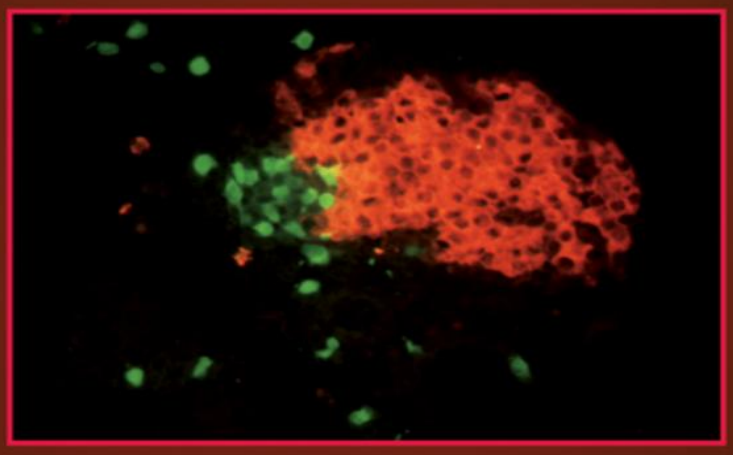
Understanding Diabetes

A Biochemical Perspective



RICHARD F. DODS

WILEY

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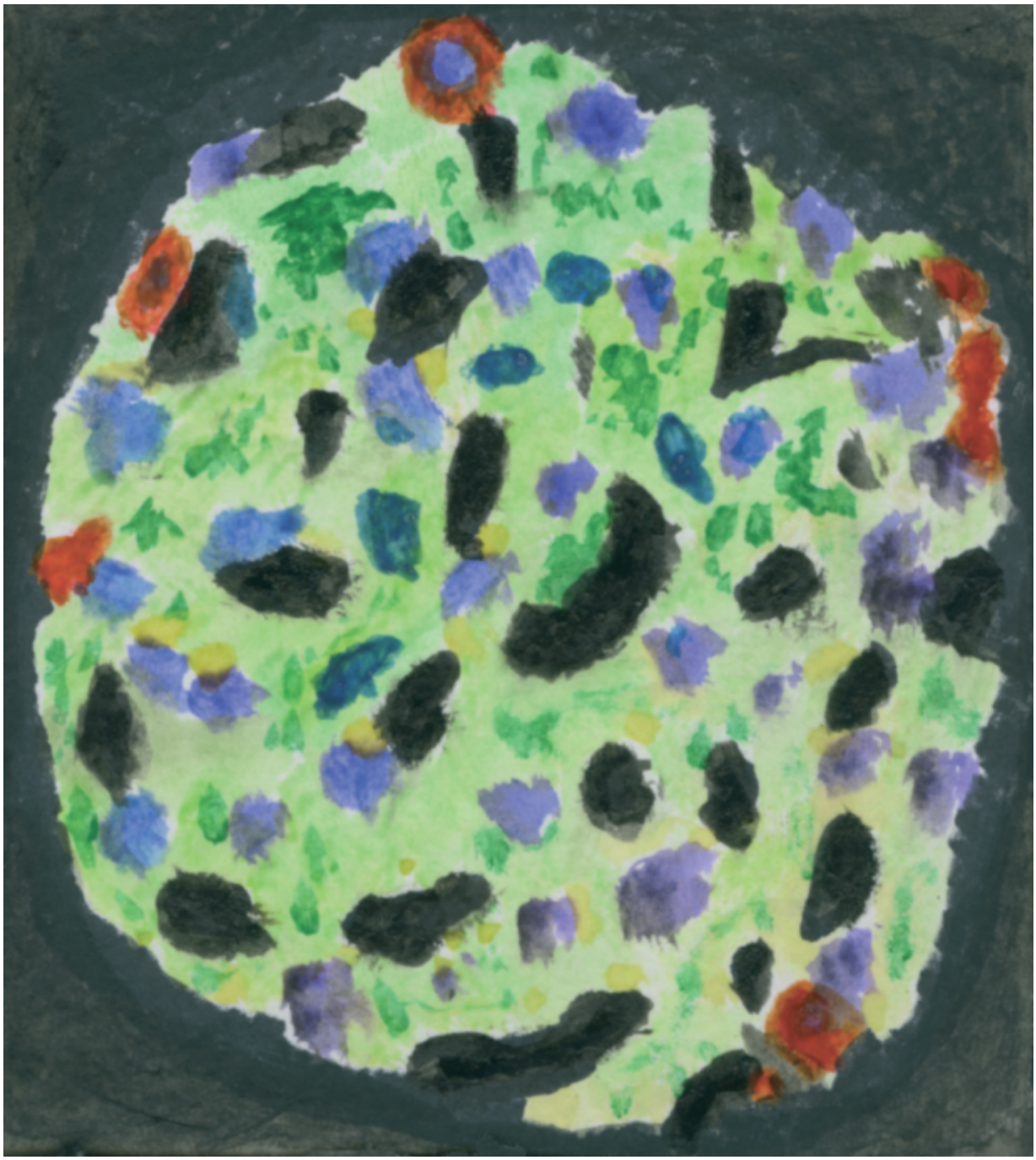

