbed. Acidic drugs generally become more ionized and less absorbable. Nonetheless, the jejunum and ileum remain the major sites of absorption for all except highly acidic drugs because of the immense absorptive surface area in these regions.

Drugs that are only soluble in an acid environment or otherwise require exposure to an acidic environment for proper absorption (e.g., ketoconazole, itraconazole, tetracycline) may be ineffective when administered through a feeding tube placed into the small bowel. The more distal the tube, the greater the potential problem. Mixing these drugs with an acidic fluid (e.g., dilute vinegar, ascorbic acid, fruit juice) should, theoretically, improve absorption but documentation supporting this assumption is lacking. In contrast, low itraconazole concentrations were noted in a case report when an extemporaneously prepared suspension with an acidic pH was administered through a postpyloric feeding tube *(42)*. It is unclear whether the low itraconazole concentrations in this case were the result of poor absorption because the acidic medium used for the drug was ineffective or because of poor GI perfusion in a critically ill patient.

A reduced extent of absorption is expected when poorly soluble drugs are delivered into the duodenum or jejunum because the time available for dissolution is decreased. The more distal the site of drug delivery the less time there is for dissolution to occur; thus, jejunal administration may be more problematic than duodenal administration. Use of a dosage form that does not require dissolution (e.g., elixir, syrup, dissolved soft-gelatin capsule) can overcome this problem and may result in greater drug absorption than gastric administration for acid-labile drugs. In one small study with digoxin, significantly more hydrolytic metabolites (2.9 vs 0.6%) were noted after oral ingestion versus administration into the jejunum *(43)*. Recovery of nonmetabolized digoxin was higher with jejunal administration (96.3 vs 90.8%) suggesting a need for lower doses when digoxin is administered into the jejunum through a feeding tube. Bypassing the stomach avoids acid hydrolysis of digoxin; therefore, more drug is available for absorption. Therapeutic drug monitoring should be performed within a couple of days whenever digoxin dosing changes from oral or gastric administration to postpyloric administration or visa versa.

The further a feeding tube is placed into the small bowel, the more important it becomes to consider the site(s) of drug or nutrient absorption. When substantial absorption occurs in the duodenum, delivery of a drug or nutrient into the jejunum could significantly reduce the extent of absorption. An example of this is seen with ciprofloxacin where healthy volunteers absorb up to 40% of an oral dose in the duodenum *(44)*. Administration of ciprofloxacin into the duodenum results in better absorption than delivery into the stomach in both healthy volunteers and patients in intensive care units *(45)*. Jejunal administration results in lower serum concentrations than those found after oral administration *(46,47)*. The majority of drugs are absorbed by passive diffusion, which is typically not limited to a specific segment of the GI tract although chemical characteristics of a drug can influence absorption at different pH levels. Unfortunately, published

data rarely specify the percent of drug absorbed in specific segments of the GI tract (i.e., stomach, duodenum, jejunum, ileum, colon) and few studies have compared serum drug concentrations following administration by mouth vs administration through tubes at different sites within the GI tract.

Most water-soluble vitamins are absorbed by passive diffusion primarily in the upper small bowel but absorption is rarely limited to the duodenum and may extend into the ileum depending on transit time. Thus, delivery of nutrients into the jejunum has little impact on the amount of most water soluble vitamins absorbed. Minerals generally require facilitated absorption or active transport because most form chelates or complexes that are too large to be absorbed efficiently by passive diffusion. Calcium, phosphorus, iron, and most trace minerals are most efficiently absorbed from the slightly acidic upper GI tract and demonstrate limited absorption in the ileum. Release of minerals from the food matrix and formation of the complexes normally occurs in the stomach; thus, theoretically jejunal administration could compromise absorption. However, routine use of nonhydrolyzed formulas for jejunal feeding has not resulted in reports of mineral deficiencies.

Administration of drugs that stimulate GI motility, as listed in Table 9, could reduce nutrient absorption by reducing GI transit time. For example, diarrhea may develop in a patient receiving metoclopramide or erythromycin. Although erythromycin may have been ordered to treat an infection, its mechanism of action still includes activity as a motilin agonist. When the mechanism of action for a drug interferes with nutrient absorption or induces enteral feeding intolerance, this is classified as a pharmacological interaction. Pharmacological effects on the GI tract must be considered in drug selection to minimize such interactions. Other methods of handling pharmacological interactions are included on Table 8.

