Foreword

Diabetes mellitus is increasing in frequency worldwide; there is even talk of its reaching epidemic proportions. No one doubts that this has something to do with changes in diet and methods of food preparation — but exactly what and how is disputed, sometimes quite acrimoniously. The dispute is not new, however, and has been raging ever since Thomas Willis wrote in 1697, “diabetes was so rare among the ancients that many famous physicians made no mention of it and Galen knew only two sick of it. But in our age given to good fellowship and gushing down chiefly unalloyed wine, we meet with examples and instances enough, I may say daily, of this disease.” He clearly implicated changes in eating habits and lifestyle in what he perceived was an increasing incidence of what we would now call type 2 diabetes.

So, what is new? Is it the ease of making a diagnosis and changing the diagnostic criteria, and our increasing awareness of it, ageing of the population, changes in lifestyle, especially as regards exercise and the availability of plentiful food, or, as seems increasingly likely, a combination of all of them?

The increasing incidence of diabetes is not confined to any particular country or to either of the two common types of illness, which, though sharing a final common path, have such different origins. The rate of increase is faster in older people, with presumed type 2, than in children and adolescents with presumed type 1 diabetes, as was already apparent from epidemiological studies of the incidence of diabetes in New York as long as 80 years ago. The increase in diabetes is, at least in part, attributable to an even more rapid increase in the prevalence of obesity. Nevertheless there is a well-established increase in the incidence of type 1 diabetes along with that of many other autoimmune diseases and it is almost certainly associated with changes in the environment and eating habits, but not with obesity.

The special role of nutrition in the management of diabetes was recognized long before the era of modern scientific medicine, but it is only within the past century that it has been firmly linked to pathogenesis. Differentiation of diabetes into two main and many subordinate types is comparatively recent, and, while suspected on clinical grounds, was only established, like so many advances in medical knowledge, by major changes in technology. Some of these, such as the use of respiratory quotients to unravel the complexities of metabolism in health and disease, have almost vanished undeservedly from the investigative armamentarium. Others, such as molecular genetics, have still to fulfill their potential. Meanwhile, diabetologists and nutritionists must depend upon advances made possible by the application of nutritional biochemistry, epidemiology, and laboratory medicine, most notably in the measurement of hormones and neurotransmitters by immunoassay, to improve their understanding and management of this increasingly important syndrome.
This book examines all aspects of the relationship between nutritional status and
the pathogenesis, diagnosis, and treatment of patients with the various illnesses that
manifest themselves as diabetes. It will be of especial value to medical practitioners
and dieticians giving day-to-day care to the growing number of patients at both ends
of the age spectrum, as well as to those in the middle. Epidemiologists and directors
of public health policy will also find in it much to interest them, as will laboratory
scientists concerned with unraveling the complex interactions between us and our
food.

The seminal discovery that diabetes, referred to by Willis as the pissing disease
because of its most prominent symptom, was associated with an abnormality of
sugar metabolism led many early investigators to direct their attention to carbohy-
drates in the diet to the exclusion of other constituents. This has gradually, but still
not completely, changed with recognition that most types of diabetes are but one
manifestation of a more general disturbance of metabolism in which fats, and, to a
lesser extent, proteins, are equally or more profoundly affected.

The rediscovery of the endocrine role of the gastrointestinal tract in determining
the fate and disposal of ingested food has been complemented, in more recent times,
by recognition of the role of the gut in regulating appetite through its ability to
release neurotransmitters such as Ghrelin and peptide PPY. Together, these make
the plea, constantly heard from the obese in the past, that their condition was “all
due to my gland’s doctor” no longer dismissible as complete nonsense.

Important as endocrine factors are in the pathogenesis of diabetes, it is impossible
to deny the role of genetic, environmental, sociological, and even commercial factors
in its genesis. The relevance of antenatal, and possibly prenatal, nutrition of the
child’s mother in determining its metabolic fate and later development of obesity,
hypertension, and other features of the metabolic syndrome was highlighted by the
epidemiological studies of David Barker, who painstakingly scrutinized the obstetric
records of large cohorts of patients and their appropriate controls in the United
Kingdom (U.K.). His conclusions have subsequently been confirmed by Nick Hales
in experiments on laboratory animals, and explain, at least in part, the observed
worldwide increase in the metabolic syndrome and all its manifestations, including
type 2 diabetes.

Incrimination of specific items of diet — notably refined sugars, including high-
fructose corn syrups and saturated fats — especially when combined in what are
disparagingly described as junk foods — and by more temperate commentators as
energy-dense foods — is even more contentious today than it was more than half a
century ago. So, too, is the importance of the glycemic index, which, though relevant
to individual foods, rarely applies to mixed meals.

