Foreword

An Evidence-based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations by Dr. Jane Higdon and Dr. Victoria Drake provides a much needed source of authoritative information on the role of micronutrients in health promotion and in disease prevention and treatment. The book is especially important because of the potential health benefits of tuning up people’s micronutrient metabolism, particularly those with inadequate diets, such as the many low-income and elderly people. A metabolic tune-up is likely to have enormous health benefits but is currently not being addressed adequately by the medical community.

Maximum health and lifespan require metabolic harmony. It is commonly thought that Americans’ intake of the more than 40 essential micronutrients (vitamins, minerals, and other biochemicals that humans require) is adequate. Classic deficiency diseases such as scurvy, beriberi, pernicious anemia, and rickets are rare, but the evidence suggests that metabolic damage occurs at intake levels between the level causing acute micronutrient deficiency diseases and the recommended dietary allowances (RDAs). When one input in the metabolic network is inadequate, repercussions are felt on a large number of systems and can lead to degenerative disease. This may, for example, result in an increase in DNA damage (and possibly cancer), neuron decay (and possibly cognitive dysfunction), or mitochondrial decay (and possibly accelerated aging and degenerative diseases). The optimum amount of folate or zinc that is truly “required” is the amount that minimizes DNA damage and maximizes a healthy life span, which is higher than the amount to prevent acute disease. Vitamin and metabolite requirements of older people are likely to differ from those of younger people, but this issue has not been seriously examined. An optimal intake of micronutrients and metabolites will also vary with genetic constitution. A tune-up of micronutrient metabolism should give a marked increase in health at little cost. It is inexcusable that anyone in the world should have an inadequate intake of a vitamin or mineral, at great cost to that person’s health, when a year’s supply of a daily multivitamin/multimineral pill as insurance against deficiencies costs less than a few packs of cigarettes. Low-income populations, in general, are the most likely to have poor diets and have the most to gain from multivitamin/multimineral supplementation. As Hippocrates said: “Leave your drugs in the chemist’s pot if you can heal the patient with food.”

Although many degenerative diseases will benefit from optimal nutrition, and optimal nutrition clearly involves more than adequate micronutrients, there are several important reasons for focusing on micronutrients and health, particularly DNA damage: (1) More than 20 years of efforts to improve the American diet have not been notably successful, though this work must continue. A parallel approach focusing on micronutrient intake is overdue and might be more successful, since it should be easier to convince people to take a multivitamin/multimineral pill as insurance against ill health than to change their diet significantly. (2) A multivitamin/multimineral pill is inexpensive, is recognized as safe, and supplies the range of vitamins and minerals that a person requires, though not the essential fatty acids. Fortification of food is another approach that is useful, but its implementation has been very slow, as with folic acid fortification. Moreover, fortification of food does not allow for differences between individuals. For example, menstruating women need more iron than men or postmenopausal women, who may be getting too much. That is why two types of vitamin pills are marketed, one with iron and one without. With better knowledge it seems likely that a broader variety of multivitamin/multimineral pills will be developed, reflecting such life-stage differences.

The above issues and many others discussed in this book highlight the need to educate the public about the crucial importance of optimal nutrition and the potential health benefits of something as simple and affordable as a daily multivitamin/multimineral pill.
multivitamin/multimineral supplement. The numerous advances in the science of nutrition and changing ideas about optimal intakes of micronutrients make *An Evidence-based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations* an excellent and timely resource. Dr. Higdon, who had a background in health care and nutrition science, and Dr. Drake, who has an expertise in toxicology and nutrition, have synthesized a large amount of recent scientific research on vitamins and nutritionally essential minerals into an organized volume that includes information on optimal micronutrient intakes to prevent and treat chronic diseases. The book also contains much needed and up-to-date information on safety and drug interactions of vitamins and minerals. The credibility of this book is enhanced by the fact that it is endorsed by the Linus Pauling Institute at Oregon State University and that each chapter has been critically reviewed by a recognized expert in the field. Tuning up the metabolism to maximize human health will require scientists, clinicians, and educators to abandon outdated paradigms of micronutrients merely preventing deficiency disease and to explore more meaningful ways to prevent chronic disease and achieve optimal health through optimal nutrition.