3.2.3. Therapeutic Index

Drugs with a relatively small therapeutic range are more likely to result in patient harm when DNIs are not anticipated and managed appropriately. Drugs for which serum drug monitoring is performed are typically drugs with a small therapeutic range and pharmacokinetic interactions are of most concern. With only a small range of concentrations within the efficacious but nontoxic range, small changes in absorption can have significant changes in therapeutic outcome. Phenytoin, carbamazepine, and digoxin are among the "narrow" therapeutic index drugs of concern when administered through a feeding tube. These drugs are discussed in the final section of the chapter.

3.3. Formula-Related Factors

3.3.1. Protein Content

Complexity of the protein source (i.e., intact protein vs hydrolyzed protein or free amino acids) appears to play a key role in physical interactions between drugs and enteral formulas. Intact proteins are complex, highly ordered chemical structures that rely on various bonds and electrostatic attractions to maintain their order and shape. Exposure to acids, salts, alcohol, or heat can result in breaking of bonds, conformational change, and loss of tertiary configuration with "unfolding" of proteins, a process referred to as denaturation. Curdling of milk on exposure to acid is an example of protein denaturation and of the differences among proteins in susceptibility to denaturation. Casein undergoes

denaturation on exposure to acid and the resulting changes in protein solubility and viscosity are visible as clumps or curds. On the other hand, whey proteins do not denature and remain fluid unless a very strong acid is used. The source of protein determines the pH at which denaturation begins and the sensitivity of the protein to various salts and alcohols. Whey protein is the most acid stable of the intact protein sources routinely used in enteral formulas (i.e., caseinates, soy, or whey) and whey-based formulas are the least likely to be physically incompatible with drugs (34). Casein and caseinates tend to form large clumps and curds similar to curdled milk, whereas soy protein forms finer precipitates.

Protein denaturation explains many of the observations related to physical interaction or incompatibility between drugs and enteral formulas. Nearly all of the drug–formula incompatibilities reported are with formulas containing intact protein, predominantly casein or caseinates, and no drug has been identified that is incompatible with hydrolyzed protein formulas while being compatible with intact protein formulas. Acidic syrups and elixirs are the most problematic dosage forms and both acid and alcohol can cause protein denaturation. Formulas containing hydrolyzed protein rarely result in physical incompatibility except with oil-based products. Of 25 drugs reported as incompatible with one or more formulas tested in an in vitro study, only three were incompatible with hydrolyzed protein formulas (27–31). Two of these three drugs were oil-based products (i.e., mandelamine suspension and MCT oil). Hydrolyzed proteins and free amino acids lack the complex chemical structure of intact proteins; thus, they are not subject to the same changes in structure and shape as intact proteins. Enteral formulas containing hydrolyzed proteins are, however, an emulsion like intact protein formulas. The interaction with oil-based drugs is more likely related to disruption of the emulsion than to effects on the hydrolyzed protein. Nitrogen content (i.e., protein concentration) and dilution of the enteral formula are not expected to alter denaturation and do not appear to influence the risk of physical incompatibility between drugs and formulas (28). Likewise, fiber is not expected to alter protein denaturation and does not appear to be a significant factor for incompatibility (27). The source of fiber in the formulas studied was soy polysaccharide, a predominantly insoluble fiber. Addition of soluble fiber to a formula is not expected to alter protein denaturation anymore than insoluble fiber. At least theoretically, however, addition of some soluble fibers (e.g., pectin, banana flakes, apple flakes) to a formula at the bedside could increase the risk of tube occlusion by gel formation, especially if an acidic drug is allowed to mix with formula.

Interactions between drugs and formula that result in physical incompatibility are a major contributor to tube occlusion and loss of enteral access. Feeding tube occlusion can compromise drug and nutrient provision to patients receiving EN therapy. Despite several studies that have assessed enteral formula compatibility with drugs in liquid dosage forms, relatively few formulas and drugs have been evaluated (27–33). The names of enteral formulas included in these compatibility studies are commonly seen in the marketplace today (e.g., Ensure, Osmolite); however, most formulas have been reformulated with different nutrient sources and ratios than formulas of the same name used in the studies. Drug formulations may also have changed over the years. Therefore, care must be exercised when interpreting enteral formula–drug compatibility studies relative to current practice. Tube occlusion is not a measured outcome in these studies; in vitro observations are typically reported. Most data are subjective descriptions of changes in the formula's physical appearance although viscosity measurements are sometimes included.

Nonetheless, when these observations are combined with data on chemical stability of formula components and drug characteristics, a few generalizations emerge. Table 11 summarizes generalizations related to physical interactions between drugs and enteral formulas that are applicable to current practice and may help the practitioner avoid many of these interactions.

