CONTEMPORARY ENDOCRINOLOGY™

The Metabolic Syndrome

Epidemiology, Clinical Treatment, and Underlying Mechanisms

Edited by

Barbara Caleen Hansen, PhD

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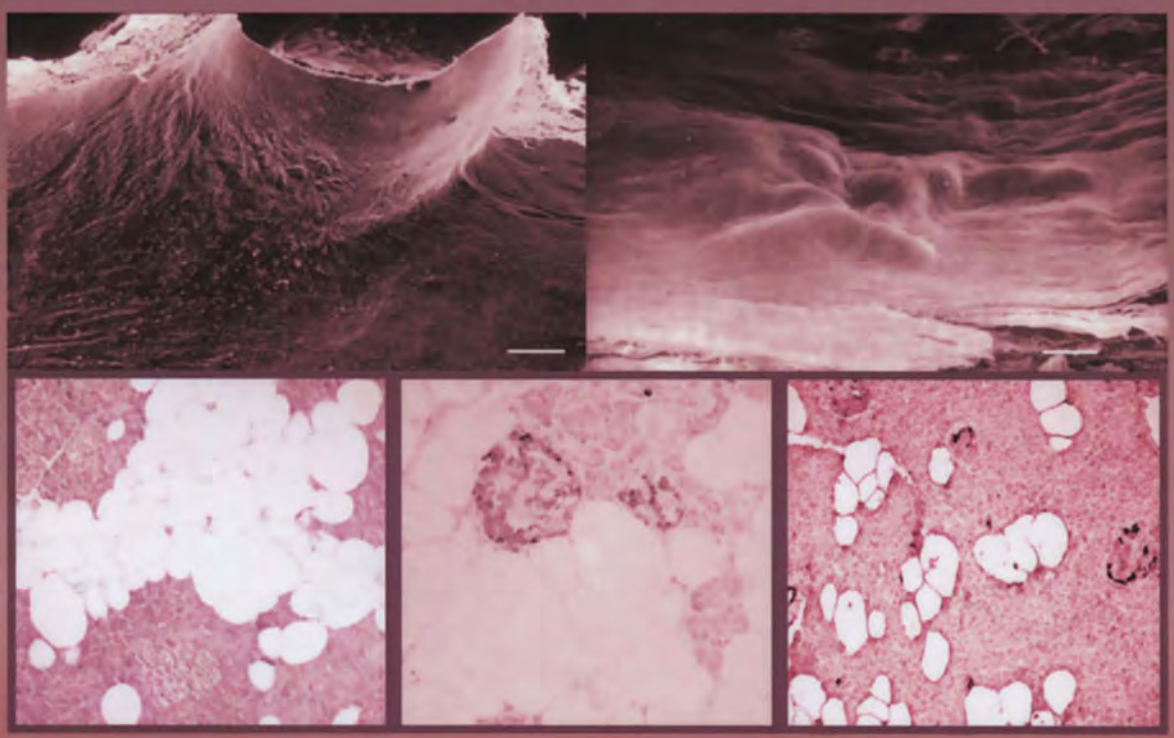

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The Metabolic Syndrome

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Cover illustrations: (Top, left) Scanning electron micrograph of a large raised lesion on the aortic artch of a 9-month-old cp/cp rat (Fig. 3A, Chapter 8; see complete caption on p. 143 and discussion on p. 141. (Right) Scanning electron micrograph of a large intimal lesion in a human coronary artery (Fig. 4A, Chapter 8; see complete caption on p. 144 and discussion on p. 143). (Bottom) Swollen adipocytes in the pancreas (Fig. 1, Chapter 12; see complete caption and discussion on p. 222).

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PREFACE

In the United States, 40 to 45% of those over 60 years of age have the *metabolic syndrome* (1,2,3), and this percentage, based on estimates of the increasing prevalence of excess body weight and the more comprehensive diagnostic criteria for the syndrome, is likely to exceed 60% in newer survey analyses. Children and adolescents, too, are being affected by the metabolic syndrome, in parallel with the increasing prevalence of overweight in young people, now estimated to include 16% of those age 6 to 19 years. Clinicians see with increasing frequency that routine office visits demonstrate the metabolic syndrome, a constellation of discrete but closely related metabolic disturbances indicative of increased risk for (or presence of) cardiovascular disease and/or diabetes. All estimates suggest the increasing impact of the metabolic syndrome on mortality and morbidity (4).

Our aim in developing this new synthesis and analysis of the metabolic syndrome has been to bring together the viewpoints of the epidemiologists, the physiologists, the molecular biologists/biochemists, and the clinicians toward understanding the current state of knowledge of both the causes and the consequences of the metabolic syndrome. These writers aim to stimulate new thinking concerning underlying mechanisms and to encourage heightened efforts to develop new therapeutics, potentially targeting uniquely intersecting pathways or points of intervention. This book is an extended call to action to slow or halt the rising tide of the metabolic syndrome (5).