This image depicts a watercolor representation (by the author) of a single pancreatic islet of Langerhans as seen through a light microscope. The nuclei are visualized through staining as blue; the glucagon produced by the α-

cells is stained as red-orange and the insulin produced by the β-cells as green.

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Preface

In this book we commence a fascinating journey that will describe attempts to conquer a disease, really a scourge, which began as far back in history as earliest man, and continues today. Unfortunately we do not presently have a cure, but I feel we are on the brink of one.

This book is written for the individual who wants to learn about the underlying biochemistry/physiology of diabetes mellitus, its history, its detection, its complications, and its treatment.

Alan Alda in an editorial published in *Science*,[1] states "Scientists urgently need to speak with clarity to funders, policy-makers, students, the general public, and even other scientists. …clarity in communicating science is at the very heart of science itself". This book was written with this statement in mind.

Although not absolutely required, a basic knowledge of biochemistry/physiology will help the reader understand certain concepts presented in this book. However, in order to make technical language, objectives, and concepts more easily understood this book includes for each chapter a *Glossary*, *Summary*, and *Problems*. The *Glossary* defines key terms used in the chapter. The *Summary* highlights the essential ideas presented in each section of the chapter. *Problems* for each chapter located in Appendix B present the principal goals of the chapter in the form of questions for the reader. Technical terminology is presented in simple, easily understandable terms with the aid of *Footnotes*.

My Goals In Writing This Book

My goals in writing this book were

- To give the reader a view of diabetes mellitus, a disease that is in epidemic proportions worldwide, by identifying its biochemical basis, classification types, causes, diagnosis and monitoring, complications, and present and future treatment modalities.
- To provide students enrolled in a university-level biochemistry course the materials to understand glucose metabolism and what occurs when the metabolism goes astray.
- To provide incentive for further research on this disease by presenting what we presently know about diabetes.
- To provide a fundamental understanding of the tests used for the diagnosis and monitoring of diabetes—assays that Medical Technologists and Clinical Chemists perform every day.
- To give diabetes counselors and educators a text and reference book that they can use with confidence.
- To provide to medical students and physicians an understanding of the underlying basis for the disease that they treat.
- To provide policy-makers with an understanding and appreciation of the disease that promotes the support of public funds for the research, treatment, and eventual cure of the disease.
- For persons afflicted with diabetes an appreciation of how science is researching this disease and the many breakthroughs that have recently occurred in comprehending the causes, complications, diagnosis, and treatment of this disease.

After reading this book I hope you will agree that these goals have been achieved.

Content

This book is intended to acquaint the reader with diabetes mellitus, a disease that is becoming pandemic.