Hepatic drug clearance may be influenced by the amount of protein provided by EN therapy. Animal studies indicated that protein intake can modify hepatic microsomal mixed-function oxidase system (MFOS) activity *(41,48,49)*. High protein intake stimulates MFOS activity; thus increasing clearance of certain drugs. Niacin, riboflavin, and large doses of vitamin C may also increase activity of the MFOS. Low protein intake may reduce renal plasma flow and creatinine clearance, thus decreasing renal elimination of certain drugs. However, much more research is needed in this area before any definitive statements can be made regarding clinical impact of these observations. Most studies concerning dietary effects on the MFOS have been done in animals.

3.3.2. COMPONENTS INFLUENCING GI MOTILITY

Formula components and characteristics that alter GI motility, as listed in Table 9, result in pharmacokinetic interactions when drug absorption is changed. Fats, especially long-chain fatty acids, slow gastric emptying to a greater extent than protein, and protein has a greater affect than carbohydrates. High osmolality also slows gastric emptying, as does increased formula viscosity. Calorically dense formulas (i.e., 2 kcal/mL) have both an increased viscosity and an increased concentration of macronutrients that can slow gastric emptying. As previously discussed under "absorptive environment" in this chapter, slowed gastric emptying generally slows absorption of drugs administered by mouth or by a gastric feeding tube. Effects on extent of drug absorption are related to the drug's solubility and acid stability.

For drugs delivered through a postpyloric feeding tube, formula effects on gastric emptying are irrelevant but effects on small bowel motility may change drug absorption. Formulas with a high osmolality delivered into the small bowel can cause nausea, vomiting, diarrhea, and abdominal pain as water rapidly enters the bowel to dilute the formula. Likewise, rapid administration or significant fluctuation in volume of formula into the small bowel can cause diarrhea. When diarrhea shortens bowel transit time, drug absorption can be reduced, especially when the drug must undergo dissolution in the small bowel. Use of dosage forms where the drug is in solution (e.g., elixirs, syrups) may reduce the impact on absorption in these situations.

3.3.3. VITAMIN K CONTENT

Formulas with a high vitamin K content can antagonize the anticoagulant effect of warfarin, a significant pharmacological interaction in which a nutrient interferes with a drug's mechanism of action. Warfarin acts by inhibiting formation of the vitamin K-dependent clotting factors (II, VII, IX, and X) in the liver and can overcome the typical daily intake of 300 to 500 µg vitamin K from the Western diet *(50)*. This interaction is best avoided by careful selection of the enteral formula for patients receiving warfarin therapy. Since the initial reports of warfarin resistance in the early 1980s, most formulas have reduced their vitamin K content *(51–55)*. Table 12 lists the current vitamin K content of several enteral formulas. It is probably best to avoid formulas containing more than100 µg of vitamin K per 1000 kcal in patients requiring warfarin anticoagulation. Patients with

Table 11

Summary of Factors and Their Degree of Contributing to Drug–Formula Physical Interactions

Protein complexity is a critical factor in drug–formula physical interactions.
- Caseinates appear to be most prone to physical interactions, followed closely by soy protein.
- Whey protein is the intact protein source least likely to be incompatible.
- Hydrolyzed proteins and amino acids rarely result in interactions except with oil-based products.

The drug vehicle for liquid dosage forms is a critical factor in drug–formula physical interactions.
- Acidic liquids are highly prone to interactions.
- Syrups are likely to be incompatible, especially when the pH of 4.0 or less.
- Alcohol contributes to interactions, especially with a low pH; thus acidic elixirs are problematic.
- Oil-based products are incompatible.

Drug–formula physical interactions do not appear to be influenced by:
- Nitrogen content.
- Fiber content.
- Dilution of the enteral formula.

disruption of normal vitamin K production by GI flora (i.e., antibiotic-induced diarrhea, gut decontamination prior to chemotherapy) are at considerably less risk of warfarin resistance secondary to excess vitamin K and intake of up to 500 µg vitamin K daily during this time would be unlikely to result in warfarin resistance. Separating warfarin administration from formula administration does not prevent warfarin resistance secondary to high vitamin K intake. However, there is some evidence that holding enteral feeding for at least 1 h before and 1 h after warfarin administration can reduce the risk of warfarin resistance in patients receiving EN therapy *(56,57)*. This likely reflects a separate pharmacokinetic interaction between warfarin and enteral formula that would also account for reports of warfarin resistance in formulas with a low to modest vitamin K content.

