IGF and Nutrition in Health and Disease

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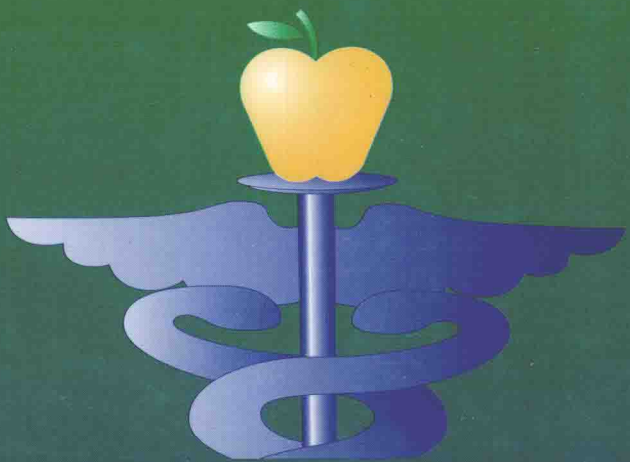

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IGF and Nutrition in Health and Disease

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Adrianne Bendich, Series Editor

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DEDICATION

M. S. H. wishes to acknowledge the profound influence of Gary Fosmire, Robert Reeves, and her parents. Thanks to her husband, Joe, for his understanding and support during this long process. This book is dedicated to her children, Matthew, Kelsey, and Elizabeth.

E. L. F. dedicates this book to her children, Laurel, Scott, and John, with thanks for their unconditional support throughout the years.

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) 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 and cutting-edge topics, 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.

IGF and Nutrition in Health and Disease, edited by M. Sue Houston, Jeffrey Holly, and Eva Feldman is the first comprehensive volume developed for health professionals and graduate students to deal with the cutting-edge science and clinical use of the insulin-like growth factor (IGF) system. The first published report of this "serum factor" appeared in 1957 and by the 1970s the biochemistry of the factor and its similarity to insulin were understood. It was not until about 15 yr ago that the binding proteins and receptors were fully identified and characterized. Currently, there are clinical studies underway to evaluate the therapeutic value of IGF — which illustrates the critical need for this volume in a rapidly moving field of relevance to human health and disease.

This text represents an important addition to the *Nutrition and Health* series and exemplifies the potential for this series to include cutting-edge, clinically relevant texts that are valuable to practitioners as well as those involved in the state-of-the-art research into the many effects of nutritional status as well as specific nutrients on the IGF system and vice versa. Moreover, this text fills a critical gap because at present, there is no text that addresses both the clinical and basic aspects of the IGF system in a thorough, up-to-date manner. The volume includes a detailed description of the IGF system, which is composed of three ligands (insulin, IGF-I and IGF-II); three receptors (insulin receptor and IGF-I and -II receptors) and six IGF binding proteins (IGFBPs 1–6). The editors have assured that the reader gains a clear understanding of the importance of the IGF system in the interactions with other critical molecules involved in growth, energy metabolism,

and the development of organs and tissues from the formation of the embryo to its requirement in century-old individuals. Of great value to clinicians, academicians, and students are the key points that are enumerated at the beginning of each chapter. Also, there are recommendations for novel research studies and identification of challenges for future investigations provided for readers at the end of chapters.

Drs. Houston, Holly, and Feldman are internationally recognized leaders in the IGF field and have investigated the role of diet and its constituents on the responses of the IGF system to changes in intakes in both humans and animal models. The editors are excellent communicators; they have worked tirelessly to develop a comprehensive 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 among IGF, growth hormone, prostaglandins, thyroid hormone, parathyroid hormone, the reproductive hormones, the renin-angiotensin system and protein, carbohydrate, and energy metabolism. Moreover, key nutrient components such as zinc, omega-3 fatty acids, glutamine, and antioxidants are reviewed with an emphasis on their interactions with the IGF system.

