# 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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