3.4. Disease-Related Factors

3.4.1. Visceral Protein Status

Malnutrition is the most important disease process in relation to DNIs in patients receiving EN therapy. The effects of malnutrition on DNIs are not specific to patients receiving EN therapy but the majority of patients started on EN are malnourished or at high risk of malnutrition. Pathophysiological interactions in many disease processes are likely mediated through development of malnutrition, especially protein malnutrition. The decreased visceral protein status and increased edema that are noted with protein malnutrition can significantly alter pharmacokinetic parameters of drugs and may alter nutrient absorption. Drugs that are highly bound to albumin (e.g., warfarin) are particularly susceptible to pathophysiological interactions. As serum albumin concentrations

Table 12
Selected Enteral Formulas and Vitamin K Content[a]

Low Vitamin K Content *(50 µg or Less/1000 Calories)[b]*	*Moderate Vitamin K Content* *(51 to 100 µg/1000 Calories)[b]*
Pediatric Formulas	Intact Protein Formulas
Nutren Junior (Nestle)	Perative (Ross)
Peptamen Junior (Nestle)	Ensure Plus HN (Ross)
Pediasure [with or without fiber] (Ross)	IsoSource 1.5 (Novartis)
Compleat Pediatric (Novartis)	Jevity (Ross)
Vivonex Pediatric (Novartis)	Osmolite HN (Ross)
Complete (Novartis)	FiberSource HN (Novartis)
	IsoSource HN (Novartis)
Intact Protein Formulas	IsoSource Standard (Novartis)
NuBasics (Nestle)	ProBalance (Nestle)
NuBasics Plus (Nestle)	Jevity Plus (Ross)
NuBasics VHP (Nestle)	Osmolite HN Plus (Ross)
Ensure Plus (Ross)	Ensure (Ross)
Osmolite (Ross)	Carnation Instant Breakfast (Nestle)
NovaSource 2.0 (Novartis)	with 2% Milk
TwoCal HN (Ross)	Ensure High Protein (Ross)
Boost Plus (Mead Johnson)	Carnation Instant Breakfast (Nestle)
NuBasics 2.0 (Nestle)	Ready to Drink
Nutren Products: 1.0, 1.5, 2.0 (Nestle)	Isocal HN (Mead Johnson)
Nutren 1.0 with fiber (Nestle)	
Replete [with or without fiber] (Nestle)	
Specialized Formulas	Specialized Formulas
Critical Care/Immune Modulation	Critical Care/Immune Modulation
Crucial (Nestle)	Impact 1.5 (Novartis)
Glucose Control	Impact (Novartis)
Glytrol (Nestle)	Impact with fiber (Novartis)
Pulmonary Function	TraumaCal (Mead Johnson)
Respalor (Mead Johnson)	Glucose Control
NutriVent (Nestle)	Glucerna (Ross)
Renal Dysfunction	DiabetiSource (Novartis)
Nepro (Ross)	Pulmonary Function
Hydrolyzed Protein/Free Amino Acids	NovaSource Pulmonary (Novartis)
Vivonex T.E.N. (Novartis)	Pulmocare (Ross)
Tolerex (Novartis)	Oxepa (Ross)
Vivonex Plus (Novartis)	Hydrolyzed Protein/Free Amino Acids
Peptamen VHP (Nestle)	Optimental (Ross)
Reabilan (Nestle)	Subdue (Mead Johnson)

Table 12

Higher Vitamin K Content (101 to 150 µg/1000 Calories)[c]	Very High Vitamin K Content (over 150 µg/1000 Calories)[d]
Intact Protein Formulas	Intact Protein Formulas
Carnation Instant Breakfast (Nestle)	Boost High Protein
No Sugar Added Sugar with 2% Milk	(Mead Johnson)
Deliver 2.0 (Ross)	
Isocal (Mead Johnson)	
Boost (Mead Johnson)	
Specialized Formulas	
Critical Care/Immune Modulation	
Protain XL (Mead Johnson)	
Glucose Control	
Choice dm (Mead Johnson)	

[a]Formulas in each category are listed from least to most vitamin K per 1000 calories. Always confirm current vitamin K content with the product label and current manufacturer's data since vitamin K content of enteral formulas can change.

[b]Formulas with low to moderate vitamin K content are generally safe to use in patients receiving warfarin therapy.

[c]Formulas with higher vitamin K content should be used cautiously in patients receiving warfarin therapy. Consider comparable formulas in the low and moderate vitamin K categories for patients with warfarin therapy. Higher vitamin K content may be beneficial for patients receiving broad-spectrum antibiotics.