The editors have chosen the most well-recognized and respected authors from around the world to contribute the 18 informative chapters in the volume. Key features of this comprehensive volume, in addition to the key points, include exhaustive lists of more than 150 references in nine of the chapters and more than 200 references in several of these chapters; there are numerous excellent figures and tables that add great insight into the complex interactions among hormones, receptors, binding proteins, cytokines, and response elements. The volume is a critical and excellent source of detailed information that is required by clinicians when educated patients ask questions about the relevance of IGF to their disease. Clinical use of IGF and its binding proteins are discussed with great objectivity and the status of the clinical research is presented in a balanced, data-driven analysis, yet in a language that makes it possible for patients to clearly understand the current state of the science. The editors have also included a list of resources on the IGF system that is invaluable to the patient and health professional.

The book chapters are logically organized in five major sections. The first section provides the reader with the fundamentals of the IGF system and the interactions with dietary manipulations. This section contains a well-organized chapter that outlines the historic beginnings of the isolation of IGF and its establishment as a system that rapidly responds to starvation, fasting, severe injury, or other catabolic states. The basics of the mechanisms of action of the IGF system at the molecular, subcellular, and cellular levels are carefully explained and form the foundation for all subsequent chapters. The second section looks closely at the interactions between IGF and nutritional state with special emphasis on conditions involving food restriction. Using more than 200 references, the first comprehensive chapter in this section describes in detail the role of protein and energy deprivation on the IGF system as well as other body systems that respond to critical physical stressors. The manifestations of the molecular biology of the IGF system in the whole animal are carefully explained using models such as a specific knock-out mouse model, a novel primate model and, where data are available, in patient populations. The differences in the levels and actions of the IGFs between man and rodent models are clearly stated. Complementing this chapter is the more clinically focused chapter on the effects of chronic malnutrition related to severe illnesses such as cancer and HIV infection; there are preliminary clinical studies that suggest a potential benefit

of IGF as a therapeutic agent. Another unique chapter in the second section includes a definitive description of the methodologies available to assess nutritional status for both clinical studies and larger survey-type epidemiological studies — an important resource for graduate students as well as research directors is the comprehensive table that outlines the pluses and minuses of each of the assessment tools described in the chapter.

Although the IGF system has been known for less than 50 yr, there have been key discoveries of many of the pathways where the IGF system functions in growth and development. The third section of this book contains five chapters that examine current levels of understanding of the essential role of IGF in embryonic and fetal development, infancy, childhood, adolescence, adulthood, and aging. Specific nutrients, such as zinc, that are critical to growth and development are reviewed in detail. Zinc is a co-factor in more than 300 metalloenzymes and a critical component of the functional domains containing zinc fingers, and also activates nuclear receptors. Zinc status affects the complex intracellular signaling required for IGF to permit normal development and growth. The next chapter describes the information that has been derived from studying pygmy populations; several of the genetic defects that result in mutations to IGF genes are also discussed. The link between normal and abnormal cellular growth resulting in tumor formation is reviewed in detail in another comprehensive chapter concerning the fetus and the neonate. There are unique tables providing normative data on the levels of serum IGF and the binding proteins in males and females from neonate through age 20. The clinical relevance of these tables cannot be overstated. There is also an in-depth discussion of the components of the IGF system found in human milk and their functions.

The newest research in the IGF field has shown that in addition to the systemic circulating levels of IGF, there are many tissues and organs that synthesize IGF *in situ*. Moreover, IGF-I is critical to the maintenance of normal bone, skeletal, and cardiac muscles, nerves, and the kidney. Each of these four areas is reviewed in depth in separate chapters that have great clinical relevance. With regard to bone health, there is an in-depth discussion of the requirements for protein for normal bone growth and maintenance, which is under the influence of the IGF system in conjunction with the sex and growth hormones. These complex interactions are illustrated in clear figures that help the reader understand these interactions. Skeletal muscle contains about half of the human body's protein and, as a dynamic system, is also the site of about one-third of the body's protein turnover. IGF-I is central to the regulation of muscle protein synthesis. This chapter not only reviews normal muscle physiology but includes an extended discussion of the effects of catabolic states on muscle tissue wasting in the face of depressed levels of IGF-I; the potential for therapy with IGF is placed in perspective. The effects of alcohol excess and the adverse effects of glucocorticoids on IGF-related muscle loss are also included. In the chapter on the nervous system, diseases reviewed include but are not limited to Alzheimer's, Parkinson's, MS, ALS, diabetic neuropathy, strokes, and traumatic brain injury. The cutting-edge research reviewed includes an analysis of the early clinical studies with IGF and the importance of maintenance of nutritional adequacy for seeing any potential efficacy. With regard to the kidney, it is a major target for IGF and stimulates renal growth during development and also affects the filtration rate; loss of renal function has a negative impact on the IGF system. There are excellent figures that clearly identify the sites and actions of IGFs and the binding proteins within the glomerulus. The interactions between the kidney and IGF are seen in children with renal failure whose IGF levels are depressed and whose growth is stunted.

