The Honeyed Siphon: Diabetes Mellitus

Past, Present, and Future

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It has been truly said that anyone who has thoroughly mastered the subject of diabetes mellitus is well on the way to a comprehensive knowledge of human medicine. Not only is diabetes a very common disorder, affecting an estimated 16 million Americans, but it can damage the structure and impair the function of virtually every organ and tissue in the body. It ranks seventh as a cause of death in the United States, and it costs the national economy over $100 billion a year.

Diabetes mellitus is a chronic disorder in which glucose, the principal fuel of cellular metabolism, cannot be taken up and used by cells. In consequence, the level of glucose in the blood rises, and many serious and far-reaching metabolic changes occur in tissues.

During the past decade, more aggressive treatment of diabetes and new methods of monitoring the disorder have become standard. And just within the past three years, several new classes of drugs have been approved by the Food and Drug Administration that provide physicians and patients with unprecedented efficiency and flexibility in controlling diabetes.

This article gives an overview of diabetes mellitus, its nature, complications, diagnosis, and treatment, with an emphasis on newer developments.

History

The disease has been recognized since remote antiquity. Aretaeus of Cappadocia (A.D. 81-138) gave the oldest surviving account of it, vividly describing it as "a melting down of the flesh and limbs into urine." He accurately reported the salient clinical features of diabetes: excessive thirst, increased urine output (the Greek word *diabetes* means 'siphon'), wasting, and a poor prognosis. In the 5th century, the Indian physician Susruta drew attention to the honey-like sweetness of the urine in diabetes. (The Latin adjective *mellitus* means 'honeyed'.)

Late in the 18th century it was discovered that some persons with excessive thirst and excessive urine output do not have sweet urine. This condition was called *diabetes insipidus* (Latin, 'tasteless') and later traced to deficiency of an antidiuretic hormone normally produced by the posterior lobe of the pituitary gland.

For many centuries diabetes mellitus was assumed to arise in the kidneys, and effective treatments simply did not exist. The first step toward an understanding of the true etiology of the disease came as recently as 1889, when von Mering and Minkowski discovered that removal of the pancreas from an experimental animal induced a condition similar to naturally occurring diabetes mellitus in human beings.

The pancreas had long been recognized as the source of a digestive juice released by a duct into the small intestine. Histologic study of the pancreas showed, in addition to the glandular tissue that produces this digestive fluid, aggregations of cells of a different kind, which were called the islets of Langerhans. In some diabetics, distinctive changes were noted in these cells.

In 1921, Frederick G. Banting and Charles H. Best succeeded in extracting from animal pancreases a principle that, when injected into persons with diabetes, brought down their blood glucose levels and largely corrected their disordered metabolism. This principle was called **insulin**, from *insula*, the Latin word for 'island'.

It was determined that insulin is produced by the B, or beta, cells of the islets of Langerhans. Biochemical analysis showed it to be a polypeptide, that is, a molecule consisting of amino acids strung together in long chains, with a molecular weight of about 6,000. The A chain of insulin consists of 21 amino acids, the B chain 30. The chains are bonded together by two disulfide bridges, one near each end of the molecule.

Insulin was found to regulate carbohydrate metabolism by mediating the rapid transport of glucose and amino acids from the circulation into the cells of muscle and other tissues. Insulin also promotes the storage of glucose in liver cells in the form of glycogen, while inhibiting the breakdown of protein to yield glucose (a process called *gluconeogenesis*).

The normal stimulus for the release of insulin from the pancreas is a rise in the concentration of glucose in circulating blood (usually called, somewhat carelessly, "blood sugar"). Such a rise typically begins within a few minutes after eating a meal. When it elicits an insulin response, so that the level of glucose in the blood falls again as it is taken into cells, *glucose tolerance* is said to be normal. The central fact in diabetes mellitus is an impairment of glucose tolerance to such a degree that symptoms result.