[d]Formulas in the very high category should not be used in patients receiving warfarin therapy, but may be a good option for other patients receiving broad-spectrum antibiotics.

decrease, drug distribution is altered and toxicity may be increased. Metabolism may be reduced in severe protein malnutrition because production of enzymes necessary for metabolism may be reduced. There are probably many effects of malnutrition on DNIs but little research has focused on this subject.

3.4.2. GI Motility

Multiple disease processes can increase or decrease GI motility, as indicated in Table 9. As previously discussed in Subheading 3.2.2., gastric emptying rate often controls the rate of drug absorption when drugs are taken by mouth or administered into the stomach and may influence absorption of specific nutrients. Effects on extent of absorption depend on specific drug characteristics. Small bowel transit time can be altered by the pharmacologic effects of drugs and drug absorption can be altered by changes in transit time. The effects of altered GI motility on DNIs are not specific to patients receiving EN therapy but many patients receiving EN have abnormal GI motility. Therefore, the practitioner managing EN therapy must be alert for possible problems related to drug and nutrient absorption in patients with abnormal GI motility who are receiving EN therapy.

4. SPECIFIC DRUGS

There are several drugs of key clinical importance relative to DNIs in patients receiving EN therapy that are discussed below. Pharmacokinetic interactions involving absorption occur with all of the drugs, although pharmacological interactions can also occur with warfarin. Mechanisms responsible for these interactions are often inadequately

defined, studies documenting the interactions are few, small, and not as rigorous as is desired for evidence-based recommendations. Table 3, step 11 includes recommendations for holding formula administration with specific drugs and Table 8 contains a summary of methods to handle pharmacokinetic and pharmacological interactions as well as the other classes of DNIs without reference to specific drugs.

4.1. Phenytoin

Phenytoin was one of the first drugs noted to have a significant interaction with enteral formula and numerous studies have evaluated this interaction since Bauer's initial report *(58)*. A review of in vivo and in vitro studies, case reports, and letters found four prospective, randomized, controlled studies that do not support the existence of an interaction *(59)*. All four studies were in a small number of healthy volunteers (i.e., 6 to 10) and only one study used continuous feeding through a nasogastric tube *(59,60)*. The remaining 25 reports and studies provide evidence of an interaction in patients although these are not prospective, randomized, controlled studies. The mechanism of the interaction has not been delineated despite multiple theories including binding to the enteral administration tubing or with an enteral formula component *(37,61)* and various pH-related explanations *(38,62,63)*. Protein complexity does not appear to be an important factor as the interaction has been reported with both intact protein and hydrolyzed protein formulas *(64,65)*. Methods reported to reduce the interaction include stopping feeding for 1 h before and 1 h after administration of phenytoin *(66)*, clamping the feeding tube for 1 h after drug administration *(67)*, diluting phenytoin suspension prior to administration *(36)*, opening phenytoin capsules and administering the contents through the tube *(68)*, and using a commercial meat-based formula with a bolus feeding schedule *(61)*.

None of the suggested methods can assure therapeutic phenytoin concentrations but stopping feeding for at least an hour before and after the phenytoin dose appears to most consistently produce therapeutic concentrations with reasonable drug doses. Holding formula for 2 h on each side of the phenytoin dose has been more effective than holding for an hour in some studies but this increases the risk of inadequate formula delivery *(58)*. Therefore, a 2-h hold time may be best reserved for patients in whom a 1-h hold fails to prevent subtherapeutic concentrations. Clamping the tube for 1 h after the phenytoin dose must be studied in a prospective, randomized manner before this method can be routinely recommended. However, a retrospective review of brain-injuried patients receiving phenytoin through gastrostomy tubes noted significantly higher serum phenytoin concentrations when the tube was clamped after the drug dose vs uninterrupted feeding *(67)*. Diluting phenytoin suspension prior to administration through a feeding tube improves phenytoin delivery in vitro compared to undiluted suspension *(36)*. The dilution factor in this study was approximately threefold with water on a volume:volume basis. As previously discussed under "dosage forms," dilution of viscous suspensions such as phenytoin at least 50:50 with water prior to administration through a feeding tube should be a standard of practice, at least for small bore nasal tubes. The effectiveness of using capsule contents administered through a feeding tube is not adequately studied as only seven healthy volunteers were included in the study suggesting this approach and formula was ingested on an intermittent oral schedule *(68)*. Administration of a capsule's contents through a small-bore tube may cause occlusion and the potential benefits are probably not adequate to balance potential risks with an unproven method. Commercial meat-based