In Chapter 1, “Diabetes Mellitus: A Pandemic in the Making”, diabetes mellitus is introduced as a disease that is attaining epidemic proportions in the United States and across the world. Parallel to the outbreak of diabetes there is another developing pandemic: overweight and obesity. The connection between these two developing pandemics is discussed in this chapter and will be further elaborated on in Chapter 6.

In Chapter 2, “A Historical View of Diabetes Mellitus”, the history of the disease is presented from the caveman to its recognition in ancient Greek medicine and the early days of the Roman Empire to Banting and Best's Nobel Prize winning discovery of insulin to Sanger's determination of the structure of insulin to Cuatrecasas's purification of the receptor site for insulin.

Chapter 3, “A Primer: Glucose Metabolism”, contains the pathways for the metabolism of glucose. It includes the principal pathways by which glucose is metabolized: glycogenesis and glycogenolysis, glycolysis, the tricarboxylic acid pathway, electron transport system and oxidative phosphorylation, phosphogluconate oxidative cycle, uronic acid cycle, hexosamine biosynthesis pathway, and gluconeogenesis are described. Included in this chapter are “beautiful concepts” as seen through the elegance of many of these metabolic pathways. The notion of “beautiful pathways” is elaborated on in the Prolog to Chapter 3.

Chapter 4, “Regulation of Glucose Metabolism” relates the mechanisms that permit glucose to enter the cell from the

blood. Included in this chapter are descriptions of insulin action, its manufacture in β-cells, the insulin signaling pathway, incretins, and other hormones that regulate insulin production, and the actions of AMP-activated protein kinase.

In Chapter 5, “Glucose Metabolism Gone Wrong”, the altered metabolism of glucose in diabetics is presented.

Chapter 6, “Classification System for Diabetes Mellitus”, deals with the classification scheme for diabetes that has been developed over the years. Described in this chapter are type 1, type 2, impaired glucose tolerance, impaired fasting glucose, gestational diabetes, statistical risk class, potential abnormality of glucose tolerance, and secondary causes of diabetes mellitus.

Chapter 7, “Diagnosis of Diabetes Mellitus”, is divided into three parts—Part 1 deals with the approach to establishing the normal range; Part 2 the modern laboratory tests for glucose; and Part 3 symptoms, diagnostic tests, and criteria used to identify diabetes.

Chapter 8, “Complications of Diabetes Mellitus and Their Pathophysiology”, describes the complications of diabetes retinopathy, angiopathy, nephropathy, infection, hyperlipidemia, atherosclerosis, ketoacidosis, lactic acidosis, hyperglycemic hyperosmolar nonketotic coma, and hypoglycemia. Their pathophysiology and prevalence will also be discussed.

In Chapter 9, “Hereditary Transmission of Diabetes Mellitus”, the hereditary factors that are involved in the susceptibility and resistance to diabetes are discussed. The histocompatibility antigens (HLA) and their association with diabetes are described.

Chapter 10, “Treatment”, goes into a discussion of advancements in the treatment of the disease. Some of what is discussed in this chapter represents ongoing research into the disease. Also treated in this chapter are measures to delay and prevent the occurrence of diabetes.

Postscript “The Future”.

Learning Aids

- Throughout the chapters, Problems, Summary, and Key Terms are listed. These aids are to guide readers as they navigate through the chapters. They permit the reader a shortcut that may be used to scan chapters that are not totally relevant to the reader's interest.
- The goals of each chapter are contained in the Problems located in Appendix B. In addition, summaries are included throughout each chapter.
- Key terms (including medical terms) are explained at each point as they are introduced in the chapter. A glossary of key terms is also included at the end of each chapter.
- Each chapter has a preamble as to its importance in understanding diabetes mellitus. In addition each chapter has a summary.
- Each chapter has numbers within parenthesis relating to references, which are listed in the reference section at the end of the chapter. Included are the URLs for many of the citations. Also the Digital Object Identifier (**DOI**©) for many articles is included. DOI has been around since 2000. DOIs identify electronic objects such as journal articles, books, and scientific data sets in a particular location on the Internet. The system is managed by the International DOI Foundation (**IDF**), a consortium of commercial and noncommercial partners. A DOI name consists of a prefix and a suffix, for example, 10.1089/jwh.2010.2029; the prefix is 10.1089 and the suffix is jwh.2010.2029. One way to use this system is to go to the URL of the IDF, which is http://www.doi.org/ and insert the DOI you are in search of in the place provided and violá the document pops up. The other approach is

to use the URL, http://dx.doi.org/ followed by the DOI name; for example: http://dx.doi.org/10.1089/jwh.2010.2029.