The metabolic syndrome, including the links among its features, its underlying causes, and its recognized clinical importance, provides the framework for this book, which considers the current status of both basic and clinical science. This is part of a series initiated by G. Reaven and A. Laws (eds.), with *Insulin Resistance: The Metabolic Syndrome X* (Humana Press, 1999). By design, it builds upon two other prior volumes: E. Shafrir and B.C. Hansen (eds.), *Insulin Resistance and Insulin Resistance Syndrome* (United Kingdom: Harwood Academic Publishing, 2002), and B.C. Hansen, J.A. Saye, and L.P. Wennogle (eds.), *The Metabolic Syndrome X: Convergence of Insulin Resistance, Glucose Intolerance, Hypertension, Obesity and Dyslipidemias—Searching for the Underlying Defects* (*Annals of New York Academy of Sciences*, New York, NY, 1999). During these eight years, many of the concepts of the metabolic syndrome have been examined, tested, and strengthened, and, while the basic parameters remain, our thinking about this syndrome and its treatment has undergone considerable refinement.

Major progress has been made in understanding the importance of this syndrome, and in recognizing it as a clinical diagnosis through its inclusion, in 2001, as a new (ICD-9-CM) code (277.7) termed the *dysmetabolic syndrome.*

The interrelationships between metabolic syndrome features and the utility of a metabolic syndrome diagnosis are debated by several authors, with the current but limited conclusion concerning treatment that the best approach may be to treat ". . . individually and aggressively all cardiovascular disease risk factors, . . ." and to treat all collectively as therapeutic agents and new developments allow. Acceptance of risk factor clustering

(obesity, hyperglycemia, elevated triglycerides and low HDL cholesterol levels, hypertension) is shared by all authors, although their perspectives vary widely on the interpretation of this undisputed fact. Both obesity and insulin resistance are frequently named as underlying or predisposing features of the metabolic syndrome; however, multiple metabolic disturbances have now been identified as early markers and potential contributors to the underlying pathology, including inflammatory cytokines and adipokines, endothelial dysfunction, tissue-specific defects in insulin action and signaling, oxidative stress, ectopic lipid deposition, and disordered neuroregulation.

Beyond the basic features of the metabolic syndrome lies a sophisticated array of pathway alterations, for example, in the complex profiling of the dyslipidemia, together with its multi-organ sources of disturbances.

While the first line of treatment, sometimes referred to as *lifestyle modifications*, including diet to produce weight reduction and reduce adiposity and exercise as a general health modifier, remains, more aggressive attention to medically modifying the specific features of the metabolic syndrome toward healthier levels is broadly supported by the authors.

Metabolic syndrome today is one of our most challenging health problems and one with an extraordinary need for early intervention and prevention to slow or halt its progression. Only through an understanding of the science underlying this syndrome can successful interventions be developed and implemented. The editors welcome your input and dialog as together we advance the field of metabolic syndrome and its prevention/treatment.

ACKNOWLEDGMENTS

This volume could not have been put together without the help of a number of people. First and foremost, we want to thank Rosemary Peternel, who has provided invaluable help in assembling all of the pieces, providing initial editorial work, and keeping us in touch with the authors. To the authors, we express our gratitude for their thoughtful contributions and their outstanding expertise. Their efforts are sure to facilitate a better understanding of the metabolic syndrome. We also wish to thank the publishers for their fine efforts to bring it all together. We thank our spouses, Dr. Kenneth D. Hansen and Mitzi Bray, for their support in all of our academic efforts. Thanks to all!

Barbara Caleen Hansen, PhD
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Color Plates

Color Plates follow p. 372.

Figure 14.5. Islet histology of *IRS2*$^{+/-}$::*Pten*$^{+/-}$ intercross mice. Representative islet histology of pancreas sections from 3-month-old (left panels) and 6–8-month-old (right panels) mice immunostained with antibodies against insulin (green) and glucagon (red) photographed with a 5× or 20× objective. Scale bars: 500 μm. Islet morphometric analysis of *IRS2*$^{+/-}$::*Pten*$^{+/-}$ intercross mice at 6–8 months of age. Islet size calculated by mean cross-sectional area of multicelled islets reported as microns $\times 10^3$/islet. Results are expressed as mean ±SEM of at least 5 mice per group. (See discussion on p. 263.)

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Figure 18.5. Schematic illustrating some of the interactions between glucose and lipid metabolism, and demonstrating that increased glucose production will increase both FFA and liver lipid deposition, which in turn will accelerate gluconeogenesis. (See discussion on p. 357.)