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Preface to the Second Edition

I am honored to revise and update Dr. Jane Higdon’s book, *An Evidence-based Approach to Vitamins and Minerals: Health Benefits and Intake Recommendations*. Since the first edition was published in 2003, there has been a dramatic expansion of the literature on the role of micronutrients in human health and disease. In this second edition, all 27 chapters have been revised to incorporate information from the relevant, more recently published peer-reviewed studies, especially studies with human subjects. This edition includes the latest recommendations by the Food and Nutrition Board (FNB) of the Institute of Medicine: the FNB established new dietary reference intakes for potassium and sodium in 2004 and revised their recommendations for calcium and vitamin D in 2010. Additionally, some of the Linus Pauling Institute (LPI) recommendations have been modified to reflect current knowledge in micronutrient research. The LPI recommendations are daily intake levels aimed at the promotion of optimum health and prevention of chronic disease in healthy individuals. A large literature indicates that inadequate or marginal intake of vitamins and nutritionally essential minerals may increase one’s risk for a number of diseases, including cardiovascular diseases, certain cancers and neurodegenerative diseases, and osteoporosis. Micronutrient inadequacy can also impair immunity and thus increase susceptibility to communicable diseases like influenza. This book reviews the present knowledge on the roles of vitamins and minerals in disease prevention and disease treatment, in addition to providing basic information on biological function, deficiency, food sources, safety, and interactions with other micronutrients and drugs.

Acknowledgments

I wish to thank the faculty, staff, and students of the Linus Pauling Institute for their editorial advice and support in the revision of this book, especially Balz Frei, PhD, director and endowed chair; Stephen Lawson, administrative officer; and Barbara McVicar, assistant to the director. I am very appreciative to all of the distinguished scientists listed in the Editorial Advisory Board, who reviewed the contents of each chapter and provided helpful comments. I am particularly grateful to Donald M. Mock, MD, PhD, and Eva Obarzanek, PhD, for their valuable expertise in revising the chapters on biotin and salt, respectively. Finally, I deeply appreciate the skillful work by Dr. Higdon in writing the first edition of this book, which has been a popular resource for both health professionals and the public.

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Preface to the First Edition

During my clinical training, I learned to approach micronutrient nutrition from the perspective of preventing or treating deficiency diseases, such as scurvy or iron-deficiency anemia. In clinical practice, I became increasingly interested in the potential for micronutrients to prevent and treat chronic diseases at intakes higher than those required to prevent deficiency. However, the standard medical and nutrition texts of the day rarely provided the kind of information I was looking for. Today, scientific and medical research on the roles of micronutrients in health and disease is expanding rapidly, as are, unfortunately, exaggerated health claims from numerous supplement manufacturers. Keeping up with the explosion of contradictory information regarding the safety and efficacy of dietary supplements has become an overwhelming task for consumers as well as health care and nutrition professionals. My goal in writing this book was to provide clinicians and consumers with a practical evidence-based reference to the rapidly expanding field of micronutrient nutrition.

While my own interest in nutrition and health led me to pursue doctoral work in nutrition and biochemistry, such a step should not be necessary for health care and nutrition professionals who want more information on the health implications of dietary and supplemental micronutrients. With the support of the Linus Pauling Institute at Oregon State University (LPI), I have synthesized and organized hundreds of experimental, clinical, and epidemiologic studies, providing an overview of the current scientific knowledge of the roles of vitamins and nutritionally important minerals in human health and disease. To ensure the accuracy of the information presented, I asked at least one recognized scientific expert in the field to review each chapter. The names and affiliations of these scientists are listed in the Editorial Advisory Board.

Throughout this book, I have tried to emphasize human research published in peer-reviewed journals. Where relevant, I have included the results of experimental studies in cell culture or animal models. Although randomized clinical trials provide the strongest evidence for the effect of micronutrient intake on disease outcomes in humans, it is not always ethical or practical to perform a double-blind, placebo-controlled trial. Observational studies can also provide useful information about micronutrient intake and disease outcomes. In reviewing the epidemiologic research, I have given more weight to the results of large prospective cohort studies, such as the Nurses Health Study, than retrospective case-control or cross-sectional studies. When available, I have included the results of systematic reviews and meta-analyses, which summarize information on the findings of many similar studies.

Nearly 35 years ago Linus Pauling, PhD, the only individual ever to win two unshared Nobel Prizes, concluded that micronutrients could play a significant role in enhancing human health and preventing chronic disease, not just deficiency disease. The basic premise that an optimum diet is the key to optimum health continues today as the foundation of the Linus Pauling Institute at Oregon State University. Scientists at the Linus Pauling Institute investigate the roles that micronutrients and other dietary constituents play in human aging and chronic diseases, particularly cancer, cardiovascular diseases, and neurodegenerative diseases. The goals of our research are to understand the molecular mechanisms behind the effects of nutrition on health and to determine how micronutrients and other dietary factors can be used in the prevention and treatment of diseases, thereby enhancing human health and well-being. The Linus Pauling Institute is also dedicated to training and supporting new researchers in the interdisciplinary science of nutrition and optimum health, as well as to educating the public about the science of optimum nutrition.