Technical Terms

Technical terms are translated into simple language in this book. When I read an article or book, I find myself spending a considerable amount of time trying to learn the meaning of technical terms with which I am not familiar. I often turn to reference books and textbooks to learn the meaning of the term. In this book I think I have remedied this by having footnotes and a glossary defining any technical terms that you may come across in the text.

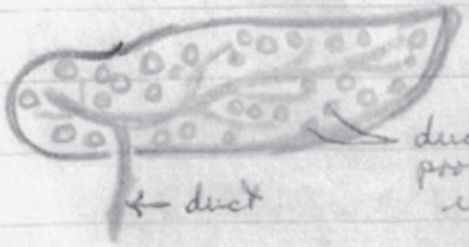
My Background And Interest In Diabetes Mellitus

As you can see from the image shown below I had an interest in diabetes mellitus early during my education. The image is from a science notebook while I was in high school, Lafayette High School in Brooklyn, New York, to be specific. Although Lafayette no longer exists it still remains alive in

my heart as to where I started my career in science.

The pancreas is both a duct and ductless gland. The ~~ductless~~ duct gland gives off pancreatic juice to the small intestine and the ductless gland gives off insulin which controls the amount of sugar in the blood stream. Shortage of insulin causes diabetes.

Pancreas



The hormone insulin was discovered by Banting in 1922. Earlier the Langerhans discovered the Islands of Langerhans. Banting discovered insulin when he saw flies gathering near the urine of dogs who had their pancreas removed. Banting remembered that sugar ~~in~~ causes flies ~~came~~ to gather and that sugar in urine indicates diabetes. Thus, he pinpointed the sickness to the pancreas. Diabetes is cured by injections of insulin which must be kept up throughout the life of the victim.

I earned a B.S. in science at Brooklyn College, an M.S. in organic chemistry at New York University and a PhD in

biochemistry at the University of Connecticut. I was a post-doctoral fellow in cancer research at Sloan Kettering Institute for Cancer Research before joining New York University Medical School as a research associate. It was at the medical center that I first became acquainted with diabetes mellitus and published papers on the biochemistry of the beta cell. My paper[2] was one of the early publications characterizing beta cell protein kinase and protein phosphatase.

I studied clinical biochemistry as an NIH fellow under the esteemed Dr Samuel Natelson at Michael Reese Medical Center in Chicago. As Director of Clinical Chemistry at Louis A. Weiss Memorial Hospital in Chicago (a position which included an Adjunct Assistant Professorship with the University of Illinois Medical School), I published papers on the use of $HbAc_1$ as a test for monitoring diabetes mellitus. This article[3] was one of the earliest suggesting $HbAc_1$ as a tool for the diagnosis of diabetes. While at Weiss, I earned a Diplomate in Clinical Biochemistry from the American Board of Clinical Chemistry.

I wrote the chapter on Diabetes Mellitus for four of the five editions (the exception being the first edition) of *Clinical Chemistry*: *theory*, *analysis*, *and correlation*, edited by Lawrence Kaplan and Amadeo J. Pesce. I have also authored two audiocassette courses for the American Chemical Society entitled "*Clinical Chemistry*" and "*Pathophysiology for Chemistry*". I established a company, Clinical Laboratory Consultants, which advised hospital and commercial laboratories in the implementation and interpretation of assays and the use of instruments for the diagnosis and monitoring of disease. Lastly I taught organic chemistry and biochemistry for 17 years at the Illinois Mathematics and Science Academy (IMSA), a world renowned secondary school funded by the Board of Higher Education of the State of Illinois. While at IMSA I published several papers on

problem-based learning and its utilization in content-rich courses.[4,5]

Dedications

This book is dedicated to

My wife who supported and encouraged me throughout the writing of this book and helped me when I grappled with sentences that were so convoluted that they made little or no sense.