formula are relatively expensive compared to standard intact protein formulas, are often not covered by third-party payers, and may require delivery through a large-bore tube. Only five healthy volunteers were included in the study with meat-based formula and intermittent ingestion of the formula occurred rather than administration via a feeding tube *(61)*. Thus, use of a meat-based formula requires more rigorous evaluation before this method can be routinely recommended. Regardless of the method(s) used to minimize the phenytoin–enteral formula interaction, serum phenytoin concentrations require close monitoring to avoid subtherapeutic concentration during EN therapy and potentially toxic concentrations when EN therapy is discontinued. Serum concentrations should be monitored once to twice weekly during the initiation and discontinuation of EN therapy or until the patient is therapeutically stable on phenytoin. Close clinical observation for signs and symptoms of inadequate disease control and drug toxicity are also warranted.

4.2. Carbamazepine

Dissolution is the rate-limiting step for absorption of carbamazepine. Anything that slows gastric emptying, such as food, allows more time for dissolution and is expected to increase absorption. However, there is concern that EN therapy decreases carbamazepine absorption and may place patients at risk of inadequate disease control when EN is required. Evidence supporting an interaction between EN therapy and carbamazepine is sparse. Studies in patients receiving tube feeding are lacking and few in vivo studies are available. One randomized, crossover study with seven healthy men, reported a relative bioavailability of 90% for carbamazepine suspension administered by nasogastric tube with continuous feeding vs oral intake following an overnight fast *(69)*. Pharmacokinetic parameters were not significantly different although serum carbamazepine concentrations were lower with feeding and significantly lower at 8 h. The maximum serum concentration approached significance for being lower with feeding. The small size of this study most likely prevented statistically significant findings. With the same intact protein formula and use of carbamazepine as compressed or chewable tablets, recovery of drug after mixing with formula for 1 h was 58% *(70)*. Drug recovery was 79% from simulated gastric juice alone and 75% from simulated intestinal fluid alone. Addition of formula to the simulated gastric juice increased drug recovery (85%) but decreased recovery from simulated intestinal fluid (59%). Carbamazepine recovery from formula alone was essentially the same as from formula plus simulated intestinal fluid. Such an in vitro study design cannot account for effects of gastric emptying rate, which could increase absorption above that from "gastric juice" in this study, especially if slow gastric emptying improved dissolution. On the other hand, concern is raised that administration of carbamazepine through a postpyloric tube may result in subtherapeutic drug concentrations whether or not formula is present in the small bowel. Holding formula for 2 h on each side of the carbamazepine dose has been recommended to minimize the interaction with carbamazepine in the clinical setting *(71,72)*. However, carbamazepine has not been shown to bind with a component of enteral formula either in vivo or in vitro. Studies in patients with feeding tubes are needed to document the incidence of an enteral formula–carbamazepine interaction and to determine the best method of managing the interaction when it occurs. Not acknowledging the interaction could result in serious complications for patients receiving carbamazepine through feeding tubes. The limited data available suggest that an interaction is most likely to be clinically

significant when drug is administered through a postpyloric tube. Formula should be held for 2 h before and 2 h after drug administration in this population. It is less clear that holding formula with drug administration through a gastric tube is necessary and it may be best to hold formula on a case-by-case basis when maintaining a therapeutic carbamazepine concentration is difficult. Carbamazepine suspension should be diluted 50:50 with water, as previously discussed in Subheading 3.2.1. *(35)*. However, it is unclear if the difference in drug recovery occurs with non-polyvinyl chloride tubes and with standard flush volumes as compared to the large flush volumes (i.e., two 50 mL flushes) used in this study.

4.3. Fluoroquinolones

Several studies have evaluated fluoroquinolone bioavailability in either healthy volunteers or patients receiving EN therapy. Most studies have evaluated ciprofloxacin and indicate lower bioavailability when quinolones are administered with enteral formula. One of three small studies in healthy volunteers failed to detect a difference in bioavailability despite using a nasogastric tube for drug delivery in two segments of the crossover design *(73)*. Other studies in healthy volunteers found a 25 to 28% reduction in ciprofloxacin bioavailability with intact protein formula *(74,75)*. Hydrolyzed protein formula was not evaluated in these or other studies. In hospitalized patients, bioavailability decreased 27 to 67%, depending on the site of feeding *(47)*. The greatest decrease is seen with jejunal feeding, as discussed previously in Subheading 3.2.2. *(46,47)*. Decreased bioavailability is also noted in critically ill patients receiving continuous EN therapy and ciprofloxacin via nasogastric tube *(76,77)*. The clinical significance of this decrease in bioavailability is not clear because ciprofloxacin concentrations have been reported to remain above the mean inhibitory concentration for many pathogens *(78)*. However, larger studies are needed to confirm adequate drug concentrations for treatment of major pathogens for which ciprofloxacin is selected before the decrease in bioavailability can be considered clinically irrelevant. Inadequate antibiotic concentrations could result in significant patient morbidity and potentially mortality.