As you read this book, it will become apparent that the Linus Pauling Institute recommendations for certain micronutrients (e.g., vitamin C) differ considerably from those of Linus Pauling himself. Dr. Pauling, for whom the Linus Pauling Institute has great respect, based his own micro-
Preface to the First Edition

nutrient recommendations largely on theoretical arguments. For example, in developing his recommendations for vitamin C intake, he used cross-species comparisons, evolutionary arguments, and the amount of vitamin C likely consumed in a raw plant food diet. At the Linus Pauling Institute, we base our micronutrient recommendations on current scientific evidence, much of which was unavailable to Dr. Pauling. The Linus Pauling Institute’s recommendation for a vitamin C intake of at least 200 mg/day for generally healthy adults takes into account the currently available epidemiologic, biochemical, and clinical evidence. Similarly, the Linus Pauling Institute’s intake recommendation for each micronutrient in this book is based on the current scientific research available, while, in many cases, acknowledging that the intake levels most likely to promote optimum health remain to be determined.

Acknowledgments

First and foremost, I wish to thank the faculty, staff, and students of the Linus Pauling Institute for providing me with the inspiration and the opportunity to write this book. Specifically, Balz Frei, PhD, the director, and Stephen Lawson, the chief administrative officer of the Linus Pauling Institute, provided valuable advice and editorial assistance throughout the project. Barbara McVicar also provided much needed technical assistance and support. I am very grateful for the support of Bruce N. Ames, PhD, who was enthusiastic about this project from the beginning. His research and his eloquent foreword have been invaluable in laying the groundwork for this book.

I would like to thank each of the distinguished scientists listed in the Editorial Advisory Board for taking the time to carefully review each chapter of this book and provide insightful and constructive comments. I am also grateful to Aram Chobanian, MD, for reviewing the information presented on salt. The artist, Pat Grimaldi of the Communication Media Center at Oregon State University, was both patient and skillful in creating the book’s illustrations.

This project would not have been possible without the generous financial support of the donors to the Linus Pauling Institute, who deserve special thanks. Finally, although I did not know him personally, I would like to thank Dr. Linus Pauling for courageously stimulating scientific, medical, and popular interest in the roles played by micronutrients in promoting optimum health and preventing and treating disease.

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How To Use This Book

Chapter Organization

Information on individual vitamins, organic (carbon-containing) compounds that are required by humans in small amounts from the diet to maintain normal physiological function, can be found in Chapters 1 through 13, in alphabetical order by vitamin. In addition to vitamins, a number of inorganic elements (minerals) are required in the human diet to support a wide range of biological functions. Information on nutritionally important minerals can be found in Chapters 14 through 27, in alphabetical order by mineral. For ease of use, the information in each chapter is organized in the following manner:

- **Function**  Current scientific understanding of the function of the micronutrient with respect to maintaining health and preventing disease.
- **Deficiency**  Risk factors, signs, symptoms, and physiological effects of frank deficiency of the micronutrient.
- **Disease Prevention**  Where controlled research is available, information on the role(s) of the micronutrient in the prevention of disease.
- **Disease Treatment**  Where controlled research is available, information on the role(s) of the micronutrient in the treatment of disease.
- **Sources**  Information on dietary, supplemental, and other sources of the micronutrient. When available, this section includes a table of dietary sources.
- **Safety**  Information on toxicity and adverse effects of the micronutrient, as well as micronutrient–drug interactions.
- **The Linus Pauling Institute Recommendation**  A daily intake recommendation based on relevant scientific research and reflecting an intake level aimed at the prevention of chronic disease and the promotion of optimum health in generally healthy individuals. Recommendations for older adults (over the age of 50 years) are also addressed in this section.