The importance of dietary fiber in determining the bioavailability of absorbable
carbohydrates in the diet is undeniable, but whether this is due to their chemical or
physical characteristics, or a combination of both, is a moot point, as are generali-
izations drawn from selected geographical epidemiological studies.

Difference in the glycemic index of foods depends as much upon their physical
form — whole versus ground brown rice, for example — as upon their chemical
composition and brings into question much of the value of what is often described
as nutritional labeling. Methods of food preparation and storage that alter the nature
and amount of protein glycated prior to ingestion, though long recognized as important by food scientists, has received scant attention from diabetologists and nutritionists in the past. This may be expected to change with the demonstration that ingested, glycated proteins have a detrimental effect upon the body akin to that produced by glycation in vivo and which is held to be responsible for many of the adverse effects of chronic hyperglycemia.

It is impossible to overemphasize the importance of micronutrients in the pathogenesis of disease. This has been recognized ever since the link between vitamin C deficiency and scurvy was first established more than two centuries ago. Nevertheless, despite many claims made for them, evidence that incriminates micronutrients in the pathogenesis of the common forms of diabetes and for their use in prevention and treatment is far from clear. None of them yet has a definite role.

Meanwhile, other nonessential constituents of the diet, such as coffee and alcoholic drinks, that have attracted opprobrium or downright condemnation by those seeking to demonstrate a link between their habitual consumption and the pathogenesis of diabetes have undergone radical revision or reversal. Large-scale, prospective epidemiological studies have revealed, contrary to expectations, their possibly beneficial rather than detrimental effect when used appropriately within the diet. How much this is due to their antioxidant content and how much to their pharmacologically active constituents is unsettled, but illustrates the importance of establishing a firm data base before proffering nutritional advice, which has been all too rare in the past.

There clearly is no simple, one-stop solution to the role of nutrition in general, and of food and drink in particular, in the pathogenesis of diabetes and obesity — as many politicians and their nutritionist gurus would have us believe. Science is the growth of knowledge based upon evidence, and readers will find within the pages that follow the evidence upon which to base answers to many of the questions posed by the rising incidence of diabetes and obesity in the modern world. They will, more importantly, also find pointers to gaps in our knowledge and areas of ignorance that have hitherto been glossed over, ignored, or just not considered, but which will, in all probability, yield to further investigation.

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Preface

Diabetes and obesity are two common disorders that have come to be appropriately recognized as enormous burdens both to the afflicted individuals, their countries, and the modern society in general. What is most striking is the relationship between obesity and impaired glucose regulation that predominantly results in overt diabetes. Consequently, as the incidence of obesity has risen in virtually every population, so has the prevalence of type 2 diabetes. Perhaps more alarming is the trend of increased incidence of obesity and type 2 diabetes among children. When one considers that both disorders are by nature chronic and tend to be associated with a host of complications, it becomes quite obvious how they can become the bane of today’s world.

The purpose of *Nutrition and Diabetes: Pathophysiology and Management* is to provide a unique forum that highlights the link between the problems of obesity and diabetes, albeit various aspects of each disorder are separately discussed in different sections of the book. However, the interrelationships of the various areas of the disease processes become quite apparent in the many overlaps among the contents of many topics covered in this book. Enormous efforts have been made by the different contributors in each section of the book to first provide an overview of each topic, then discuss the mechanistic aspects of the given problem, and to finally link the pathophysiological processes to the treatment. The book is divided into three sections: Pathophysiology and Treatment of Obesity; Pathophysiology and Treatment of Diabetes; and The Role of Oxidative Stress in the Pathogenesis and Treatment of Diabetic Complications. Each section begins with an introduction.

*Nutrition and Diabetes: Pathophysiology and Management* is intended to be a reference handbook for physicians, nutritionists, and other health-care workers who deal daily with the various problems associated with obesity and diabetes. Researchers who need to see the gaps that still need to be filled in our understanding of the disease processes, as well as strategies for drug development for effective management of the problems, will find the book to be of significant interest. The book should also be of significant interest to public-policy makers involved in formulating health policies, especially in developing countries. Finally, by reading this book, individual subjects afflicted with either obesity or diabetes or both would learn a lot about how to help themselves and about understanding the basis of the treatment provided by their health-care team.