The final section includes clinically based chapters that review the disease states of diabetes, gastrointestinal (GI) diseases, endocrine dysfunctions, cardiovascular disease, and cancer. The chapter on diabetes describes the importance of IGF and the binding proteins in insulin and glucose regulation. IGF is a key regulator of glucose uptake and use by muscle; the production of the IGF-binding protein 1 is directly proportional to the liver's production of glucose. Thus, there is a very high level of relevance of the IGF system to the development and progression of diabetes. In addition to the discussion of diabetes, there is also information provided about insulin resistance and polycystic ovarian syndrome that are both more prevalent in obese individuals. As mentioned earlier, many tissues synthesize their own IGF and this is also true for the GI tract. The chapter on GI diseases and parenteral nutrition includes detailed illustrations of the growth of the small intestinal lining, indicating the importance of the balance between IGF stimulation of cellular division vs the uncontrolled mitotic division of epithelial cells that could result in colon or other GI tract cancers. Parenteral nutrition bypasses the physiological signals that affect the oral ingestion feedback loops that are controlled in part by IGF. Additionally, there are discussions of the potential for IGF to be used clinically in the treatment of short bowel syndrome and/or inflammatory bowel disease. With regard to the chapter on critical illnesses, the key point is that critical illness is often no longer acute, and chronic severe conditions result in changes in IGF secretion as well as secretion of other hormones such as thyroid, growth hormone, and the sex hormones; these changes are presented in excellent graphs that will prove to be very helpful to clinicians and other health care professionals. The chapter on cardiovascular effects carefully examines the interactions between the IGF and renin-angiotensin systems in normal as well as pathogenic conditions. This clinically based chapter reviews the changes in IGF in congestive heart failure, hypertension, and cardiac cell death. The potential for using IGF as a cardiac treatment is discussed. The final chapter on cancer describes the growing epidemiological data that associate cancers of the prostate, breast, and colon with both higher than average serum IGF-I levels and lower than average IGF-binding protein 3. The association of IGF, better than average dietary composition and growth and a higher rate of cancers in the tallest people has spurred a strong interest in this area of research. There is also an expanding research interest in the preventive value of low calorie diets for longevity and reduction in cancer risk. This final chapter exemplifies the state of the science in the IGF field — an in-depth examination of the epidemiological data, extensive studies in animal models, and the potential for a greater understanding of the core mechanisms of action of critical molecules that are involved in the growth and development of the organism as well as the development and prevention of human diseases.

Drs. Houston, Holly, and Feldman, as editors, have balanced the most technical information with discussions of the central importance of the IGF system for normal development and growth and have linked these functions to the nutritional status of the individual. The volume, therefore, provides relevant information for graduate and medical students, health professionals, and academicians. Hallmarks of the chapters include incisive key points to begin each chapter; complete definitions of terms with the abbreviation fully defined for the reader and consistent use of terms between chapters. There are numerous referenced tables, graphs, and figures as well as extensive, fully annotated up-to-date references; all chapters include a conclusion section that provides the highlights of major findings and the majority of chapters also include a final section entitled "Recommendations and Challenges for the Future." The volume contains a highly anno-

tated 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 in the functioning of the IGF system, especially in the growth of infants and children. The overarching goal of the editors is to provide fully referenced information to health professionals so they have a balanced perspective on the value of the IGF system for future benefits to human health. Finally, it must be noted that all of the authors and the editors agree that much more research is required to be able to fully understand the biological mechanisms of action and interactions between the IGF system and human nutritional status.