- **References**  In addition to the Linus Pauling Institute Recommendations, the Food and Nutrition Board (FNB) of the Institute of Medicine appoints committees of expert scientists to set Dietary Reference Intakes (DRIs), which are used to plan and evaluate diets of apparently healthy people. Three different DRIs appear regularly throughout this book:
  - The *Recommended Dietary Allowance* (RDA) is defined as the average daily dietary intake level of a specific nutrient sufficient to meet the requirement of nearly all (97%–98%) healthy individuals in a particular life-stage group. Because RDAs generally reflect intake levels designed to prevent deficiency, they are presented in the *Deficiency* section of each chapter.
  - An *Adequate Intake* (AI) is provided if there is insufficient evidence to determine an RDA. The AI is based on experimentally derived intake levels or observed average intake levels of apparently healthy people. For example, the AI of a nutrient for infants is generally based on the average daily intake of that nutrient supplied by human milk in healthy, full-term infants who are exclusively breastfed. Because AIs reflect intake levels thought to prevent deficiency, they are also presented in the *Deficiency* section of each chapter.
  - The *Tolerable Upper Intake Level* (UL) is defined as the highest level of a nutrient determined to pose no risk of adverse effects for almost all individuals in the general population. The UL is discussed in the *Safety* section of each chapter.
Appendices

Several appendices have been included to facilitate the use of this book by clinicians as well as consumers.

- **Nutrient—Nutrient Interactions** A table summarizing the information on nutrient—nutrient interactions discussed in the book.

- **Drug—Nutrient Interactions** A table summarizing the information on nutrient—drug interactions discussed in the book.

- **Quick Reference to Diseases** A useful chart that allows the reader to locate micronutrient information by disease or health condition.

- **Glossary**

- **The Linus Pauling Institute Prescription for Health** A list summarizing the Linus Pauling Institute Recommendations for a healthy diet, lifestyle, and supplement use.
2 Folic Acid

The terms *folic acid* and *folate* are often used interchangeably for this water-soluble B-complex vitamin. Folic acid, the more stable form, occurs rarely in foods or the human body but is the form most often used in vitamin supplements and fortified foods. Naturally occurring folates exist in many chemical forms. They are found in foods as well as in metabolically active forms in the human body. In the following discussion, forms found in food or the body are referred to as *folates*, whereas the form found in supplements or fortified foods is referred to as *folic acid*.

**Function**

**One-carbon Metabolism**

The only function of folate coenzymes in the body appears to be in mediating the transfer of one-carbon units. Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids.

**Nucleic acid metabolism.** Folate coenzymes play a vital role in DNA metabolism through two different pathways (Fig. 2.1):

1. The synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes.
2. A folate coenzyme is required for the synthesis of methionine, and methionine is required for the synthesis of S-adenosylmethionine (SAM).

SAM is a methyl group (one-carbon unit) donor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA. Methylation of DNA may be important in cancer prevention.

![Fig. 2.1 Folate and nucleic acid metabolism: 5,10-methylene tetrahydrofolate (THF) is required for the synthesis of nucleic acids, and 5-methyl THF is required for the formation of methionine from homocysteine. Methionine, in the form of S-adenosylmethionine, is required for many biological methylation reactions, including DNA methylation. Methylene TH-folate reductase is a flavin-dependent enzyme required to catalyze the reduction of 5,10-methylene THF to 5-methyl THF.](image-url)
Amino acid metabolism. Folate coenzymes are required for the metabolism of several important amino acids. The synthesis of methionine from homocysteine requires a folate coenzyme as well as a vitamin B₁₂-dependent enzyme. Thus, folate deficiency can result in decreased synthesis of methionine and a build-up of homocysteine. Increased levels of homocysteine may be a risk factor for heart disease as well as several other chronic diseases.

Nutrient Interactions

The metabolism of homocysteine, an intermediate in the metabolism of sulfur-containing amino acids, provides an example of the interrelationships of nutrients necessary for optimal physiological function and health. Healthy individuals use two different pathways to metabolize homocysteine (Fig. 2.2). One pathway (methionine synthase) synthesizes methionine from homocysteine and depends on a folate coenzyme and a vitamin B₁₂-dependent enzyme. The other pathway converts homocysteine to another amino acid, cysteine, and requires two vitamin B₆-dependent enzymes. Thus, the amount of homocysteine in the blood is regulated by three vitamins: folate, vitamin B₁₂, and vitamin B₆.

Deficiency

Causes

Folate deficiency is most often caused by a dietary insufficiency; however, it can occur in a number of other situations, for example, alcoholism is associated with low dietary intake and diminished absorption of folate, which can lead to

---

Fig. 2.2 Homocysteine metabolism: S-adenosylhomocysteine is formed during S-adenosylmethionine-dependent methylation reactions, and the hydrolysis of S-adenosylhomocysteine results in homocysteine. Homocysteine may be remethylated to form methionine by a folate-dependent reaction that is catalyzed by methionine synthase, a vitamin B₁₂-dependent enzyme. Alternately, homocysteine may be metabolized to cysteine in reactions catalyzed by two vitamin B₆-dependent enzymes.
folate deficiency. In addition, certain conditions such as pregnancy or cancer result in increased rates of cell division and metabolism, causing an increase in the body's demand for folate. Several medications may also contribute to deficiency (see “Drug Interactions,” p. 14).