Being a polypeptide, insulin is broken down by digestive enzymes, and even today continues to defy attempts to make it effective when administered orally. But even though Banting and Best's insulin had to be injected daily, it enabled persons with diabetes to lead relatively normal lives for the first time and greatly prolonged their life expectancy.

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Types and Causes

The tendency of diabetes to run in families had long been noted. At first the disease was assumed to be an inherited disorder of the pancreas, in which insulin production sooner or later failed. But it gradually became evident that such a simple explanation simply did not cover the facts. Persons whose pancreases have been removed develop diabetes that can be controlled with insulin in a dose of 15-20 units a day. On the other hand, some persons with naturally occurring diabetes require as many as 200 units a day.

Experimental animals whose pancreases have been removed develop a much milder diabetes if their pituitary glands are removed as well. Excessive levels of cortisol, a secretion of the adrenal cortex, can impair glucose tolerance and induce a condition like diabetes mellitus. In response to a drop in blood glucose, the alpha cells of the pancreatic islets produce a polypeptide hormone, glucagon, that raises blood glucose by causing breakdown of glycogen and protein in the liver. The analysis and coordination of the complexities of carbohydrate metabolism is an ongoing process.

Today we recognize that diabetes mellitus is not one disease but a group of disorders having in common the inability of the body to use glucose properly. While a few persons have a genetic inability to synthesize chemically normal insulin, for the vast majority of diabetics that is not the problem at all. Most cases of diabetes fall into one of two classes: type 1, until recently called insulin-dependent diabetes mellitus (IDDM), and type 2, until recently called non-insulin-dependent diabetes mellitus (NIDDM).

By definition, in *type 1 diabetes* (formerly called *juvenile-onset diabetes* because it generally appears before age 25) injections of insulin are a condition of survival. Persons with this disorder have little or no ability to produce insulin from their beta cells. The etiology is complex and poorly understood. A genetic component is recognized, but only about 50% of identical twins of type 1 diabetics will develop the disease. Current theories focus on *autoimmunity* (production by the immune system of antibody to insulin), perhaps induced by infection with certain viruses that attack the pancreatic islets. High blood glucose levels can actually damage islet tissue and aggravate the diabetic state. Type 1 diabetes is occasionally seen in very young infants, but onset is usually during childhood or adolescence. The disorder is irreversible.

Because persons with *type 2 diabetes* (formerly called *adult-onset* or *maturity-onset diabetes*) retain a variable amount of beta cell function, they do not require insulin for survival. Many of them, however, must eventually take insulin in order to achieve satisfactory control of blood glucose levels. Hence the terms *insulin-dependent* and *non-insulin-dependent* are no longer in favor. In type 2 diabetes the genetic element is far more prominent: virtually 100% of identical twins of type 2 diabetics will eventually become diabetic also. Type 2 diabetes is far more common than type 1, accounting for about 95% of all cases of diabetes mellitus diagnosed. Persons with this disorder show one or both of two biochemical abnormalities: inadequate insulin production in response to a rise in blood glucose, and insulin resistance.

Insulin resistance means the failure of insulin to perform its expected function, the transport of glucose into cells. This is a peripheral phenomenon—that is, it happens at the cellular level, and can occur even when the quality and quantity of insulin produced by the pancreas are normal. It apparently results from a decrease in the number of insulin receptor sites on cells, from a malfunction of the biochemical glucose transport system, or both. Insulin resistance is often associated with high levels of circulating antibody to insulin receptors. Thus, while type 1 diabetes seems to be due to autoimmunity to one's insulin-producing beta cells, the problem in type 2 diabetes may be autoimmunity to insulin receptor sites on muscle and other body cells.

The phenomenon of insulin resistance explains why some persons with type 2 diabetes have *hyperinsulinemia*—markedly elevated blood levels of insulin in the fasting state, often coexisting with elevated blood glucose levels. Insulin resistance correlates closely with obesity in diabetes. It occurs less frequently in lean diabetics, whose principal problem is usually primary failure of insulin production. Insulin resistance is often seen in persons with or without frank diabetes who have other endocrine or systemic disorders, including dyslipidemias, hypertension, hyperuricemia, and chronic infection. Some women with polycystic ovaries, hirsutism, and anovulation also have insulin resistance and hyperinsulinemia.