In conclusion, *IGF and Nutrition in Health and Disease* 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 the interactions between IGF system and nutrition in optimizing human health. 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

PREFACE

The complexity and significance of the insulin-like growth factor (IGF) system is staggering. From conception through postnatal growth, development, reproduction, and aging, in health and disease, the IGF axis orchestrates critical aspects of metabolism and physiology. The IGF proteins and their cell receptors are widely expressed in the body and many important functions of IGF system are rapidly being discovered. The impact of nutrition as a fundamental influence on anabolism, growth, and in some instances pathology, is intertwined with IGF in ways that are only just beginning to be appreciated. Nutritional state is one of the most potent regulators of IGFs. Understanding the interactions among nutrition and the IGF axis is critical to understanding the role of these growth factors in normal growth and development and in pathological states. Conversely, IGFs are key mediators by which growth, cell differentiation, and division is influenced by nutrient availability. This volume is the first comprehensive review of nutrition and the IGF system in health and disease. It brings together internationally known and distinguished researchers, physicians, and professors of biology, medicine, nutrition, molecular biology, physiology, biochemistry, animal science, and endocrinology. Inclusion of the most recent basic, clinical, and epidemiological data, across all phases of the life span, as well as perspectives from multiple disciplines, is a major aim of this volume.

IGF encompasses a complex system that includes two proteins (IGF-I and IGF-II), at least six distinct carrier proteins (IGFBP-1–6) that have unique roles in modulating IGF bioactivity as well as independent actions, and two major cellular receptors (IGFR-I and IGFR-II) with significant cross-reactivity with the insulin receptor. Many excellent reviews of the IGF system, chronicling their initial characterization 40–50 yr ago, and ongoing delineation of their roles are available (Appendix A). Virtually all cells and tissues in the body are affected by IGFs in some fashion. As endocrine factors, the IGFs were first recognized as "sulfation factors" that mediated the effects of growth hormone (GH) on cartilage growth and were named "somatomedins" as their critical role in somatic growth during pre- and postnatal life became apparent. In a larger context, IGF actions are part of the hypothalamic–pituitary axis and inseparable from GH. In addition, as the nomenclature suggests, the overlap between IGFs and insulin in terms of structural homology and biological properties is significant. IGFs have rapid insulin-like metabolic actions as well as more long-term growth-promoting activities. There is significant cross-reactivity between IGF-I and the insulin receptor at the cellular level. The importance of the IGF system, in relation to nutrition in the pathogenesis, prevention, and treatment of insulin resistance and diabetes mellitus and their related complications is being actively investigated (Chapter 14).

In addition to the endocrine activity, the pleiotropic effects of the IGFs are related to their local paracrine and autocrine production and activity. Cell differentiation, DNA and protein synthesis, and cell survival are examples of the potent effects of the IGFs in various tissues and organ systems. The specific roles and relative activities of the IGF proteins vary by tissues. The complexity and importance of the IGF system as it is

interrelated with nutrition and metabolic status is approached from many perspectives and in the context of a variety of conditions under normal and pathological circumstances in the present volume. The essential components and molecular aspects of the IGF system and some of the newer concepts in the insulin/IGF signaling pathways lay the groundwork (Chapter 1) for discussion of the direct effects of nutrient availability on the IGF system in Part II. The remaining sections of this volume describe IGF and nutrition in major organ systems and their roles in pathological conditions. Resources related to IGF and nutrition, including the professional societies, organizations, and journals are provided in Appendix B.

Fasting, starvation, and nutritional imbalances have profound effects on the IGFs that are independent of pituitary GH secretion and actions. Protein and energy availability, and micronutrients such as zinc (Chapters 2 and 5), regulate IGF-I gene expression as well as circulating levels of the IGFs, and ultimately the biological activity of IGFs in growth and development. Much of bone health and disease involves some aspect of the IGF system (Chapter 10). Calcium, vitamin D, and protein intakes exert strong influences on bone metabolism that are mediated in part by IGF activity. Observational and interventional studies in the elderly provide strong evidence for the relationship among protein intake, IGF-I, and osteoporosis.