**Symptoms**

Individuals in the early stages of folate deficiency may not show obvious symptoms, but their blood levels of homocysteine may increase. Rapidly dividing cells are most vulnerable to the effects of folate deficiency, so when the folate supply to the rapidly dividing cells of the bone marrow is inadequate, blood cell division becomes abnormal, resulting in fewer but larger red blood cells. This type of anemia is called *megaloblastic* or *macrocytic* anemia, referring to the enlarged, immature red blood cells. Neutrophils, a type of white blood cell, become hypersegmented, a change that can be found by examining a blood sample microscopically. As normal red blood cells have a lifetime in the circulation of approximately 4 months, it can take months for folate-deficient individuals to develop the characteristic megaloblastic anemia. Progression of such an anemia leads to decreased oxygen-carrying capacity of the blood and may ultimately result in symptoms of fatigue, weakness, and shortness of breath. It is important to point out that megaloblastic anemia resulting from folate deficiency is identical to the megaloblastic anemia resulting from vitamin B₁₂ deficiency, and further clinical testing is required to diagnose the true cause of megaloblastic anemia.

**Recommended Dietary Allowance**

Traditionally, the dietary folate requirement was defined as the amount needed to prevent a deficiency severe enough to cause symptoms such as anemia. The most recent recommended dietary allowance (RDA) (Table 2.1) was based primarily on the adequacy of red blood cell folate concentrations at different levels of folate intake, as judged by the absence of abnormal hematological indicators. Red cell folate has been shown to correlate with liver folate stores. Maintenance of normal blood homocysteine levels, an indicator of one-carbon metabolism, was considered only as an ancillary indicator of adequate folate intake. As pregnancy is associated with a significant increase in cell division and other metabolic processes that require folate coenzymes, the RDA for pregnant women is considerably higher than for women who are not pregnant. However, the prevention of neural tube defects (NTDs) was not considered when setting the RDA for pregnant women. Rather, reducing the risk of NTDs was considered in a separate recommendation for women capable of becoming pregnant, because the crucial events in neural tube development occur before many women are aware that they are pregnant.

**Dietary Folate Equivalents**

When the Food and Nutrition Board (FNB) of the Institute of Medicine set the new dietary recommendation for folate, they introduced a new unit, the dietary folate equivalent (DFE):

<table>
<thead>
<tr>
<th>Life stage</th>
<th>Age</th>
<th>Males (µg/day)</th>
<th>Females (µg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0–6 months</td>
<td>65 (AI)</td>
<td>65 (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7–12 months</td>
<td>80 (AI)</td>
<td>80 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1–3 years</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Children</td>
<td>4–8 years</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Children</td>
<td>9–13 years</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14–18 years</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Adults</td>
<td>≥19 years</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>All ages</td>
<td>–</td>
<td>600</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>All ages</td>
<td>–</td>
<td>500</td>
</tr>
</tbody>
</table>

AI, adequate intake; DFE, dietary folate equivalent.
Immunity

Vitamin A is commonly known as the anti-infective vitamin, because it is required for normal functioning of the immune system. The skin and mucosal cells (cells that line the airways, digestive tract, and urinary tract) function as a barrier and form the body’s first line of defense against infection. Retinol and its metabolites are required to maintain the integrity and function of these cells. Vitamin A and RA play a central role in the development and differentiation of white blood cells, such as lymphocytes, which play critical roles in the immune response. Activation of T lymphocytes, the major regulatory cells of the immune system, appears to require all-trans-RA binding of RARs.

Growth and Development

Both vitamin A excess and deficiency are known to cause birth defects. Retinol and RA are essential for embryonic development. During fetal development, RA functions in limb development and formation of the heart, eyes, and ears. In addition, RA has been found to regulate expression of the gene for growth hormone.

Red Blood Cell Production

Red blood cells, similar to all blood cells, are derived from precursor cells called stem cells. Stem cells are dependent on retinoids for normal differentiation into red blood cells. In addition, vitamin A appears to facilitate the mobilization of iron from storage sites to the developing red blood cell for incorporation into hemoglobin, the oxygen carrier in red blood cells.

Nutrient Interactions

Zinc. Zinc deficiency is thought to interfere with vitamin A metabolism in several ways:
- Zinc deficiency results in decreased synthesis of retinol-binding protein (RBP), which transports retinol through the circulation to tissues (e.g., the retina) and also protects the organism against the potential toxicity of retinol.
- Zinc deficiency results in decreased activity of the enzyme that releases retinol from its storage form, retinyl palmitate, in the liver.
- Zinc is required for the enzyme that converts retinol into retinal.

