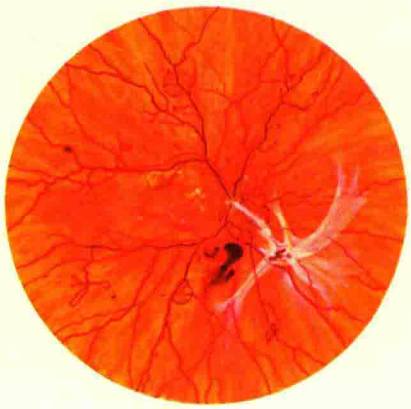
# Diabetes Mellitus

# DIABETES MELLITUS

Seventh Edition



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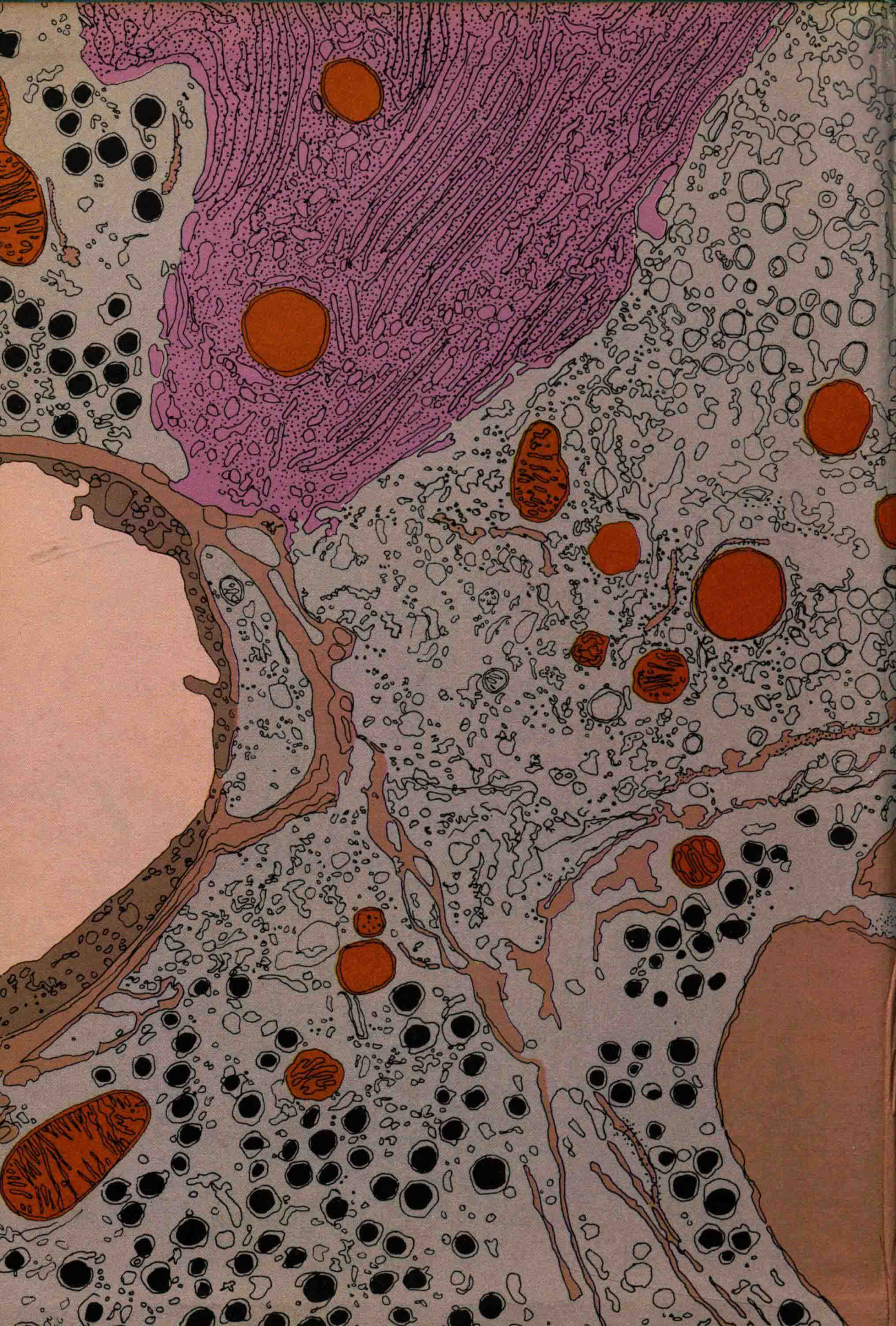
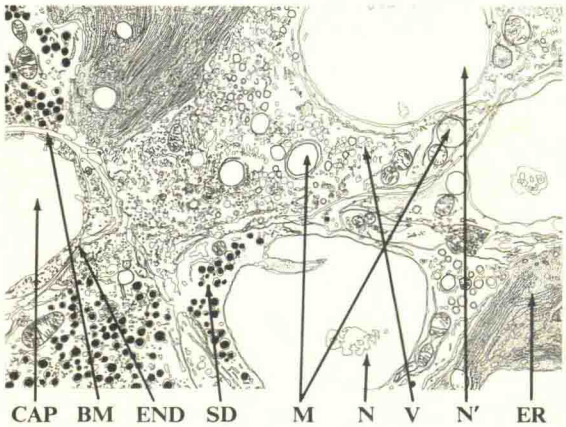