My cousin, Stanley Menson, who helped initiate my interest in science with his turtle tank. He was a biology teacher for the deaf and succumbed from the complications of type 2 diabetes too soon.

My grandchildren, Rachel and Shannon, who I hope will follow in my footsteps into the wonderful world of science.

My son, Steven, who has already followed me into science as an electrical engineer.

Acknowledgments

I sincerely appreciate the contributions of those who initially reviewed portions of the text and found them worthy enough of being incorporated into a book. They were Edward Hobart, M.D., Lawrence Kaplan, Ph.D., and Amadeo Pesce, Ph.D. I thank Professor Anne Cooke who contributed the remarkable cover micrograph of T-cells attacking beta islets. I greatly appreciate the information supplied to me by Thomas F. Mich, Ph.D, retired Vice-President of Chemical Development World-Wide, Warner Lambert Pharmaceutical Company regarding medicinals prescribed for diabetics. He passed away on October 22, 2012 due to a complication of diabetes mellitus, type 2. He will be missed.

No acknowledgement is complete without mentioning the team of experts who turned the text, figures, and other supplementary materials into a book. Anita Alekhwan, Senior Acquisitions Editor, who oversaw the entire operation and provided me with very wise suggestions, her assistant Cecilia Tsai, Editorial Assistant, Kellsee Chu, Senior Production Editor who coordinated the production phase, Haseen Khan, Project Manager of Laserwords who did the editing, and Dean Gonzalez, Illustration Manager who took my crude line drawings and put them into publishable form. To all of the above my genuine thanks for without you there would be no book.

1 Alan Alda, actor, writer, and founding board member of the Center for Communicating Science, State University of New York at Stony Brook from The flame challenge. Editorial. Science 2012;335:1019.

2 Dods RF, Burdowski A. Adenosine 3′5′-cyclic monophosphate dependent protein kinase and phosphoprotein phosphatase activities in rat islets of Langerhans. Biochem Biophys Res Commun 1973;51:421.

3 Dods RF, Bolmey C. Glycosylated hemoglobin assay and oral glucose tolerance test compared for detection of diabetes mellitus. Clin Chem 1979;25:764.

4 Dods RF. A problem-based learning design for teaching biochemistry. J Chem Educ 1996;73:225.

5 Dods RF. An action research study of the effectiveness of problem-based learning in promoting the acquisition and retention of knowledge. J Educ Gifted 1997;20:423.

Chapter 1: Diabetes Mellitus: A Pandemic in the Making

> It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.
>
> Sir Arthur Conan Doyle, British mystery author & physician (1859–1930)

On December 20, 2006, the General Assembly of the United Nations passed resolution 61/225, the United Nations World Diabetes Day Resolution, designating November 14 as World Diabetes Day. On October 29, 2010, the President of the United States, Barack Obama, declared November 2010 as National Diabetes Month in the United States.[1]

Diabetes mellitus[2] is an array of diseases that have a common symptom— abnormally high blood glucose levels. Diabetes mellitus is a noncommunicable disease. It is not transmitted from person to person by viruses or bacteria as is HIV or cholera. Diabetes mellitus is a chronic, costly, and often debilitating disease. This will be our working definition of diabetes mellitus until later in the book where we shall learn more specifics about the disease. The President, in his Proclamation, uses the terms type 1 and type 2 diabetes. By the end of Chapter 6, you will fully understand both these terms.[3] In this chapter we will learn about the extent of the diabetes problem both in the United States and globally. Later in this chapter we will learn of a related pandemic in the making—obesity and overweight. Finally, we will describe the connections between the diabetes and obesity/overweight pandemics.