At present, the health consequences of zinc deficiency on vitamin A nutritional status in humans are unclear.

Iron. Vitamin A deficiency may exacerbate iron-deficiency anemia. Vitamin A supplementation has beneficial effects on iron-deficiency anemia and improves iron nutritional status among children and pregnant women. The combination of supplemental vitamin A and iron seems to reduce anemia more effectively than either supplemental iron or vitamin A alone. Moreover, studies in rats have shown that iron deficiency alters plasma and liver levels of vitamin A.

Deficiency

Vitamin A Deficiency and Vision

Vitamin A deficiency among children in less developed nations is the leading preventable cause of blindness. The earliest evidence of vitamin A deficiency is impaired dark adaptation or night blindness. Mild vitamin A deficiency may result in changes in the conjunctiva (corner of the eye) called Bitot spots. Severe or prolonged vitamin A deficiency causes a condition called xerophthalmia (dry eye), characterized by changes in the cells of the cornea (clear covering of the eye) that ultimately result in corneal ulcers, scarring, and blindness.

Vitamin A Deficiency and Infectious Disease

Vitamin A deficiency can be considered a nutritionally acquired immunodeficiency disease. Even children who are only mildly deficient in vitamin A have a higher incidence of respiratory disease and diarrhea as well as a higher rate of mortality from infectious disease compared with children who consume sufficient vitamin A. Vitamin A supplementation has been found to decrease both the severity and the incidence of deaths related to diarrhea and measles in less developed countries, where vitamin A deficiency is common. The onset of infection reduces blood retinol levels very rapidly. This phenomenon is generally believed to be related to decreased synthesis of RBP by the liver. In this manner, infection stimulates a vicious cycle, because inadequate vitamin A nutritional status is related to increased severity and likelihood of death.
from infectious disease.\textsuperscript{18} However, a review of four studies concluded that vitamin A supplementation is not beneficial in reducing the mother-to-child transmission of HIV.\textsuperscript{19} One study found that HIV-infected women who were vitamin A deficient were three to four times more likely to transmit HIV to their infants.\textsuperscript{20}

**Recommended Dietary Allowance**

The recommended dietary allowance (RDA) for vitamin A was revised by the Food and Nutrition Board (FNB) of the Institute of Medicine in 2001. The latest RDA is based on the amount needed to ensure adequate stores (4 months) of vitamin A in the body to support normal reproductive function, immune function, gene expression, and vision (Table 7.1).\textsuperscript{21}

**Disease Prevention**

**Cancer**

Studies in cell culture and animal models have documented the capacity for natural and synthetic retinoids to reduce carcinogenesis significantly in skin, breast, liver, colon, prostate, and other sites.\textsuperscript{2} However, the results of human studies examining the relationship between the consumption of preformed vitamin A and cancer are less clear.

**Lung cancer.** At least 10 prospective studies have compared blood retinol levels at baseline among people who subsequently developed lung cancer and those who did not. Only one of those studies found a statistically significant inverse association between serum retinol and lung cancer risk.\textsuperscript{22} The results of the β-Carotene And Retinol Efficacy Trial (CARET) suggest that high-dose supplementation of vitamin A and β-carotene should be avoided in people at high risk of lung cancer.\textsuperscript{23} About 9000 people (smokers and people with asbestos exposure) were assigned a daily regimen of 25,000 IU retinol and 30 mg β-carotene, while a similar number of people were assigned a placebo. After four years of follow-up, the incidence of lung cancer was 28% higher in the supplemented group compared with the placebo group. A possible explanation for such a finding is that the oxidative environment of the lung, created by smoke or asbestos exposure, gives rise to unusual carotenoid cleavage products, which are involved in carcinogenesis. Currently, it seems unlikely that increased retinol intake decreases the risk of lung cancer, although the effects of retinol may be different for nonsmokers than for smokers.\textsuperscript{22}

**Breast cancer.** Retinol and its metabolites have been found to reduce the growth of breast cancer cells in vitro, but observational studies of dietary retinol intake in humans have not confirmed this.\textsuperscript{24} Most epidemiological studies have failed to find significant associations between retinol intake and breast cancer risk in women,\textsuperscript{25–28} although one large prospective study found that total vitamin A intake was inversely associated