The loss of normal anabolic response to IGFs occurs in malnutrition, but also in catabolic states brought about by metabolic and physical stresses such as infection, injury, and organ failure. The conflicting, competing or perhaps overlapping influences of nutrition and catabolic stress on IGF function during critical illness are considered from a number of perspectives (Chapters 2, 3, 11, and 16).

Many chronic diseases cause profound metabolic changes that lead to catabolism and unintentional weight loss. Persistent inflammation and other anti-anabolic factors in chronic disease can lead to the loss of energy and protein reserves and protein energy malnutrition that cannot be explained nor reversed by altered dietary intake (Chapter 3). The imbalance of anabolic and catabolic signals provides the underlying mechanisms for the wasting (cachexia) and malnutrition of chronic diseases. Understanding the specific role of IGF in the prolonged catabolism of conditions such as heart failure (Chapter 17), chronic critical illness (Chapters 2, 11, 16), inflammatory bowel disease (Chapter 15), and chronic renal failure (Chapter 13) is important to minimizing the malnutrition, morbidity, and mortality of chronic diseases.

Malnutrition is reflected in altered circulating levels of IGF-I and some of the IGFBPs, particularly IGFBP-1, in the blood. This ability of IGF-I to serve as a marker of the adequacy of nutrient intake has been recognized since early research in animals. The possibility of assessing nutritional status with a marker such as IGF-I that is itself a potent anabolic agent is appealing (Chapter 4). Understanding the impact of nutrition support modalities such as parenteral nutrition is furthered by understanding its direct effects on the IGF system (Chapter 15). In addition, the acuity and sensitivity of serum IGF-I concentrations to nutrient adequacy is particularly vital in situations of acute catabolic stress such as critical illness where existing markers of nutrition are limited and when starvation, but also avoidance of overfeeding, is of paramount importance.

The regulation of IGF by nutritional status has many implications across the life span. The IGF–GH axis is a critical component in the orchestration of normal prenatal and postnatal growth (Chapters 6 and 7), and reproduction (Chapter 8). Compromises in

normal growth, reproductive function, and IGF activity by malnutrition have been demonstrated in animal models, but the specific sites of nutritional regulation and the implications for human growth and development remain to be elucidated. Many age-related disabilities in older years are believed to be tied to changes in the IGF proteins (Chapter 9). Circulating levels of IGF-I, IGFBP-1, and perhaps other IGFs, are nutritionally regulated throughout life.

The IGF system is integrally involved in such diverse tissues as skeletal muscle (Chapter 11), the nervous system (Chapter 12), the heart (Chapter 17), the gastrointestinal system (Chapter 15), and the kidneys (Chapter 13). The IGFs offer promising therapies for many debilitating conditions such as multiple sclerosis, Alzheimer's disease, ALS, kidney failure, heart failure, diabetic neuropathy, stroke, and traumatic injury. The interaction of IGF and nutrition in normal functioning as well as disease development and therapy is just beginning.

In cancer research, there has been tremendous interest in the IGF proteins because of their critical role in apoptosis, cell division, and differentiation. The impact of biologically active components in food, overall nutritional state, and possible interactions with IGF are relevant to our understanding of the fundamental mechanisms of tumorigenesis and how the environment and thus potentially modifiable factors can induce or prevent cancer (Chapters 6 and 18).

We are a long way from fully understanding the relationships between the IGF system and nutritional state, but the potential interactions and impact on health and disease are profound and compelling. Understanding the interplay between nutrition and the IGFs has tremendous implications for understanding fundamental biological processes, disease prevention, therapy, and health. Ultimately, it is hoped that this volume introduces and/or expands knowledge for researchers, health professionals and students, but also fosters continued exploration of these two vitally important and intertwined fields of study. The editors thank all of the contributors, who despite being incredibly busy, gave up their time to make this volume come together. The authors acknowledge the technical assistance of Jessica Jannicelli, Nicole Furia, and the staff at Humana Press. In addition, the authors express their sincere appreciation to Paul Dolgert, Editorial Director, Humana Press, and Adrianne Bendich, Series Editor of the *Nutrition and Health* series.

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