



# **DIABETES**

*With a Chapter on* **HYPOGLYCEMIA**

*by 54 Authors*

*Edited by*

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**WITH 192 ILLUSTRATIONS, 23 IN FULL COLOR**

**DIABETES**

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*For information address Paul B. Hoeber, Inc.,  
Medical Division of Harper & Brothers  
49 East 33rd Street, New York 16, N.Y.*

*Library of Congress catalog card number: 60-5334*

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## PREFACE

The recent tremendous progress in many facets of research dealing with metabolic changes in diabetes and its concomitants (complications) prompted the writing of this book for scientists with varied interests, but particularly for internists, basic medical scientists, and students. It is a unique condensation of the latest and most authoritative information at both the basic science and clinical levels, written in a clear and straightforward manner by more than 40 experts from widely dispersed areas of the world. The authors were selected not only on the basis of their outstanding research contributions but also for their demonstrated effectiveness as teachers and authors. The editor made special efforts to attain coordination of the discussions throughout the book. Some repetition is unavoidable and, indeed, desirable. In attaining conciseness, we have dwelt lightly upon controversial issues and on unimportant diagnostic and therapeutic procedures. We have put much more emphasis upon new information than old. While presenting the accumulated knowledge, we have attempted to impart understanding by indicating how basic scientific observations apply to clinical problems. Many figures and tables are used for illustrations. Most chapters contain summaries of the important conclusions. A limited number of selected references are included.

Following an interesting discussion by Dr. Charles Best of major epochs in the history of diabetes, there are presented descriptions of the chemistry of insulin, its secretion, its distribution throughout the body, and its fate as well as its role in carbohydrate, fat, and protein metabolism. There also is consideration of allied actions of other hormones, particularly glucagon, epinephrine, corticosteroids, and growth hormone.

The effect of these hormones on insulin responsiveness and the stabilization of carbohydrate metabolism is stressed. Factors are described in the serum which are antagonistic to insulin, accounting for marked insulin resistance. Many aspects of the etiology, pathogenesis, pathology, clinical manifestations, and diagnosis of diabetes are discussed. There is extensive consideration of the clinical management of diabetes, including the use of general hygienic measures, diet, insulin, and oral antidiabetic agents. Meticulous attention is given to a discussion of the most recent and extensive investigations dealing with tolbutamide, chlorpropamide, metahexamide, phenethylbiguanide, and other oral antidiabetic compounds. Several chapters are devoted to major concomitants of diabetes and to different types of diabetes. The special problems of diabetes in children and during pregnancy are discussed in individual chapters. Extensive attention is given to the problem of hypoglycemia, including consideration of its many causes, damaging effects, diagnosis, and therapy.

Much of the information in this book is not only valuable in understanding the problems of diabetes but also those of obesity, arteriosclerosis, growth disturbances, adrenopathies, and other metabolic disorders.

The editor is very grateful to all of the authors and Paul B. Hoeber, Inc. for their excellent cooperation in preparing this book. There are also numerous individuals to whom all the contributors are indebted for collecting data and in preparing the manuscripts; included in this group are the editor's two secretaries, Mrs. Marguerite S. Brown and Mrs. Priscilla W. Crittenden. Eli Lilly and Company, through Dr. S. O. Waife, kindly aided in the production of the colored plates.

R. H. W.

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## *Chapter I*

# **EPOCHS IN THE HISTORY OF DIABETES**

*Charles H. Best*

Epochs mark the beginning and sometimes the end of an era. Certain eras, which might be termed "The Clinical Characterization of Diabetes" or "The Endocrine Glands in Diabetes," will continue indefinitely. Others, for example "The Preinsulin Era," have ended abruptly. The era of the study of "The Metabolic Lesions in Diabetes" or of "Enzymatic Abnormalities in Diabetes" will be long. Our present conception of the relative importance of eras will change and many minor and inappropriately named ones will disappear. One way of depicting eras is as coloured lines, perhaps centuries long or years short, populated at intervals by dots of various sizes representing epochs. One epoch may affect several eras and the picture which I constructed, in a preliminary way, persuaded me promptly to abandon this method of illustration!

The reference in the Papyrus Ebers to a condition that may have been diabetes mellitus is indefinite but it does suggest that the written record of our subject may go back to 1500 B.C. or even to 3000 B.C. A good clinical description was given by Celsus (30 B.C. to A.D. 50). The name "diabetes" was first introduced by another Roman physician, Aretaeus of Cappadocia (A.D. 30 to A.D. 90). The word means "to pass

through” and the disease was considered to be a weakness of the kidney because of the polyuria. It is surprising to find that in the European literature on diabetes there seems to be no mention of the presence of sugar in the urine until the seventeenth century, when Willis of Oxford noted the sweetness. He thought that this must come from the blood. Willis was by no means the first to associate glycosuria with diabetes. Avicenna, a well-known Arab physician about A.D. 1000, gave a very complete description of the disorder, including some of the complications such as diabetic gangrene, furunculosis, and phthisis and he remarked on the presence of a honeylike substance in the urine of diabetic patients. But many centuries before Avicenna, Chinese, Japanese, and Hindu writings indicate that a disorder associated with a sweet urine was known to these peoples.

The observations of Thomas Willis, however, marked the beginning of a new era when interest in diabetes quickened. Gradually it became accepted that glycosuria was a constant feature and of diagnostic value. Cawley in 1788 was apparently the first to associate diabetes with the pancreas. He found multiple calculi and destruction of pancreatic tissue at autopsy of a patient dying of diabetes. Before him, Brunner in 1682 had observed polyuria and polydypsia after removal of the pancreas in experimental animals but he did not associate this with diabetes. In 1796 a sound foundation for dietary restrictions was laid by Rollo.\* In the year 1815 Chevreul identified the sugar appearing in the urine as grape sugar. In 1841 Trommer and in 1848 von Fehling developed the well-known cupric oxide tests for urinary sugar. At the same time Bouchardat outlined specific dietary schedules in which fat replaced some of the carbohydrate. He stressed the importance of low caloric intake and introduced fasting days. These principles were followed and further developed by Cantani, von Noorden, Naunyn, Allen, Faltz, Petren, and many others. Bouchardat used a gluten bread. He recognized the value of (a) alcohol in moderation as food in certain cases, (b) fresh vegetables, and (c) exercise. He also used alkali in the treatment of diabetes. This had been proposed by Miahle. Fasting, undernutrition, and perhaps alkali were the only therapeutic measures that could prolong the life of a diabetic before the discovery of insulin.

The nineteenth century would have been remarkable if Claude Bernard's (1813-1878) basic contributions to our knowledge of carbohydrate metabolism had stood alone. The most recent major work on Bernard (1938) written by one of my mentors in physiology, J. M. D.

\* Oscar Minkowski's copies of the books by Brunner and by Rollo were given to me by Frau Minkowski when Prof. B. A. Houssay took me to see her in Buenos Aires in 1951.