<table>
<thead>
<tr>
<th>Life stage</th>
<th>Age</th>
<th>Males µg/day (IU/day)</th>
<th>Females µg/day (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0–6 months</td>
<td>400 (1333 IU) (AI)</td>
<td>400 (1333 IU) (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7–12 months</td>
<td>500 (1667 IU) (AI)</td>
<td>500 (1667 IU) (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1–3 years</td>
<td>300 (1000 IU)</td>
<td>300 (1000 IU)</td>
</tr>
<tr>
<td>Children</td>
<td>4–8 years</td>
<td>400 (1333 IU)</td>
<td>400 (1333 IU)</td>
</tr>
<tr>
<td>Children</td>
<td>9–13 years</td>
<td>600 (2000 IU)</td>
<td>600 (2000 IU)</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14–18 years</td>
<td>900 (3000 IU)</td>
<td>700 (2333 IU)</td>
</tr>
<tr>
<td>Adults</td>
<td>≥19 years</td>
<td>900 (3000 IU)</td>
<td>700 (2333 IU)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>≤18 years</td>
<td>–</td>
<td>750 (2500 IU)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>≥19 years</td>
<td>–</td>
<td>770 (2567 IU)</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>≤18 years</td>
<td>–</td>
<td>1200 (4000 IU)</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>≥19 years</td>
<td>–</td>
<td>1300 (4333 IU)</td>
</tr>
</tbody>
</table>

AI, adequate intake.

\textsuperscript{18} Higdon, An Evidence-based Approach to Vitamins and Minerals (ISBN 9783131324528) © 2012 Georg Thieme Verlag KG
with the risk of breast cancer in premenopausal women with a family history of breast cancer. Blood levels of retinol reflect the intake of both preformed vitamin A and provitamin A carotenoids such as \( \beta \)-carotene. Although a case-control study found serum retinol levels and serum antioxidant levels to be inversely related to the risk of breast cancer, two prospective studies did not observe significant associations between blood retinol levels and subsequent risk of developing breast cancer. Currently, there is little evidence in humans that increased intake of preformed vitamin A or retinol reduces breast cancer risk.

### Disease Treatment

#### Pharmacological Doses of Retinoids

Retinoids are used at pharmacological doses to treat several conditions, including retinitis pigmentosa, acute promyelocytic leukemia, and various skin diseases. It is important to note that treatment with high doses of natural or synthetic retinoids overrides the body’s own control mechanisms, so retinoid therapies are associated with potential side effects and toxicities. In addition, all of the retinoid compounds have been found to cause birth defects. Thus, women who have a chance of becoming pregnant should avoid treatment with these medications. Retinoids tend to be very long acting: side effects and birth defects have been reported to occur months after discontinuing retinoid therapy. The retinoids discussed below are prescription drugs and should not be used without medical supervision.

**Retinitis pigmentosa.** Retinitis pigmentosa describes a broad spectrum of genetic disorders that result in the progressive loss of photoreceptor cells (rods and cones) in the eye’s retina. Early symptoms of retinitis pigmentosa include impaired dark adaptation and night blindness, followed by the progressive loss of peripheral and central vision over time. The results of a randomized controlled trial in more than 600 patients with common forms of retinitis pigmentosa indicated that supplementation with 4500 \( \mu \)g (15 000 IU)/day of preformed vitamin A (retinol) significantly slowed the loss of retinal function over a period of four to six years. In contrast, supplementation with 400 IU/day of vitamin E increased the loss of retinal function by a small but significant amount, suggesting that patients with common forms of retinitis pigmentosa may benefit from long-term vitamin A supplementation but should avoid vitamin E supplementation at levels higher than those found in a typical multivitamin. Up to 12 years of follow-up in these patients did not reveal any signs of liver toxicity as a result of excess vitamin A intake. High-dose vitamin A supplementation to slow the course of retinitis pigmentosa requires medical supervision and must be discontinued if there is a possibility of pregnancy.

**Acute promyelocytic leukemia.** Normal differentiation of myeloid stem cells in the bone marrow gives rise to platelets, red blood cells, and white blood cells that are important for the immune response. Altered differentiation of those stem cells results in the proliferation of immature leukemic cells, giving rise to leukemia. A mutation of the RAR has been discovered in patients with a specific type of leukemia called acute promyelocytic leukemia (APL). Treatment with all-trans-RA or with high doses of all-trans-retinyl palmitate restores normal differentiation and leads to improvement in some APL patients.

**Diseases of the Skin**

Both natural and synthetic retinoids have been used as pharmacological agents to treat disorders of the skin. Etretinate and acitretin are retinoids that have been useful in the treatment of psoriasis, whereas tretinoin and isotretinoin have been used successfully to treat severe acne. Retinoids most likely affect the transcription of skin growth factors and their receptors. Use of pharmacological doses of retinoids by pregnant women causes birth defects.