Diagnosis

The classical symptoms of diabetes mellitus are polyuria (increased volume of urine), polydipsia (excessive thirst), polyphagia (excessive hunger), weakness, and weight loss. Some patients experience itching, visual disturbances, or other symptoms.

The excessive urine output in diabetes is a result of osmotic diuresis. Normally any glucose that is filtered from the blood by the renal glomeruli is taken back into the circulation as the glomerular filtrate passes through the renal tubules, so that no glucose appears in the urine. When, however, the blood glucose level exceeds the so-called renal threshold of about 180 mg/dL, the tubules are unable to reabsorb all of the filtered glucose, and some of it appears in the urine.

In addition, as the glucose-rich filtrate passes through the tubules, it "pulls" water from the circulation in a fruitless effort to restore osmotic equilibrium. The result is an increase in the volume of urine excreted. Increased urine output leads to dehydration and causes thirst, which is followed by increased fluid intake and further diuresis.

Highly specific diagnostic criteria for diabetes mellitus have been established by the American Diabetes Association and sister organizations throughout the world. The figures given below follow revisions published in 1997. All criteria depend

on determination of the glucose concentration of venous plasma. Blood glucose levels may be tested after an 8-hour fast, at specified intervals postprandially (that is, after a meal) or after a measured glucose load, or at random. The 2-hour postprandial level is most valuable in ruling diabetes in or out. In normal persons the fasting blood sugar (FBS) should not exceed 110 mg/dL (6.1 mmol/L) and the 2-hour postprandial blood sugar (2-hr PPBS) should not exceed 140 mg/dL (7.8 mmol/L).

In a glucose tolerance test (GTT), the fasting blood sugar is first determined; the subject then receives a measured dose of glucose (usually 75 g; less in children) orally; and blood glucose determinations are performed at fixed intervals afterwards, usually at 1/2 hour, 1 hour, 2 hours, and 3 hours. (A 5-hour glucose tolerance test may be performed to document hypoglycemia, but is not useful in diagnosing diabetes mellitus. The glucose load may be given intravenously when impairment of carbohydrate absorption from the gut is suspected, but again this is not relevant to the diagnosis of diabetes.)

In a person with classical symptoms of diabetes mellitus, a blood glucose over 200 mg/dL (11.1 mmol/L) is considered diagnostic of the disease. Even in the absence of such symptoms, a fasting blood sugar level over 126 mg/dL (7.0 mmol/L) on two occasions is likewise diagnostic of diabetes mellitus. And even when the fasting blood sugar level is under 126 mg/dL, a positive diagnosis can still be made when on two occasions a glucose tolerance test shows the 2-hour level, and at least one intervening level (that is, at 1/2 hour, 1 hour, or both), to be at or above 200 mg/dL.

A person who does not meet diagnostic criteria for diabetes mellitus is said to have *impaired glucose tolerance* (IGT) if the FBS is less than 126 mg/dL and the 2-hour PPBS is between 140 and 200 mg/dL with at least one intervening value at or above 200 mg/dL. Persons with impaired glucose tolerance are at risk of developing frank diabetes mellitus. They do not require drug treatment but their blood glucose must be monitored at intervals and they are advised to be careful about diet, exercise, and weight. In the past, the terms *latent diabetes*, *subclinical diabetes*, *chemical diabetes*, *prediabetes*, and *potential diabetes* have been used for impaired glucose tolerance. The American Diabetes Association has formally declared all these terms obsolete.

Before proceeding to a discussion of the pathophysiology and treatment of diabetes mellitus, we should look at two important variant forms of the disease. *Gestational diabetes* is defined as carbohydrate intolerance of variable severity with onset or first recognition during pregnancy. Gestational diabetes occurs in 3-6% of all pregnancies, and although it typically resolves after delivery, as many as 60% of women with this disorder will eventually develop type 2 diabetes.

