

Treatment
of
**DIABETES
MELLITUS**

**JOSLIN
ROOT
WHITE
MARBLE**

TENTH EDITION

The Treatment of

**DIABETES
MELLITUS**

Tenth Edition, Revised, Illustrated

**ELLIOT P. JOSLIN
HOWARD F. ROOT
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ALEXANDER MARBLE**

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Tenth Edition

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PREFACE TO THE TENTH EDITION

THIS edition is a partial fulfillment of a duty owed to patients, physicians and Boards of Health who have helped us to report the results of treatment. The treatment of diabetes, although still grossly inadequate, is steadily improving in direct proportion with the degree of its control, as Bouchardat, Cantani and Naunyn taught long ago. Our data show diabetics are living so much longer, even forty and fifty years after the onset of diabetes, that they are explorers and we doctors are their guides. We have tried to keep this constantly before us. In this undiscovered country the test for sugar in the urine is still the diabetic's compass. The physician's judgment today is aided by new laboratory methods and discoveries.

Recent methods of treatment have not led us to discard the old, but have made the old more practical and less costly. We must do more to reduce expense, and somehow or other bring it about that a diabetic adult is contacted every three months and children every four weeks. Taking account of stock once a year may suffice in business, but not in diabetes; knowing the old and planning the new must take place more often than once in twelve months.

As for the oral treatment of diabetes our experience, with at least 3000 patients so treated, is recorded. The oral drugs have given fresh hope to the patients and have been convenient particularly in the older ones with deficient eyesight. No one claims them to be equal to insulin and as yet there is no final conclusion as to their mode of action. Their incidental contributions to the patient have been an added respect for insulin and the need for closer adherence to the diet, and for the doctor, the opening up of many new pathways for research.

Prevention of diabetes, or at least the deferment of its onset and its complications, is now the goal for which everyone is striving. Boulin crystallized the idea by opening his pre-diabetic clinic in Paris. Prevention takes precedence over heredity. One in three or four in the country has a diabetic relative and one cannot prevent 60,000,000 people getting married. In the course of one week at the Boston Lying-In Hospital 9 diabetic mothers had 11 healthy children, and among them 2 sets of twins on the same day.

The literature on diabetes is overwhelming. We regret the omission of references to important contributions. In the periodical *Diabetes* alone there have been some 300 leading articles and 3000 abstracts in the six years since 1952 when our ninth edition was published.

The means for treatment of the diabetic are more adequate than ever, but the problem is how to put them into effect more generally. In addition to describing in detail the specific treatment of diabetes itself, we have felt obliged to present data in two forms; one which shows how treatment has been improving, and the other which shows the complications which have appeared when treatment has been neglected or delayed. The data are

based on a total of 52,560 patients who have consulted us. Deaths from coma have fallen from 64 per cent to 1.0 per cent and from tuberculosis to 0.2 per cent of the total, although each of these complications once was a major cause of death. Indeed deaths from gangrene have also declined to about 1 per cent, although the problems of the care of lesions of the lower extremities have multiplied, since patients live so long and need so much rehabilitation. Cardiovascular-renal disease has replaced former causes of death, reaching 77 per cent. When we began treating diabetics, coma and tuberculosis seemed more hopeless than does today the possibility of a cure or postponement of premature cardiovascular-renal disease.

The complications of diabetes, our methods of attack upon them, and our results occupy a large share of the book—and why? Virgil wrote, “*Mortui vivos docent.*” As a result of our 18055 fatalities we have gradually accumulated data which compel us to state unequivocally, that of those complications, which have ravaged our diabetics, most can be explained by failure to control the disease. One still reads that retinitis, nephropathy and neuritis bear no relation to control, but our detailed investigation of diabetics who have come under our own supervision proves the contrary.

The treatment of the uncomplicated disease, diabetes itself, is simple enough provided the patient understands and follows the rules. Success depends upon continual control. Most any diabetic, young or old, will live ten years today with a moderate restriction of diet plus insulin, but therein lies the danger. Conclusions are unwarranted unless they are computed and analyzed, based upon a duration of three, four, even five decades following the onset of the disease. For this reason the chapter on children bears the title “*Diabetic Children and Their Later Lives,*” because most of a diabetic child’s life is lived as an adult. From studies begun with children, with adolescents and young adults, we know others like ourselves are convinced that with strict control of the disease headway is being made toward the abolition of that needless triopathy—neuritis, retinitis, nephritis. The measures used to conquer coma and tuberculosis were relatively simple, but to overcome neuritis, nephritis, retinitis and cardiovascular degeneration one must depend upon diet, exercise, insulin and education but, above all else, upon control of the human nature of the patient. With a missionary’s zeal one must convert not alone his mind and soul but also his doctor, to the realization that it is worth the effort to control the disease as shown by a sugar-free urine, normal blood sugar and cholesterol.