**Artist's Concept of an Islet of Langerhans (Electron Micrograph, 10,000×)**

The hormone insulin is a product of beta cells. Alpha cells contain dense secretion droplets in a membrane-bound vacuole. The alpha cells may secrete glucagon, the glycogenolytic hormone.

| | | | |
|---|---|---|---|
| **CAP** | Capillary | **V** | Vesicles |
| **BM** | Basement membrane | **N′** | Nucleus of beta cell |
| **END** | Endothelium | **ER** | Endoplasmic reticulum; intracellular membrane systems and associated ribosomes of acinar cells |
| **SD** | Secretion droplets | | |
| **M** | Mitochondria | | |
| **N** | Nucleus of alpha cell | | |

# Foreword

Since the publication of the sixth edition of DIABETES MELLITUS in 1958, progress in the field of diabetes and carbohydrate metabolism has been enormous. Oral therapy for maturity-onset diabetes, for instance, has become an established mode of treatment. Methods for studying insulin in the blood have been developed, and important advances in protein chemistry have made possible the delineation of structural differences in insulin from various species. This, in turn, has inspired a whole new field of interest in the immunologic aspects of insulin. Other advances have facilitated greater understanding of the nature and extent of the biochemical errors in diabetes. Finally, both prospective studies of diabetes in the relatives of diabetics and electron microscopy are improving our present understanding of early juvenile diabetes and its complications.

Because of our interest in diabetes, which began with the first commercial production of Insulin, we at Eli Lilly and Company have maintained an active research program in the basic scientific and clinical aspects of diabetes mellitus. Our continuing interest is the basis for the preparation of the seventh edition.

The goals of this volume are twofold. First, Eli Lilly and Company wishes to make available to the medical profession information, developed in its research laboratories and clinical units, which emphasizes those topics most often included in inquiries from physicians all over the world. Second, we hope to provide our readers with a concise manual for the management of diabetes mellitus. In order to fulfill the latter goal, an attempt has been made to stress the points that seem to be of greatest practical use. Therefore, we have tried to make this book a source of pertinent information on methods of management that have been found clinically dependable and that have endured the test of time.

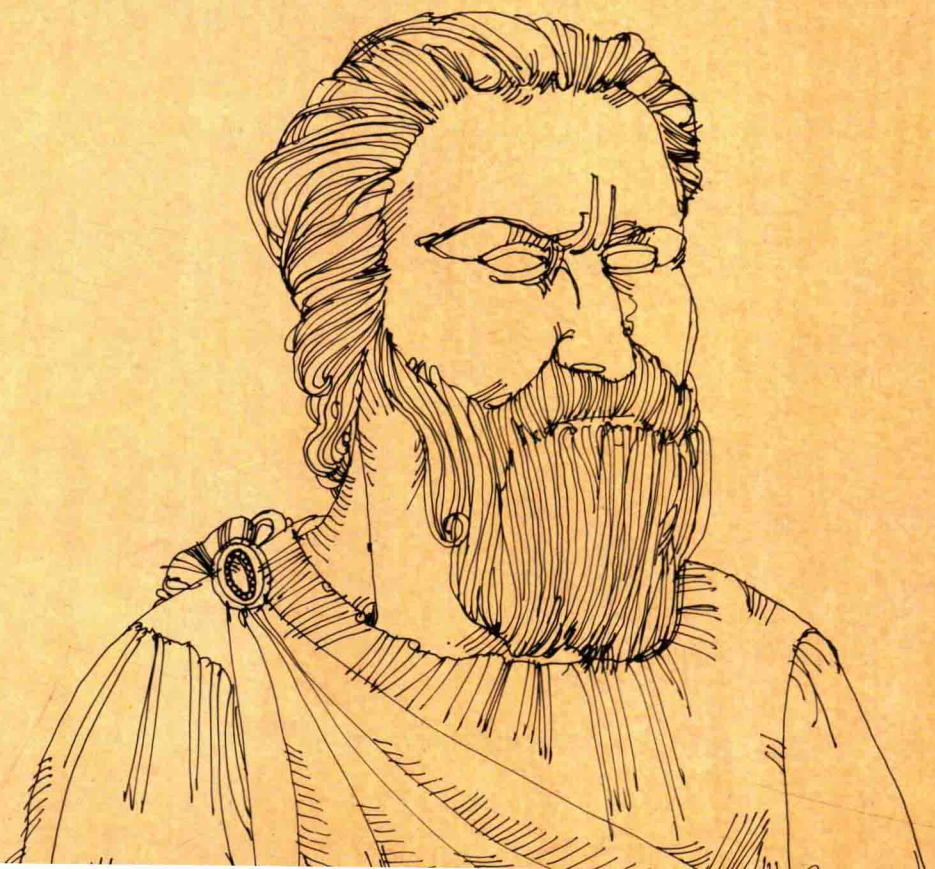
The published works of many investigators have been consulted freely, but, owing to the vast bibliography, references to some publications may have been omitted inadvertently.