Diabetes occurring during pregnancy increases the risk of maternal pyelonephritis and of certain congenital anomalies. In addition, it is often associated with polyhydramnios (excessive volume of amniotic fluid) and fetal macrosomia (abnormally large fetal size), often leading to dystocia (difficult delivery).

It is recommended that all pregnant women be screened for gestational diabetes between the 24th and 28th week of pregnancy. Screening is performed by determining the plasma glucose one hour after a 50 g oral glucose load. A level above 140 mg/dL (7.8 mmol/L) is an indication for a 3-hour glucose tolerance curve. Gestational diabetes can usually be managed by diet alone, but insulin may be required.

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Secondary diabetes is an impairment of glucose tolerance resulting from some other disease or extraneous factor. Pancreatectomy and chronic pancreatic disease (chronic pancreatitis, hemochromatosis) abolish or impair the normal insulin response to a rise in blood glucose. In certain endocrine diseases (Cushing disease, acromegaly), circulating substances can block the effect of insulin and induce clinical diabetes. Some drugs (thiazide diuretics, adrenocorticosteroids) reversibly impair glucose tolerance. In some genetic disorders, including muscular dystrophy and Turner syndrome, there is a predisposition to the development of diabetes.

Pathophysiology and Complications

As mentioned earlier, the effects of the diabetic state on general health and survival are widespread and potentially devastating. The most acute complication of diabetes mellitus is ketoacidosis, which by definition occurs only in type 1 diabetes. *Diabetic ketoacidosis* is a medical emergency; without treatment it can progress to coma and death. Occasionally it is the presenting symptom of previously unsuspected diabetes. It can also occur in previously controlled type 1 diabetes if the patient becomes careless about diet or insulin, abuses alcohol, or contracts a severe infection.

The diabetic with severe insulin deficiency may be said to be "starving in the midst of plenty." That is, although the blood glucose concentration may be more than ten times normal, hardly any of this glucose is getting into cells, and the body responds in much the same way as it does in starvation. Two important mechanisms by which the body conserves its most vital functions during periods of starvation are the production of glucose by the breakdown of glycogen (glycogenolysis) and the production of ketones by the breakdown of fatty acids. Both of these processes occur in the liver.

Clearly the production of more glucose is just what the diabetic doesn't need. And although ketones can be utilized as an emergency fuel by brain and muscle tissue during starvation, ketone production gets hopelessly out of control in diabetes. The buildup of acidic ketones (beta-hydroxybutyric acid and acetoacetic acid) in the blood induces a condition of *acidosis*. This acidosis, combined with extreme hyperglycemia, results in severe osmotic diuresis and dehydration. Hence a catastrophic cascade of biochemical derangements leads rapidly to a life-threatening metabolic emergency.

Patients with type 2 diabetes occasionally develop a similar disorder, which has been called *nonketotic hyperosmolar syndrome*. This is more likely to develop in elderly patients, particularly those with impaired renal function, severe infections, or

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other systemic conditions. Even though ketosis does not occur, severe hyperglycemia, osmotic diuresis, and dehydration lead to a rise in the osmolality (the concentration of osmotically active particles—here chiefly glucose molecules) of the serum, with potentially lethal consequences.

Limitations of space will not permit an exhaustive discussion of the more chronic complications of diabetes, but the principal ones must be mentioned. Diabetes mellitus has long been recognized as an independent risk factor for cardiovascular disease. In simple terms, the hyperglycemic state is toxic to blood vessels. Moreover, diabetes is often associated with other risk factors, including disorders of lipid metabolism (specifically elevated serum cholesterol), obesity, hypertension, and impairment of renal function.

Coronary artery disease leading to angina pectoris, heart attack, or congestive heart failure; cerebral vascular disease leading to dementia or stroke; and peripheral vascular disease leading to intermittent claudication, erectile dysfunction, or gangrene of an extremity requiring amputation, are known as macrovascular complications of diabetes. More subtle, but equally devastating, are the microvascular complications: retinopathy, nephropathy, and neuropathy.