1 Metabolic Syndrome— Past and Future

An Introduction to the Features of This Book

Barbara Caleen Hansen, Rosemary Peternel, and George A. Bray

CONTENTS

BACKGROUND

This volume is a review by clinicians and researchers of the broad spectrum of research on the *metabolic syndrome* and its underlying disturbed pathways. It provides insights useful in understanding some of the features and processes in the development of diabetes and cardiovascular disease. Although there are differences of opinion about the value of the metabolic syndrome, it has one important aspect: It focuses attention on clinical considerations related to diabetes and heart disease.

The present volume is divided into three parts: The first part covers the epidemiological and clinical treatment perspectives; the second part is a discussion of endothelial function, inflammation, and dyslipidemia—features central to insulin resistance and vascular disease, including the contributions of C-reactive protein and adipocytes/adipose tissue; and the third part explores insulin secretion and action and their underlying mechanisms, involving pancreatic islet pathophysiology, glucagonsrelated peptides, the insulin receptor signaling cascade, deposition of fat in muscle, alterations in atypical protein kinase-C (APK-C), and the role of the liver.

There are also pointers for future research directions, for improved diagnostic criteria, and for recognition of important pathways that will allow for better treatment alternatives and understanding of micro- and macrophysiological processes. As expected with a cross-disciplinary book of this type, some chapters cover topics that appear in other chapters providing different perspectives on the same problem. Several themes are reinforced throughout this volume: First, multiple, simultaneous treatment strategies

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are needed to improve individual risk factors and the pathophysiology they represent; second, changes in behavioral lifestyle are needed, including reducing obesity, smoking and alcohol use, improving diet, and increasing daily exercise; and third, drugs targeting peroxisome proliferator–activated receptors, as well as other multifunctional drugs, hold promise for overall improved health status and reduction or prevention of the metabolic syndrome.

NATURAL HISTORY

The metabolic syndrome can be considered as a clustering of several risk factors, including hypertension, dyslipidemia, impaired glucose tolerance, and central adiposity. The recognition of this clustering has evolved over almost 90 years. According to Panteleimon Sarafidis' and Peter Nilsson's historical account of the origins of the metabolic syndrome, during World War I, two Austrian physicians, Karl Hitzenberger and Martin Richter-Quittner, identified a link between hypertension and diabetes (1). Furthermore, they identify Eskil Kylin and Gregorio Maranon, respectively a Swede and a Spaniard, who published similar findings in this period (1). Another discovery that Sarafidis and Nilsson refer to is H.P. Himsworth's distinguishing between insulin-resistant and insulin-sensitive diabetics in 1936—suggesting a common pathophysiological background linking metabolic risk factors (1). During the 1940s, M.J. Albrink and J.W. Meigs associated obesity with hyperglycemia and dyslipidemia, as reported by Sarafidis and Nilsson (1). Also during the 1940s, Jean Vague described the male fat distribution and its consequences (2–6). The link between the syndrome features and cardiovascular disease was made as early as the 1960s by Welborn and by Camus, the latter coining the term *trisyndrome métabolique* (7–9).

Nutrition and lifestyles were implicated during the 1960s, and fatty acids were identified as contributing to diabetes and insulin resistance. Advances in the 1970s and early 1980s expanded our understanding of the link of these to coronary heart disease, even in the absence of diabetes, and linked the metabolic risk factors to atherosclerosis (10–12). In 1988, G.M. Reaven grouped several metabolic disorders together as *syndrome X* and proposed that insulin resistance was the underlying event explaining dyslipidemia, high blood pressure, and diabetes (13), and this characterization was further examined by DeFronzo and Ferranini in 1991 (14). These factors were then observed to be influenced by both genetic and environmental factors. Many other names were proposed for this syndrome (15–19), including the *plurimetabolic syndrome* (1988) (20), the *deadly quartet* (1989) (21), *syndrome X plus* (1991) (22), *metabolic syndrome X* (13), the *metabolic syndrome* (23), the *insulin resistance syndrome* (1991) (14), the *cardiovascular disease risk factor cluster* (1992) (24), and *diabesity* (1993) (25); however, from the mid-1990s onward, the term *metabolic syndrome* has been most used. Since the underlying mechanisms are not yet known, the insulin resistance syndrome (the secondary contender for a syndrome title), which implies cause, has been less used.

Over the past 10 years, the definition of the metabolic syndrome has been hotly debated, and debate continues on even whether there is or is not such a syndrome (26). (Also, see Reaven, Chapter 2 in this volume.) The organization-endorsed definitions began with the World Health Organization proposal of 1998 (27), and this was followed in 1999 by an insulin resistance–focused definition by the European Group for the Study