This volume has been prepared by John A. Galloway, M.D., Medical Research Division, Eli Lilly and Company, with a discussion on juvenile diabetes by Eric Marler, M.D., and on Insulin manufacture, assay, and synthesis by H. J. Henry, E. L. Grinnan, Ph.D., and E. W. Shuey, Ph.D., of the Lilly Research Laboratories. Numerous individuals within and outside Eli Lilly and Company reviewed copy and offered comments. The artwork was prepared by Alvin Shemesh, M.D., Medical Communications Division, and Ben Field, Merchandising Design.

S. O. WAIFE, M.D.
*Editor*

Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine. Its cause is of a cold and humid nature, as in dropsy. The course is the common one, namely, the kidneys and bladder; for the patients never stop making water, but the flow is incessant, as if from the opening of aqueducts. The nature of the disease, then, is chronic, and it takes a long period to form; but the patient is short-lived, if the constitution of the disease be completely established; for the melting is rapid, the death speedy. Moreover, life is disgusting and painful; thirst unquenchable; excessive drinking, which, however, is disproportionate to the large quantity of urine, for more urine is passed; and one cannot stop them either from drinking or making water. Or if for a time they abstain from drinking, their mouths become parched and their bodies dry; the viscera seem as if scorched up; they are affected with nausea, restlessness, and a burning thirst; and at no distant term they expire.

ARETAEUS THE CAPPADOCIAN, A.D. 81-138



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# Definition and Diagnosis of Diabetes

# 1

## DEFINITION

Diabetes mellitus is a chronic systemic disease characterized by disorders in (1) metabolism of insulin and of carbohydrate, fat, and protein and (2) the structure and function of blood vessels. The principal early symptoms and signs are usually related to the metabolic defects; findings late in the disease are linked with complications resulting from vascular defects.

Diabetes mellitus ordinarily appears as one of two recognized clinical pictures—the juvenile (or youth-onset, ketosis-prone) type or the more common maturity-onset, ketosis-resistant type. The incidence of these two kinds of diabetes is shown in Figure 1, and their characteristics are listed and compared in Table 1.

The essential abnormalities in youth-onset (ketosis-prone) diabetes are related to absolute insulin deficiency, whereas those of maturity-onset diabetes are more often the result of a delayed release of endogenous insulin in relation to carbohydrate challenge. However, some patients with maturity-onset, ketosis-resistant diabetes may have a subnormal capacity for insulin synthesis and release.

The vascular abnormalities associated with diabetes are often referred to as the "complications of diabetes." They consist in microangiopathic changes which give rise to characteristic lesions in the retina and the kidney.