Diabetic eye disease is responsible for approximately 25% of all newly reported cases of blindness in the United States. The principal form of diabetic eye disease is a condition called nonproliferative retinopathy, which results directly from degenerative changes in retinal capillaries. Features of nonproliferative retinopathy that can be observed on funduscopic examination include microaneurysms; "soft" or "cotton wool" exudates, which are really areas of microinfarction; "hard" or "waxy" exudates, which are deposits of lipid and protein from leaking capillaries; and "flame" hemorrhages (the term refers to their shape).

A few patients, principally those with type 1 diabetes, develop a proliferative retinopathy characterized by neovascularization—the proliferation of new capillary loops on the retinal surface. Both types of retinopathy can impair vision by the direct destruction of retinal tissue and also by predisposing to retinal edema, detachment of the retina, and severe hemorrhage into the vitreous. Diabetics are also at increased risk for both glaucoma and cataracts. In addition, hyperglycemia often causes visual blurring. Hence the earliest sign of diabetes may be the need for frequent changes in lens prescription.

The principal impact of diabetes mellitus on the kidney takes the form of a distinctive type of degeneration in the basement membrane of the glomeruli. The earliest sign of diabetic nephropathy is the appearance of protein in the urine. Patients with significant and persistent proteinuria typically progress to renal failure within a few years.

Diabetic neuropathy can take many forms. Involvement of one or several peripheral sensory nerves can lead to hypesthesia, hyperesthesia, paresthesia, or burning pain. Involvement of the autonomic nervous system can lead to delayed gastric emptying, urinary bladder dysfunction, diarrhea, and erectile impotence.

In addition to these complications, persons with diabetes are more prone to infection, including urinary tract infection, candidal vaginosis, and candidal and staphylococcal infections of the skin, and to a number of other cutaneous disorders.

Treatment

Diabetes is a lifelong disease and one in which the type and aggressiveness of treatment profoundly affect the prognosis. Currently the central goal of treatment is to maintain blood glucose levels as close to normal as possible at all times. Recent studies have shown that tight control of blood glucose levels can significantly prevent or retard the development of microvascular complications, and most authorities believe that the same will eventually be shown for other complications. In one sense, the most important role of the healthcare provider in diabetes is in educating and motivating the patient and in providing psychological support.

The basis of all treatment in diabetes is careful control of diet, maintenance of a healthy weight, and adequate exercise. Standard diets providing an appropriate balance of carbohydrate, fat, and protein for any desired level of calories have been in use for many years. These diets are based on the exchange system. Foods are divided into groups on the basis of their nutritional composition. The patient is permitted a certain number of exchanges from each group at each of four meals—breakfast, lunch, dinner, and bedtime snack. Diabetics who take insulin must follow caloric restrictions closely and adhere to a tight meal schedule in order to maintain adequate control of blood glucose and avoid insulin reactions. It is currently recommended that a registered dietitian be involved in the initial dietary instruction of diabetics and their families, and be consulted as the disease evolves and dietary needs change.

The first insulin products made from animal pancreases were administered in as pure a state as could be attained by the pharmaceutical manufacturing methods of 75 years ago. As with other biologicals, the dosage of insulin was measured in units of activity rather than in milligrams. (For many years insulin was produced in two strengths, 40 U/mL and 80 U/mL, called simply U-40 and U-80. During the 1980s the international medical community instituted a change to a single concentration, U-100.)

The subcutaneous route of administration was found to be most satisfactory, and diabetics quickly learned to give their own injections. Because the effect of a single injection of "pure" insulin wore off in a few hours, it was necessary to administer several injections a day. Hence a number of products were developed in which insulin was bound to substances such as protamine and zinc that retarded their absorption from the injection site.