The interaction between fluoroquinolones and enteral formula appears to be drug dependent and influenced by the hydrophilicity of the drug. In 13 healthy volunteers, ofloxacin was found to have 90% bioavailability with an intact protein formula compared to 72% bioavailability for ciprofloxacin *(74)*. Immediate loss of unbound antibiotic was noted in an in vitro study when quinolone antibiotics were mixed with intact protein formula *(79)*. Recovery was about 54% for ofloxacin, 39% for levofloxacin, and 17.5% for ciprofloxacin. Loss of drug did not appear to correlate with cation content of the formula, suggesting that binding of quinolones with divalent cations (i.e., calcium and magnesium) may not be responsible for the interaction. Loss of drug from binding to the feeding tube itself does not seem to be a problem and no specific component of the enteral formula has been identified as binding drug *(80)*.

Holding formula for 1 h or more before and 2 h after the dose is the recommended method to minimize effects of enteral feeding on serum concentrations of ciprofloxacin and norfloxacin *(71,72)*. Although less hydrophilic quinolones appear to be less affected by an interaction with enteral formula, the safest approach is to hold formula for 1 h before and 2 h after quinolone administration through a feeding tube. Thus, a therapeutically appropriate quinolone with less frequent dosing may be a better choice for patients

receiving EN therapy. Using a different antibiotic with appropriate coverage for the infection would be another option to avoid the interaction. It is important to note that the commercially available 5 and 10% CIPRO oral suspension (ciprofloxacin from Bayer Corporation) "should not be administered through feeding tubes due to its physical characteristics" per literature included in the package *(81)*.

4.4. Warfarin

The pharmacological interaction between warfarin and vitamin K in enteral formulas was previously addressed under Subheading 3.3. A second pharmacokinetic interaction was also mentioned as possibly explaining the continued problem of warfarin resistance after reduction of vitamin K content in most enteral formulas more than 10 years ago *(55–57)*. Warfarin has been reported to bind to some filterable component of the formula but this mechanism of warfarin resistance has not been adequately studied *(57)*. Protein is the most likely filterable component to be involved with warfarin binding, especially because warfarin is a highly protein-bound drug. Assuming protein is the binding component, formulas containing free amino acids would not be expected to cause warfarin resistance; hydrolyzed proteins might, depending on the length of remaining peptide chains. Neither free amino acid nor hydrolyzed protein formulas have been evaluated. Holding formula administration for 1 h before and 1 h after warfarin administration should be an effective method of managing the pharmacokinetic interaction *(56)*. Warfarin therapy must be carefully monitored for an alteration in anticoagulant response whenever EN therapy is initiated or discontinued and when formula changes occur to assure patient safety.

4.5. Theophylline

Theophylline elimination is increased with high protein intake and decreased by a high-carbohydrate, low-protein diet *(82)*. Rate and extent of absorption may be affected by food with rapid release of some sustained-release preparations when taken with food. Effects of EN therapy on theophylline are poorly studied although one small study suggested that continuous nasogastric feeding interfered with theophylline absorption *(83)*. Nevertheless, holding formula administration for 1 h before and 2 h after drug administration is recommended *(71,72)*. Two single-dose studies in healthy volunteers found no difference in extent of absorption for sustained-release theophylline preparations with intact protein formula taken by mouth (100 mL every hour for 10 h) compared to fasting *(84,85)*. Studies are not available in healthy volunteers with feeding tubes in place or in patients receiving EN therapy. Studies are necessary to determine whether holding formula administration before and after theophylline administration provides any clinical benefit. At this time, it is difficult to justify holding formula unless the patient has experienced erratic theophylline serum concentrations or inadequate disease control after initiation of EN therapy.

4.6. Levothyroxine

A pharmacokinetic interaction involving absorption has been reported between soy protein and levothyroxine sodium *(71,72)*. Interference with drug absorption results in higher than expected fecal loss of levothyroxine sodium with soy protein formulas. Soy polysaccharide is the most common fiber source in enteral formulas, but its effect on

levothyroxine sodium pharmacokinetics has not been assessed. Without more definitive information, it is probably best to avoid enteral formulas containing soy protein. A large percentage of formulas containing fiber contain soy polysaccharide, thus it may not be practical to avoid soy polysaccharide when a fiber-containing formula is appropriate. It is prudent to monitor thyroid function within several days for patients receiving levothyroxine sodium who start EN therapy because this is a poorly studied interaction, but it is most important if the formula contains soy products. On the other hand, a change in clinical status that warrants initiation of EN therapy probably warrants evaluation of the patient's levothyroxine dose whether the formula contains soy products or not.