**Figure 1. The Incidence of Various Types of Diabetes**

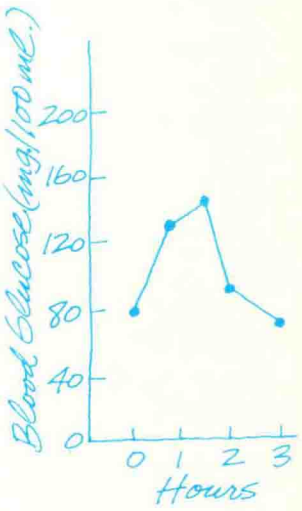

**Table 1. Ketosis-Resistant (Adult-Onset) Diabetes Compared with Ketosis-Prone (Juvenile) Diabetes**

| | KETOSIS-RESISTANT | KETOSIS-PRONE |
|---|---|---|
| Age of Onset | Frequently over 35 | Usually, but not always, during childhood or puberty* |
| Type of Onset | Usually gradual | Abrupt |
| Family History of Diabetes | Commonly positive | Frequently positive |
| Nutritional Status at Time of Onset | Obesity usually present | Usually undernourished |
| Symptoms | Maybe none | Polydipsia, polyphagia, and polyuria |
| Hepatomegaly | Uncommon | Rather common |
| Stability | Blood sugar fluctuations are less marked | Blood sugar fluctuates widely in response to small changes in Insulin dose, exercise, and infection |
| Control of Diabetes | Easy, especially if patient adheres to proper diet | Difficult |
| Ketosis | Uncommon except in the presence of unusual stress or moderate-to-severe sepsis | Frequent, especially if treatment program is insufficient in food and/or Insulin |
| Plasma Insulin (Endogenous) | Plasma-insulin response may be (1) adequate but delayed so that postprandial hypoglycemia may be present when diabetes is discovered or (2) diminished but not absent | Negligible to zero |
| Vascular Complications of Diabetes and Degenerative Changes | Frequent | Infrequent until diabetes has been present for perhaps 5 years |
| Diet | If diet is utilized fully, hypoglycemic therapy may not be needed | Mandatory in all patients |
| Insulin | Necessary for 20 to 30 percent of patients | Necessary for all patients |
| Oral Agents | Efficacious | Rarely efficacious |

*This age level is arbitrary. Intensive screening programs, especially when glucose tolerance tests of "nondiabetic" relatives of diabetics are carried out, are detecting patients who are likely to have ketosis-prone diabetes before disease progresses to the stage of growth-onset diabetes.

These are described in the chapter on "Chronic Complications of Diabetes." There is a third member in the diabetic triad—neuropathy. It is thought by some to be due to the metabolic defect[1] and by others to be the result of vascular disease.[2]

## CARBOHYDRATE TOLERANCE TESTS




Although a number of tests may be utilized in the diagnosis of diabetes, the most commonly accepted one is an oral glucose tolerance test. This may consist merely in determining the blood sugar in a fasting state and two hours after a meal containing approximately 100 Gm. of carbohydrate. (In a nondiabetic, the blood sugar returns to normal level within two hours after glucose loading.) A more satisfactory method is the *standard glucose tolerance test*, in which 100 Gm. of carbohydrate (or 1.75 Gm. per Kg. of body weight) are administered and the blood sugar is determined at 30, 60, 90, 120, and 180 minutes and, in selected cases, at four, five, and six hours.

Because it is less expensive and more convenient than the standard oral glucose tolerance test, the *two-hour postprandial blood sugar determination* is commonly used as a screening procedure. It places less stress on patients whose diabetes is moderate to markedly severe. However, when carbohydrate intolerance is mild (i.e., the fasting blood glucose levels are normal and/or the postprandial levels are under 200 mg. per 100 ml.), the standard oral glucose tolerance test is used. In approximately 75 percent of the patients observed[3] in a recent study, the two-hour value of the standard glucose tolerance test was found to be lower than that of the two-hour postprandial blood sugar test.

The criteria for diagnosing diabetes by means of the standard oral glucose tolerance test differ from clinic to clinic and author to author.[4-8] The critical blood sugar levels used by various authorities are compared in Table 2 and Figure 2.[9] Four factors must be considered in the interpretation of these results. First, when a diagnosis of true diabetes mellitus is made, a number of conditions and situations which also may result in diminished carbohydrate tolerance must be excluded. These are listed in Table 3.

*Diagnosis*

Second, it must be recognized that the criteria in Table 2 may have diminishing value in older patients. The Tecumseh[10] and other studies have shown that the incidence of "abnormal" carbohydrate tolerance ranges from 53[11,12] to 100 percent[13] in older patients. The work of Streeten *et al.*[14] has demonstrated that carbohydrate intolerance occurs in 77 percent of elderly subjects. The latter workers assert that this abnormal tolerance of the elderly is related neither to delayed absorption of administered glucose nor to impairment in the secretion of insulin but rather to a higher level of a circulating insulin antagonist or some other form of peripheral defect in the glucose uptake from the blood.