### Sources

#### Retinol Activity Equivalents

Different dietary sources of vitamin A have different potencies; for example, \( \beta \)-carotene is less easily absorbed than retinol and must be converted to retinal and retinol by the body. The most recent international standard of measure for vitamin A is retinol activity equivalents (RAE), which represent vitamin A activity as retinol:
2 µg β-carotene in oil provided as a supplement can be converted by the body to 1 µg retinol, giving it an RAE ratio of 2:1. However, 12 µg dietary β-carotene from foods are required to provide the body with 1 µg retinol, giving dietary β-carotene an RAE ratio of 12:1. Other provitamin A carotenoids in foods are less easily absorbed than β-carotene, resulting in RAE ratios of 24:1. The RAE ratios for β-carotene and other provitamin A carotenoids are shown in Table 7.2. An older international standard, still commonly used, is the international unit (IU): 1 IU is equivalent to 0.3 µg retinol.

**Food Sources**

Free retinol is not generally found in foods. Retinyl palmitate, a precursor and storage form of retinol, is found in foods from animals. Plants contain carotenoids, some of which are precursors for vitamin A (e.g., α-carotene, β-carotene, and β-cryptoxanthin). Yellow and orange vegetables contain significant quantities of carotenoids. Green vegetables also contain carotenoids, although the pigment is masked by the green pigment of chlorophyll. A number of good food sources of vitamin A are listed in Table 7.3 along with their vitamin A content in RA Es. In those foods where retinol activity comes mainly from provitamin A carotenoids, the carotenoid content and the RA Es are presented.

<table>
<thead>
<tr>
<th>Table 7.2</th>
<th>Retinol activity equivalent (RAE) ratios for β-carotene and other provitamin A carotenoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity consumed</td>
<td>Quantity bioconverted to retinol</td>
</tr>
<tr>
<td>1 µg dietary or supplemental vitamin A</td>
<td>1 µg retinol</td>
</tr>
<tr>
<td>2 µg supplemental β-carotene</td>
<td>1 µg retinol</td>
</tr>
<tr>
<td>12 µg dietary β-carotene</td>
<td>1 µg retinol</td>
</tr>
<tr>
<td>24 µg dietary α-carotene</td>
<td>1 µg retinol</td>
</tr>
<tr>
<td>24 µg dietary β-cryptoxanthin</td>
<td>1 µg retinol</td>
</tr>
</tbody>
</table>

Table 7.3 | Food sources of vitamin A |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Food</td>
<td>Serving</td>
</tr>
<tr>
<td>Cod liver oil</td>
<td>1 teaspoon</td>
</tr>
<tr>
<td>Fortified breakfast cereals</td>
<td>1 serving</td>
</tr>
<tr>
<td>Egg</td>
<td>1 large</td>
</tr>
<tr>
<td>Butter</td>
<td>1 tablespoon</td>
</tr>
<tr>
<td>Whole milk</td>
<td>1 cup (8 fluid ounces)</td>
</tr>
<tr>
<td>2% fat milk (vitamin A added)</td>
<td>1 cup (8 fluid ounces)</td>
</tr>
<tr>
<td>Nonfat milk (vitamin A added)</td>
<td>1 cup (8 fluid ounces)</td>
</tr>
<tr>
<td>Sweet potato, canned</td>
<td>½ cup, mashed</td>
</tr>
<tr>
<td>Sweet potato, baked</td>
<td>½ cup</td>
</tr>
<tr>
<td>Pumpkin, canned</td>
<td>½ cup</td>
</tr>
<tr>
<td>Carrot, raw</td>
<td>½ cup, chopped</td>
</tr>
<tr>
<td>Cantaloupe</td>
<td>½ medium melon</td>
</tr>
<tr>
<td>Mango</td>
<td>1 fruit</td>
</tr>
<tr>
<td>Spinach</td>
<td>½ cup, cooked</td>
</tr>
<tr>
<td>Broccoli</td>
<td>½ cup, cooked</td>
</tr>
<tr>
<td>Kale</td>
<td>½ cup, cooked</td>
</tr>
<tr>
<td>Collards</td>
<td>½ cup, cooked</td>
</tr>
<tr>
<td>Squash, butternut</td>
<td>½ cup, cooked</td>
</tr>
</tbody>
</table>

RAE, retinol activity equivalent.
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Page numbers in italics refer to illustrations or tables

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