Diabetes Prevalence and Cost in the United States

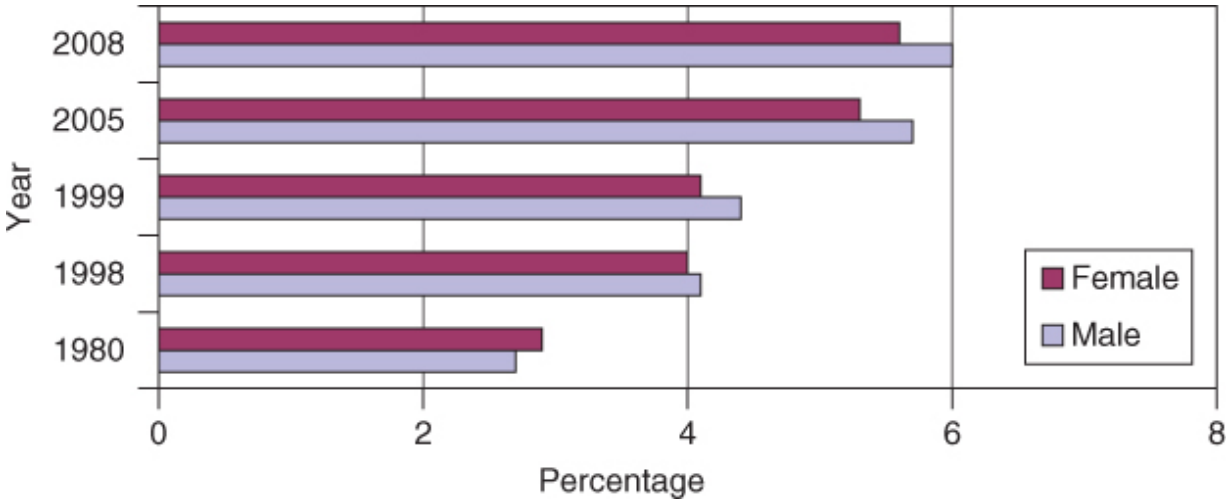
A Dire Prediction Based on Alarming Data

The[4] Centers for Disease Control and Prevention (**CDC**) estimated that as of 2008 there were as many as 18.1 million Americans who had been diagnosed with diabetes (8 in 100 Americans). This number is presumed low because it is estimated that 6.0 million cases remain undetected. Thus, 10 in 100 adult Americans actually had the disease in 2008 [1]. Between 1980 and 2008, the number of diagnosed diabetic Americans has nearly tripled.

An analysis of this data according to age, gender, and race is revealing. All of the following data derived from the CDC is for civilian, noninstitutionalized individuals with diagnosed diabetes.

Figure 1.1 shows the age-adjusted percentage of diagnosed cases of diabetes by sex. You may notice that percentages were similar for males and females until 1999, at which time the percentage for males with diabetes began to increase at a greater rate than for females.

Figure 1.1 Age-adjusted percentage of civilian, noninstitutionalized persons with diagnosed diabetes by sex for selected years. (*See insert for color representation of the figure.*)



As you can see from Figure 1.2, the number of white diabetics increased 104% in the period 1980–2008; that of blacks increased 91% and of Asians/Pacific Islanders 62%. Blacks were diagnosed with diabetes at consistently higher percentages than whites and Asians. All races increased in percentage from 1980 to 2008. For Hispanics (Fig. 1.3), the largest increase in percentage was for Mexican/Mexican-Americans, 42.2%. All Hispanic groups, Puerto Ricans, Mexican/Mexican-Americans, and Cubans had percentages that significantly increased from 1997 to 2008.

Figure 1.2 Age-adjusted percentage of civilian, noninstitutionalized persons with diagnosed diabetes by race: whites, blacks, and Asians/Pacific Islanders for selected years. (*See insert for color representation of the figure.*)