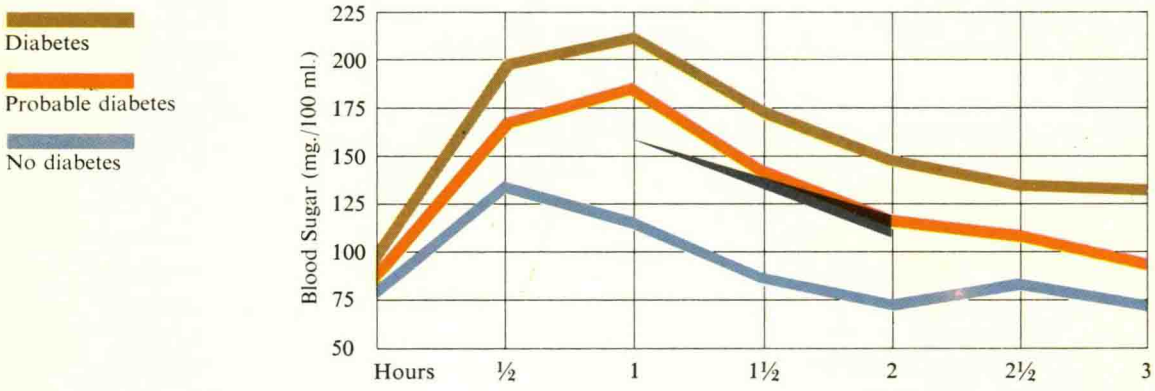
*Age*

**Table 2. Criteria for Diagnosis of Diabetes with Standard Glucose Tolerance Test**

| | VENOUS BLOOD SUGAR (TRUE GLUCOSE IN MG. PER 100 ML.)* | | | | |
|---|---|---|---|---|---|
| | FASTING | 1/2 HOUR | 1 HOUR | 1 1/2 HOURS | 2 HOURS |
| Normal | <100<br>**<100** | <160<br>**<160** | <160<br>**<160** | | <100<br>**<110** |
| Probable diabetes | Normal or <110-120 | 130-159 | 160-180<br>**>160** | **>135** | 110-120<br>**>110** |
| Diabetes | Normal or >110 | >150<br>**>160** | >160 | **>140** | **>120** |

*The values in regular type were assigned by Duncan;[7] those in bold type, by Fajans.[5]

**Figure 2. Criteria Used for Interpretation of Glucose Tolerance Tests**




The wedge-shaped area marks the border line between "normal" and "abnormal" results.

**Table 3. Clinical Conditions Which May Lead to an Abnormal Oral Glucose Tolerance Test**

- Improper feeding before the test
- Malnutrition
- Obesity
- Infection
- Fever
- Endocrine abnormalities
  - Hypothyroidism and hyperthyroidism
  - Pituitary disorders
  - Acromegaly
  - Adrenal cortical hyperfunction
  - Pheochromocytoma
- Renal disease
- Intracranial tumors
- Advanced age
- Neoplastic disease
- Medications such as thiazide diuretics, steroids, epinephrine, and morphine
- Nonhereditary conditions associated with diabetes
  - Hemochromatosis
  - Pancreatitis
  - Carcinoma of the pancreas
  - Pancreatic trauma
- Postgastrectomy syndrome
- Islet-cell tumors
- Lipid disorders, including lipoatrophic diabetes
- Burns and surgery
- Psychological factors*

*In view of the fact that these represent stress, a resulting abnormal glucose tolerance test probably indicates the presence of true diabetes.

Pozefsky *et al.*,[15] using cortisone-glucose tolerance tests, noted that "during the second hour of the test, tolerance declined progressively with advancing age. The age-related loss of tolerance was greatest at 120 minutes, amounting to an average increase in blood glucose level of 17.6 mg./100 ml. for each successive decade of life." They conclude that because of this influence of age on glucose tolerance, the standards for normality for younger persons cannot be applied to the elderly. They propose a scheme whereby normal values for the cortisone-glucose tolerance test can be established by reference to the performance of individuals who are of comparable age.

*Reproducibility*

A third point to be considered in interpreting the results of a given glucose tolerance test is the lack of their reproducibility in both normal and diabetic subjects. McDonald *et al.*,[16] using the modified criteria of Fajans and Conn,[17] found an incidence of 1 percent of abnormal tests on at least one of six tests given over a one-year period to 334 normal subjects. In diabetes, also, the degree of carbohydrate intolerance may fluctuate; a test may be normal one time, but marked intolerance may be noted at another.[16] This phenomenon is demonstrated in Table 4 (page 9), which presents the degree of variability of carbohydrate tolerance in the various stages of diabetes. The extreme situation is represented by occasional reports of the total remission of severe diabetes.[18-20] The occurrence of these variations indicates that a single glucose tolerance test may not necessarily rule out the presence or absence of diabetes. However, in most instances, three or four additional tests at intervals of two to three months will usually settle the question.