Diabetic camps taught us a great lesson. Our children, who have died in the last few years, have lived twenty-six years instead of two years. But today a study of these longer living diabetics shows they needed more opportunities for postgraduate education and rehabilitation. This became so urgent that we have the Hospital Teaching Clinic to which ambulatory patients can return for a few days for a review of their condition and at reduced rates, brought about by concentration of teaching and the shortening of hospital stay. By no means are we alone in such undertakings and it is fortunate that different methods are being tried in various areas of this country and the world with the same purpose in mind.

In 1948 we knew of but one patient who had had the disease twenty-five years and was perfect. This qualified him for the Quarter Century Victory Medal of the Boston Safe Deposit and Trust Company which was designed by Amelia Peabody. Today there are 82 such patients. As yet we have not seen a diabetic with the disease uncontrolled for twenty-five years who could meet the criteria. Have you? The time should come when diabetics will even outlive their contemporaries, because of their better hygiene and closer medical supervision by which conditions, bearing no relation to diabetes, will be discovered earlier and remedied and thus overcome the handicap of the diabetes.

To so many we are indebted in the compilation of the Tenth Edition. To Doctors Warren and LeCompte for the Chapter on the Pathology, to Dr. Nancy Nichols for clarifying the mineral metabolism, to Dr. Renold for his Chapter on Physiology and his studies and comments on our prize remission diabetic with the normal blood sugar lowering component in the blood and to Dr. Schwartz and Dr. Renold for their Table and description of 12 cases of lipo-atrophic diabetes. Our colleagues Dr. Krall and Dr. Bradley have helped much by their contributions to the text and Dr. Allen Joslin by caring for patients so that we all could be authors.

Many secretaries have helped us but had we not had the benefit of the painstaking supervisory assistance of Miss Anna C. Holt, for thirty-five years at the Library of the Harvard Medical School, the book could not have been completed this year. As formerly every courtesy has been extended to us by our publishers, Messrs. Lea & Febiger to whom we are most grateful.

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The Treatment of DIABETES MELLITUS

Chapter 1

PRESENT CONCEPTS OF DIABETES

ELLIOTT P. JOSLIN, M.D.

PREVENTION of diabetes today demands priority in any consideration of the disease. The salient facts emphasizing this responsibility are, (a) the rapidly increasing number of diabetics, of whom many live longer than formerly, (b) their great fecundity, permitting the transmission of a hereditary gene, (c) the aging of the population into the fifth and sixth decades when onset of the disease is most common, (d) the lessening of the need for physical work and the abundance of food consumed with resulting obesity, and finally (e) the earlier detection and more aggressive treatment both of the mild and severe case gives a better opportunity for control of the disease.

The prevention or the deferment of onset and the control of diabetes are within the range of possibility because of our better knowledge of the long pre-diabetic state in the great majority of cases, and the means for earlier detection and control of the disease, even when the onset is acute, by the production of a remission through rest to the insulin-producing cells of the pancreas. Finally there is a better understanding of the disease and its susceptibility to diet, exercise, the insulins and now the sulfonylureas.

With Boulin, let us agree that we should cease assuming that diabetes is irreversible. Animal experimentation has demonstrated the opposite. Consider our own borderline unclassified glycosuria cases, 1946 of them, whom Dr. Marble traced and after about ten years found only 9.9 per cent had become diabetic. These were the ones in whom obesity, heredity and the Jewish race were predominant. No claim to have cured a diabetic is made, but may not frank diabetes have been so postponed in many of the remaining 90 per cent that it has not yet become manifest? No longer should we say, "*Le médecin arrive trop tard.*"

Today, these remissions of diabetes early in its course in which the pancreas is *rested* are one of the most hopeful features of the disease. Undoubtedly, Bouchardat recognized the same, because of his remark that in no disease was a relapse more common, Cantani felt the same about control, and so did Naunyn when he pointed out that the apparently