These products allowed the typical diabetic to maintain fair control with only a single morning injection. Unmodified insulin (now universally called regular insulin) remained a valuable resource to correct the occasional spell of hyperglycemia,

particularly because it could be given intravenously when rapid onset of action was needed. Some diabetics achieved the best control when they mixed two types of insulin together and administered them as a single injection.

Delayed-action insulins remain essential tools in the control of diabetes. They are often called "cloudy" insulins because, unlike regular insulin, they contain visible suspended material and must be shaken before being drawn up into a syringe. Table 1 shows intervals between administration and the onset, peak, and duration of biologic action for commonly used insulin products. In addition to these, mixtures of regular and NPH insulin are available in various proportions (70/30 and 50/50) to provide greater flexibility of dosing (a combination of rapid onset and prolonged duration of action).

Table 1. Types of Insulin in Current Use

Type	*Onset (hr)*	*Peak (hr)*	*Duration (hr)*
Regular	0.5	2-4	6-8
NPH	1-2	6-12	18-24
Lente	1-3	6-12	18-24
Ultralente	4-6	8-20	24-48

Most insulin-dependent diabetics nowadays use combinations of shorter- and longer-acting insulins and take two to four injections a day.

Until the 1980s, all insulin used in the treatment of diabetes was prepared from animal pancreases, chiefly beef and pork. The daily injection of this foreign polypeptide resulted in the formation of antibody to the animal insulin. Some patients became so allergic to insulin that they were unable to use it. Many developed skin dimpling at their usual injection sites because of local atrophic reactions mediated by the antibody.

For these reasons, and because the demand for insulin threatened to outstrip the supply, recombinant DNA technology was used to program cultures of nonpathogenic bacteria or yeasts to synthesize a hormone that is chemically identical to human insulin. Although human insulin is more expensive than animal insulins, it is gradually replacing the natural products, and most new diabetics are started on it.

Each patient's insulin dosage requirements are highly individual and depend on the type and severity of disease, lifestyle and activity level, dietary habits, and other less tangible variables. Not only the appropriate total daily insulin dosage but also the number of injections, the types of insulin used, and the fraction of the total dose administered in each injection, must be determined by trial and error.

Early in the treatment of type 1 diabetes, relatively low doses of insulin may suffice for a time (the so-called *honeymoon effect*) even though, later on, the dosage must be increased. In so-called *brittle diabetes*, wide and unpredictable variations in insulin requirements can occur from day to day. Exercise improves glucose tolerance and lowers the need for insulin; inactivity and infections, including the common cold, impair it and raise the need for insulin.

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An overdose of insulin, or an appropriate dose followed by strenuous exercise or inadequate food intake, can lead to hypoglycemia. This so-called insulin reaction is characterized by tremors, cold sweats, hunger, lightheadedness, restlessness, and confusion. If severe and untreated it may progress to seizures, coma, and death. The treatment is to administer glucose, orally if possible, otherwise intravenously.

An insulin pump is a compact, battery operated device controlled by a computer chip. It contains a reservoir of insulin and delivers this at a predetermined rate by way of a fine plastic tube connected to a needle inserted under the skin of the abdomen. The needle is changed every two or three days. The pump provides a steady infusion of insulin, with increased doses as needed, thus obviating the need for several needle sticks each day. This device is ideally adapted to the needs of certain diabetics, but it is not automatic or autonomous. The wearer must program it to deliver a steady flow of insulin at a low dosage and also a larger bolus injection for each meal.

An important recent advance has been the modification of the natural insulin molecule by rearrangement of two of its amino acids to produce an insulin with a much faster onset of activity, which reaches its peak effect earlier than regular insulin. This modified insulin is produced by a nonpathogenic strain of *E. coli* that has been genetically programmed for the purpose. Since the difference between this new insulin and the natural hormone consists in the transposition of the amino acids lysine (Lys) and proline (Pro) near the end of the B chain, the new product is called *lispro insulin*.