*Capillary versus venous blood*

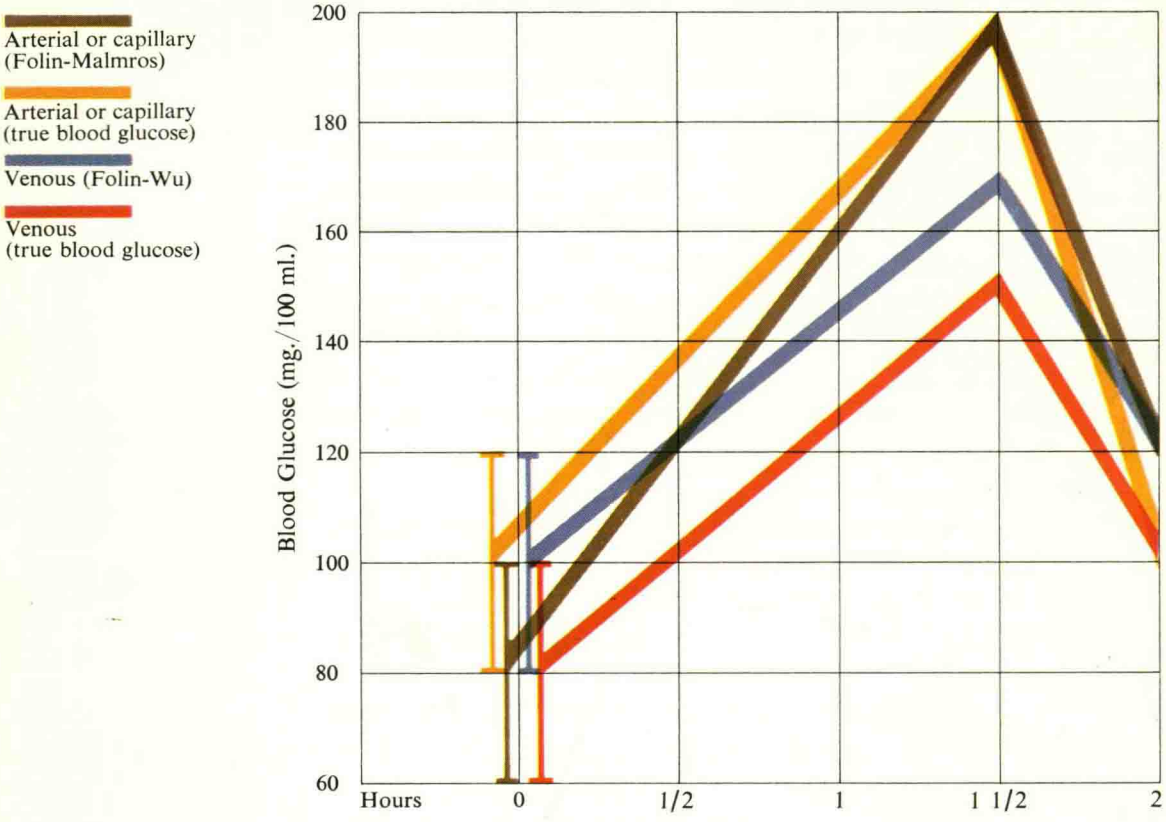
A fourth factor is related to the source of the blood sample and the method of analysis employed to determine its glucose content. For instance, when the Folin-Wu method (which measures all reducing substances) is used, about 20 mg. per 100 ml. should be subtracted in order to convert the value obtained to the "true glucose"* level. Furthermore, there are differences in the sugar content of capillary and venous blood. Therefore, when a specimen (capillary blood) is collected by a finger prick, 30 mg. per 100 ml. should be deducted to convert the value to a true glucose level (Figure 3).[8]

In addition, since the glucose concentration is considerably higher in plasma than in red cells, the hematocrit of the samples being tested must be taken into consideration.[21, 22] It has been reported[21] that a 10 percent variation in the hematocrit will result in a blood sugar change of 3.6 mg. per 100 ml. in the opposite direction. Hence, mild abnormalities in glucose tolerance observed in anemia may be apparent and not real.

Other tests used in the diagnosis of diabetes are the intravenous glucose tolerance test, the cortisone-glucose tolerance test, and the oral and

*The only method that measures glucose per se is one which utilizes the enzyme glucose oxidase. However, extensive studies have shown a marked similarity between the levels obtained when this enzyme is used and those obtained with analysis of sugar filtrates by means of the Somogyi-Nelson and Autoanalyzer® methods.

**Figure 3. Normal Values for the Standard Oral Glucose Tolerance Test**




*Other tests*

intravenous tolbutamide tolerance tests. The *intravenous glucose tolerance test* is used in such situations as disorders of the small bowel, hyperthyroidism, and certain research when it is desirable to avoid variations in glucose absorption that may occur with the oral tests. The technic of the intravenous glucose tolerance test varies. The dose of glucose is usually 0.5 Gm. per Kg. This may be administered as a 20 percent solution over a twenty-minute period or as a 50 percent solution over a three-minute period. In both methods, multiple venous or capillary blood specimens are taken for average periods of one to two hours. The interpretation of results depends upon the method used but is based principally on the rate of fall of the glucose level from the peak obtained after infusion of the glucose. The details of this test have been reviewed by Amatuzio.[23]

The *cortisone-glucose tolerance test* is described in the chapter on "Diabetes and Heredity." The use of the *tolbutamide tolerance test* has been discussed by several authors.[24-26] These latter procedures may have special value in determining the presence or absence of diabetes when this is unresolved by a borderline standard oral glucose tolerance test. However, because the oral route of administration of glucose more nearly simulates physiological conditions, the oral glucose tolerance test remains the workhorse for diagnosis of diabetes.