severe diabetic treated aggressively often later surprised one by being mild. As soon as insulin came, we recognized that the units could be decreased soon after onset. We never advised the omission of insulin even if only one unit, because we felt so sure the disease would return and we did not want to give false hopes to the patients by the omission and later resumption of insulin. Now with these remissions more in mind we recognize they occur in old as well as in young diabetics, and that this period for the disease presents a golden opportunity for treatment which may never return (Brush). What brings these remissions about? Must they always be transitory? Can they not be prolonged for weeks, months, years or a lifetime? Case 50845, a girl of 19, with a probable onset of diabetes in October but first seen in December 1957, was rescued from coma with 1600 units of insulin December 4-15, 1957, at the Norwood Hospital by Doctors Buckley, Cadigan and Sieracki and later seen by us January 9, 1958, with the urine sugar free and receiving 45 units of insulin. In the course of a week she was aglycosuric and with normal glycemia. The blood sugar fasting was 90 mg., and 64 mg. at 11 A.M. with 4 units of insulin and carbohydrate 180, protein 90, fat 90 grams. Upon January 23, Dr. Martin and Dr. Renold found twice the usual insulin-like activity material in the blood, 300 micro-units per milliliter. The 4 units of insulin were continued but omitted on February 6 and 7, and on February 8 the test for the insulin-like material was repeated and was 150 microunits per milliliter. The urine was sugar free and the capillary blood sugar after breakfast was 177 mg. The urine continued to be sugar free with 4 units of insulin daily. On March 29, the test was repeated and was 50 mg. microunits per milliliter. The urine contained 0.1 per cent sugar. This was following a mild upper respiratory infection and the reappearance of catamenia. The blood sugars were 100 mg. and 120 mg. respectively. Upon April 26, the blood sugar lowering material in the blood was 100 microunits per milliliter, but on May 24, the value had risen to 640 microunits and the patient remained in good condition, with a blood sugar of 133 mg. and glycosuria 1.3 per cent one hour after breakfast.

The significance of the sugar-lowering material in the blood, following a period in which 1600 units of insulin were necessary to rescue the patient, is certainly important. If there are two types of diabetes—juvenile and adult—to which does this patient belong? Might there not be one type with two manifestations? Should not the aggressive treatment at the beginning of her disease in some fashion be continued? Is progress into the full diabetic status inevitable? Why not continue the Brush treatment of rest for the pancreas? That is our intention. As for the significance of these findings, time alone will tell.

How many diabetics are there in the United States in 1958? The most reliable source of information in our opinion is that based upon the investigation of the number of cases in the town of Oxford, Massachusetts by Wilkerson and Krall. There it was demonstrated by examinations of the urine and blood of the inhabitants of this typical American town that the prevalence was 1.7 per cent. Using this figure for the 172,830,000 people in the United States at the end of 1957, we have approximately 2,950,000 individuals or about 3,000,000 people in the United States with diabetes.

Excellent data were contributed as a result of a National Health Survey in 1935 and 1936. This is now being repeated on a larger scale.

Variations in the incidence of diabetes in different countries and areas of the same are explainable largely because of wide differences in compilations of statistics based upon death certificates. Therefore, personal statistics and those of insurance companies are of great value. Errors in estimates based upon death certificates occur because the word "diabetes," for various reasons, does not appear on the certificate. Thus, in 1936 and 1946, and again in 1958, Lombard and I were able to demonstrate that at the time of death in only two-thirds of our known diabetic patients was the word "diabetes" entered on their certificates.

Consequently, whenever one sees a statistical report of diabetes based on death certificates as a cause of death, add one-half to it to arrive at a more accurate incidence of diabetes in the community.

Diabetes at the beginning of the century ranked twenty-seventh as a cause of death, but now is eighth for the United States and fifth in the statistics of the Metropolitan Life Insurance Company. The life insurance companies have sensed the change in the status of diabetes. In 1940, there was but one insurance company in the United States and Canada offering insurance to diabetics. Now over 75 per cent of all insurance companies insure them, and with continually liberalizing policies. Along with the increasing duration of life and growing health of diabetics, their ability for employment is more and more being utilized.

The causes for death of diabetics have changed so remarkably that it radically alters plans for the management of the disease. Tuberculosis which undoubtedly was responsible for the death of half the patients fifty years, or even a generation ago in many large city hospitals, has now dropped to 0.2 per cent. Diabetic coma has fallen from 64 per cent to 1 per cent, but vascular disease in the heart, brain and kidneys is now responsible for at least 75 per cent of the deaths. Gangrene has dropped to 1 per cent, but its cost is still enormous and estimated at a million dollars yearly in the Boston area alone. For the children complications in the kidney are steadily mounting to be the chief foe. Due to the longer lives of diabetics, cancer has risen to 11.3 per cent. Now we know by our own studies that it bears no relation to diabetes. Cancer should be discovered earlier in these patients and treated better because they are under closer medical supervision.

The possible influence of heredity is startling. On January 21, 1958, a woman, case 50888, came to me with diabetes. She had had 14 children, 8 now alive. On the following day another woman came who had 13 children and whose husband was a diabetic. Case 51193, came on March 13, 1958, with diabetes of twenty-three years duration. Her twin brother, one sister and her parents have it and one brother died of it. Recently, I personally questioned 100 successive cases, old and new, of all ages and the heredity was 60 per cent. Already this percentage has been exceeded by our 82 Quarter Century Victory Medal diabetics, a figure also reached by our diabetic children who have survived the disease by twenty years. With a better knowledge of their ancestors I feel sure all diabetics would show an hereditary origin.