4.7. Penicillin V Potassium

Directions for penicillin V potassium recommend the drug be taken on an empty stomach because decreased absorption occurs with food (86). Absorption is reported to be 30 to 80% and erratic with feeding (71,72). Holding administration of formula for 1 h before and 2 h after administering the drug is recommended to mitigate this pharmacokinetic interaction. However, studies in patients receiving EN therapy are lacking as are studies in any population receiving the drug and enteral formula through a feeding tube. Recommendations for holding formula administration follow guidelines for taking the drug on an empty stomach, generally recognized as 1 h before a meal or 2 h after. Selecting another antibiotic that provides appropriate coverage and site penetration also would be an appropriate method of managing the interaction.

5. CONCLUSION

Using a broad definition, DNIs in patients receiving EN therapy fall into several categories including physical, pharmaceutical, pharmacological, physiological, pharmacokinetic, and pathophysiological interactions. Physical compatibility, pharmaceutical issues, and osmotic characteristics have received the most attention, but even these topics are poorly researched. Unfortunately, in this age of evidence-based medicine, expert opinion and consensus rather than strong research data still dominate the domain of DNIs in patients receiving EN therapy. Data identifying interactions between drugs and enteral formula components or administration techniques are minimal and sometimes conflicting. Likewise, evidence supporting techniques used to manage DNIs in patients receiving EN therapy is often limited. Available data may be old and may not be applicable to products in use today. Well-designed prospective human studies in patients with feeding tubes in place are difficult to find. Research is needed on essentially every aspect of DNIs in this patient population. Until such research is completed, extrapolation from pharmaceutical principles and pharmacokinetic theories, case reports, and in vitro data will remain the mainstay of evidence for identifying and managing DNIs in patients receiving EN therapy. The practitioner must be ever vigilant for DNIs that interfere with appropriate drug and nutritional therapy in patients receiving EN. Nevertheless, the specific steps discussed throughout this chapter and summarized in Tables 3 and 8 can reduce the risk of interactions and adverse outcomes for patients.

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About the Editors

Joseph I. Boullata is Professor of Pharmacy Practice at Temple University, and Nutrition Support and Critical Care Specialist at Temple University Hospital in Philadelphia, PA. He received his PharmD from the University of Maryland in Baltimore after completing undergraduate degrees in Nutrition Science from the Pennsylvania State University and in Pharmacy from the Philadelphia College of Pharmacy and Science. He completed a pharmacy residency at the Johns Hopkins Hospital and a nutrition support fellowship at the University of Maryland Medical System. Dr. Boullata has performed research and published in the areas of nutrition and critical care, authoring several chapters and papers in peer-reviewed journals. He holds active membership in several national professional organizations including the American College of Clinical Pharmacy, the American Society for Clinical Nutrition, the American Society of Health-System Pharmacists, the American Society for Parenteral and Enteral Nutrition, and the Society of Critical Care Medicine. He also serves on the editorial board of two professional journals.

Vincent T. Armenti has recently joined the staff at Temple University as Professor of Surgery in the Abdominal Organ Transplant Program. He was previously Professor of Surgery in the Transplant Division, as well as the Director of the Metabolic and Nutrition Support Service at Thomas Jefferson University Hospital in Philadelphia, PA. He received his PhD in Anatomy at Thomas Jefferson University and his MD at Jefferson Medical College. He completed his surgical training at St. Vincent's Hospital and Medical Center of New York. This was followed by a fellowship in renal and hepatic transplantation at Thomas Jefferson University Hospital. Dr. Armenti has been awarded grants to support his research interests in transplantation and nutrition. He continues to maintain two national databases for pregnancy outcomes. With many peer-reviewed publications and book chapters, and abstracts to his credit he has presented his work as well as delivered lectures internationally, nationally and locally. Besides being an elected Fellow of the American College of Surgeons, Dr. Armenti maintains active membership in several international and national societies including the American Society for Parenteral and Enteral Nutrition, the American Society of Transplant Surgeons, the American Society of Transplantation and the International Society for the Study of Hypertension in Pregnancy. He has also served on institutional, local, and national committees as well as editorial boards for two professional journals.