## STEROID DIABETES

"Steroid diabetes" is the name given to an impairment in carbohydrate metabolism resulting from the use of the various adrenal corticosteroids. Although this side-effect is most often observed when the agents are used systemically, in rare instances it may occur following the topical application of steroids in the treatment of dermatologic disorders.[27] Those glucocorticoids apparently associated with the greatest impairment of carbohydrate metabolism are characterized by the presence of an 11-oxy group.

*Diminished carbohydrate tolerance*

The diminished carbohydrate tolerance is the result of several mechanisms. The principal one is the increase of glucose production by the liver as a result of gluconeogenesis (i.e., formation of glucose from fat and protein). There is no evidence that the diabetogenic effect of steroids is due to destruction or more accelerated degradation of insulin. Another mechanism responsible for decreased glucose tolerance is the mobilization of fatty acids from tissue stores (see page 55). There is no evidence, however, that the glucocorticoids have an effect on the intermediary metabolism of lipids. Other mechanisms that have been postulated include an antagonism to insulin action by the growth hormone and decreased utilization of glucose by the tissues.

Steroid diabetes has been reported in 14 percent of patients treated with glucocorticoids for more than three days.[28] This form of diabetes may have several features, including (1) glycosuria with hyperglycemia of varying degree, (2) normal or diminished glucose tolerance, (3) absence of acidosis and acetonuria even when hyperglycemia is marked, and (4) elevated serum pyruvate levels.

In most instances, steroid diabetes is reversed when the drug is discontinued. According to Fajans and Conn[29] and others, however, the occurrence of hyperglycemia and glycosuria in a patient whose pretreatment carbohydrate tolerance was normal may be indicative of true early diabetes mellitus.

## THIAZIDE DIABETES

"Thiazide diabetes" is the name applied to a form of impaired carbohydrate metabolism resulting from the administration of the various thiazide diuretics. The incidence of this side-effect is variable, and the hyperglycemic response may be inconsistent. In some known diabetics, it apparently has occurred immediately upon initiation of thiazide therapy, whereas it has remained mild or is totally absent in others. Ordinarily, the increased hyperglycemia that develops in these diabetics can be counteracted by raising the dose of the hypoglycemic agent the patient is receiving, i.e., a sulfonylurea compound or Insulin.* Although this impairment in carbohydrate intolerance rarely causes serious consequences, diabetic acidosis was found in

*In this book, "Insulin" with a capital letter refers to the commercial product to distinguish it from "insulin," the natural hormone.

two pregnant women after diuretic treatment,[30] pancreatitis occurred in four patients after long-term treatment with the thiazides,[31] and a fatal case of thiazide-induced diabetes has been reported.[32]

Despite considerable research, the mechanism by which this type of carbohydrate intolerance is produced has not been fully defined. Rapoport and Hurd[33] have associated the difficulty with relative hypokalemia. They found that patients treated with thiazides showed improvement in glucose tolerance following the administration of substantial doses of potassium. Reduction in the serum insulin-like activity (ILA) was found to be precipitated or worsened by the use of a thiazide diuretic in four patients with diabetes mellitus.[34] This value rose only partially after discontinuation of the drug.

On the other hand, the diabetogenic effect of these agents may be attributed to increased gluconeogenesis associated with heightened adrenal function, as indicated by a rise in 17-ketosteroid and hydroxycorticosteroid levels after the use of thiazide diuretics.[35]

The effects of thiazide diuretics on carbohydrate metabolism were measured in nine diabetics and three normal controls.[36] No abnormality was demonstrable in the serum insulin-like activity response to glucose, the insulin tolerance test, urinary steroid excretion, serum potassium, serum nonesterified fatty acids, or serum amylase. However, a reduction of glutathione in whole blood was reported in six of seven patients.

On the basis of available information, added impairment of carbohydrate intolerance among diabetic subjects or mild impairment among nondiabetics should be anticipated when thiazides are used. In most diabetics, the diminished carbohydrate tolerance is reversed when the dosage of the hypoglycemic agent—Insulin or sulfonylurea—is increased. The occurrence of this side-effect does not defeat the usefulness of the thiazides.