I would like to express my sincere gratitude to a lot of people who have helped in my career in different ways. First, I would like to thank all my former teachers, particularly Professor Vincent Marks and John E. Gerich, M.D., who inspired in me the love of metabolic and diabetes research at the University of Surrey and the Mayo Clinic, respectively. I am also greatly indebted to Vay Liang W. Go, M.D., presently of the University of California Los Angeles, for giving me the opportunity to work
with him at the National Institutes of Health, Bethesda, Maryland, and for his continued mentorship in my academic career. Secondly, I would like to express my gratitude to all my former students and fellows at Duke University, Durham, North Carolina, who have helped to shape my career by making seminal contributions to my research. Some of these former trainees of mine, such as Dr. Marc Garfinkel, director of islet transplantation at the University of Chicago, and Dr. William Kendall of the Duke University Medical Center, who are now among my best friends, deserve special mention. I am also particularly grateful to another one, Marcus Darrabie, currently a medical student at Duke, who helped with the illustrations used in my chapters in this book.

Finally, I would like to acknowledge the great patience, personal sacrifice, and unqualified support of my wife, Clarice, and our four children, Ogechi, Chiedu, Chucky, and Ike. I am eternally grateful to them for giving me the luxury of extended periods of time away from home in my career and during the preparation of this book. I wish to dedicate this book to my parents, Eugene and Caroline (deceased), for their sacrifices in providing me a most rewarding education that prepared me for an academic career and for their love and support for what I do.
Emmanuel C. Opara, Ph.D., is a research professor and co-director, Engineering Center for Diabetes Research and Education at the Pritzker Institute of Medical Engineering, Illinois Institute of Technology, Chicago, and a senior investigator at the University of Chicago Human Islet Transplant Program. He was previously a member of faculty of the Duke University School of Medicine in Durham, North Carolina (1988–03), a visiting fellow at the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health, Bethesda, Maryland (1986–88), and a World Health Organization (WHO) Fellow in endocrinology/metabolism at the Mayo Clinic, Rochester, Minnesota (1984–86).

Dr. Opara’s main research focus is diabetes, and he has worked in many areas of diabetes research for more than 20 years. Currently, he is mainly working on developing a bioartificial pancreas using the approach of islet cell microencapsulation. He also studies the role of oxidative stress in the pathogenesis and progression of diabetes and digestive disease. His other research interests include the role of nutritional factors in the etiology and management of diabetes. He has about 200 publications of original articles, abstracts reviews, and book chapters on these subjects.

Dr. Opara is a member of many professional organizations, including: American Diabetes Association, American Federation for Medical Research, American Pancreatic Association, American Gastroenterological Association, Society for Black Academic Surgeons, Transplantation Society, and International Pancreas and Islet Transplantation Association.
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Section I

Pathophysiology and Treatment of Obesity
Introduction

For more than two decades, there has been an exponential increase in the incidence of obesity around the world. This trend has been more apparent in the United States of America where the incidence of obesity in adults has more than doubled over that period. With this uncontrolled rise in obesity has been a concomitant increase in the diseases associated with obesity, such as type 2 diabetes, hypertension, and cardiovascular disease. It is perhaps more disturbing to note that over this same period, there has even been a higher increase in the prevalence of obesity in the American pediatric community. Not surprisingly, we have also seen an unprecedented increase in the number of diagnosed cases of type 2 diabetes in children and adolescents. It is therefore most timely to have different aspects of this problem addressed by reputable experts who routinely deal with it. Thus, this section is focused on the disease obesity, which is defined as an excess of body fat, which increases body weight beyond physical and skeletal requirements.

It is well-established that a delicate balance between energy intake and expenditure is required to maintain a healthy body weight. Certainly, the amount of energy intake depends both on the quantity and quality of food consumed. On the other hand, energy expenditure is critically dependent upon the basal metabolic rate, the thermic effect of food, and mandatory and volitional physical activity. Although many factors affect food consumption, it is very clear that appetite and satiety, which are regulated by neuroendocrine factors, play a key role, as is efficiently reviewed in this section. The role of the factors released from the canal through which food is consumed and processed, prior to utilization by various tissues, is also important in regulating the fate of the nutrients.

Obviously, obesity is the result of an imbalance between food intake and disposal, and it is a consequence of the failure of one or more factors involved in any of the two processes. Once a primary cause of the failure is recognized, it is required that appropriate steps first be taken to try and correct the problem. In most cases, returning an overweight individual to normal weight through reversal of the failed processes of maintaining a normal body weight does not achieve the desired objective by conventional treatment, and extraordinary measures, such as surgery, become unavoidable, as outlined in this section. Unfortunately, adoption of a drastic procedure to treat obesity, such as surgery, comes at price to the patient. There are also key issues required in routine management of such patients. These issues and the other chronic complications of obesity, such as the metabolic syndrome, insulin resistance, and type 2 diabetes, are also addressed in this section.
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