## STAGES OF DIABETES

The natural history of diabetes, particularly in its early course when the abnormality in carbohydrate metabolism is mild or absent, is becoming an increasingly important field. Diabetes is like a drama, in which the individual's genetic makeup is the stage; his ability to resist the onset of the disease, the hero; and the life stresses, such as obesity, pregnancy, infection, surgery, aging, serious illness, or certain endocrinopathies, the villains.

The first act of the drama is called "*prediabetes*"[37] or, by some, "diabetes pre-mellitus." Strictly speaking, these terms denote the presence of some finding or findings that generally are associated with the eventual development of frank clinical diabetes. Notably absent, however, is evidence of diminished carbohydrate tolerance as indicated by the standard glucose or cortisone-glucose tolerance tests (Table 4).

Since the concept of prediabetes is relatively recent and the spec-

ificity of most of the features has not been firmly established, this diagnosis is usually made retrospectively, i.e., after patients develop frank clinical diabetes.

Findings indicative of prediabetes in a given patient include diabetes in an identical twin or, less likely, diabetes in both parents or close relatives; obesity; diabetes-like vascular manifestations; and, in the female, a history of miscarriages or large babies, toxemia of pregnancy, and other more controversial obstetric associations.[38] The most significant physical change appears to be an increase in the venular-arteriolar ratio in the conjunctiva.[39] Electron microscopy of needle biopsy specimens taken from the earlobe shows venular dilatation with leakage. In addition, thickening of the glomerular basement membrane has been found in a large percentage of patients with a genetic predisposition toward diabetes. Also, biochemical studies indicate that prediabetic patients have increased ILA in their blood.[40] Finally, in a limited number of families with a high incidence of diabetes, a humoral substance (synalbumin antagonist [see pages 15 and 16]) which opposes Insulin action has been demonstrated.[41,42]

*Development of diabetes*

The next step in the progression of the disease is *subclinical diabetes.* At this point, glucose tolerance ordinarily is normal, but carbohydrate intolerance can be demonstrated by means of the cortisone-glucose tolerance test. Also, the standard glucose tolerance test may show abnormal results during pregnancy or stress. Subclinical diabetes is the first stage in which islet-cell decompensation can be said to occur.

When the standard glucose tolerance test becomes abnormal yet the fasting blood glucose levels remain normal, *latent diabetes* is considered to be present. (The Joslin Clinic group does not differentiate between subclinical and latent diabetes. These workers combine subclinical and latent diabetes in a category they call "chemical diabetes.") Finally, when the

**Table 4. Metabolic and Vascular Changes in Various Stages of Diabetes**

| DIABETIC STAGE | CARBOHYDRATE TOLERANCE | | | INSULIN-LIKE ACTIVITY AND SYNALBUMIN ANTAGONIST | VASCULAR CHANGES |
|---|---|---|---|---|---|
| | FASTING BLOOD SUGAR | GLUCOSE TOLERANCE | CORTISONE-GLUCOSE TOLERANCE | | |
| Prediabetes | Normal | Normal | Normal | May be increased | + |
| Subclinical | Normal | Normal (abnormal during pregnancy) | Abnormal | Increased | + |
| Latent | Normal or increased | Abnormal | Test not necessary | Increased | + + |
| Overt | Increased | Test not necessary | Test not necessary | Increased | + + + |

fasting blood glucose levels are consistently abnormal, the term "*overt diabetes*" is used. All four stages are summarized in Table 4.[37]

Treatment of the early stages of diabetes consists in maintaining normal body weight by means of a reasonable diet, daily exercise, and avoidance of infection and factors known to cause metabolic stress. No specific treatment is recommended for prediabetes and subclinical diabetes;[43] however, sulfonylurea therapy is being used in the management of nonobese young patients with subclinical diabetes.[44] Present results indicate improvement in carbohydrate tolerance in the majority of these patients. Overt diabetics, of course, should have their diets adjusted, whether they are receiving hypoglycemic therapy or not.

## PREVALENCE OF DIABETES

Of great importance to the practicing physician is the increased number of patients who have clinical diabetes. There were two million diabetics fifteen years ago; three million currently have the disease; and the U. S. Public Health Service[45] predicts that approximately four million will become clinically diabetic by 1970.

However, it is believed that only about 55 percent of diabetics are recognized. Of the remaining 45 percent, only 1 to 1 1/2 percent are diagnosed each year. Undetected diabetes occurs at a rate of 8.1 cases per one thousand people. The high incidence of diabetes indicates that its presence should be suspected in a large majority of the population. It has been estimated that the number of people who now have or will develop clinical diabetes may exceed 10 percent. Since diabetes is largely a disease of the elderly, it is obvious that practicing physicians will encounter diabetic patients with greater frequency as the number of older people in the American population increases.

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