Lispro insulin, marketed as Humalog, has the same molecular weight and the same biochemical functions as the natural hormone. When administered intravenously, its effects are virtually indistinguishable from those of regular insulin. However, when it is injected subcutaneously, it reaches its peak serum level in 30-90 minutes, as compared to 50-120 minutes for regular insulin. It also has a shorter half-life, that is, its biologic effects wear off faster than those of regular insulin.

The advantage of lispro insulin is that patients who need to take insulin before each meal to achieve adequate control of their diabetes can inject it within 15 minutes before meals, instead of 30-60 minutes before meals as needed with regular insulin. Lispro insulin has found its principal use in those type 2 diabetics for whom oral agents provide inadequate control of meal-related rises in blood glucose. Because of its rapid onset and short duration, it cannot be used alone by type 1 diabetics, who need a longer-acting insulin to maintain long-term control of blood glucose. Unlike other insulins, lispro insulin is not available without a prescription. It is not recommended for use in pregnancy because its effects on the fetus have not been assessed.

For many years, insulin-dependent diabetics monitored their blood glucose by testing their urine for glucose four times a day. Testing was rendered simple by the availability of home test kits. Reagent tablets added to a dilute urine specimen in a test tube yielded a color reaction giving a rough estimate of the amount of glucose present. Later kits featured test tape to be dipped into undiluted urine or held in the urine stream during voiding. Diabetics subject to ketosis also tested their urine for acetone by a similar test procedure.

Although these urine sugar tests were simple and inexpensive, they were also highly imprecise, since they reflected blood glucose levels prevailing some hours before the specimen was obtained, were sensitive to variations in renal function and water balance, and could not detect hypoglycemia.

The development of simple and relatively inexpensive methods by which the patient can perform self-monitoring of blood glucose levels has permitted a much more precise regulation of diabetic control, including early detection or prevention of hypoglycemia. All of these methods use fingerstick blood and provide quantitative readings of glucose level that are accurate within 10-20 mg/dL. With the less expensive methods, the patient places a drop of blood on a test strip and observes a color change. A number of portable, battery-operated electronic devices are available that give a digital readout of the glucose level.

The frequency and timing of self-monitoring depend on the needs of the individual. Rigorous control of type 1 diabetes typically requires testing at least three or four times a day. Testing may be done before meals, two hours postprandially, and at bedtime. The dosage of insulin is adjusted accordingly.

A single determination of blood glucose reveals the patient's status at a single moment in time, but provides no information about the degree of control even a few hours earlier, much less during the several weeks preceding the test. A different type of test, quantitative measurement of glycosylated (or glycated) hemoglobin, enables the physician to measure long-term control. The A_{1c} fraction of hemoglobin, found in normal red blood cells, forms a stable compound with the glucose of plasma. Measuring the percent of hemoglobin A_{1c} (HbA_{1c}) that has become thus glycosylated gives an estimate of average blood glucose levels during the 8-12 weeks preceding the test. A result of 6% or less is found in persons without diabetes. The goal of treatment is to keep the level at or below 8%. In prospective studies of persons with diabetes, a favorable prognosis with respect to vascular complications correlates closely with glycemic control as measured by the glycosylated hemoglobin.

As mentioned earlier, insulin is often used nowadays in the treatment of type 2 diabetes to improve control of postprandial blood glucose rises. However, patients with this disorder, who make up the great majority of diabetics, often retain considerable functioning islet tissue, and many have more problems with insulin resistance than with insulin deficiency. The basis of therapy in non-insulin-dependent diabetes mellitus therefore consists not in replacing deficient insulin but in attempting to stimulate the pancreas to produce its own insulin, in combating insulin resistance, and in modifying the absorption of dietary glucose.

In about 10% of persons with type 2 diabetes, glucose tolerance can be restored to normal simply by observing a more healthful diet, increasing physical exercise, and losing excessive weight. For patients in whom these measures fail to provide adequate control, drug treatment is indicated. Monotherapy (that is, addition of a single drug to the regimen already in place) is effective, at least when first instituted, for a majority of type 2 diabetics.

The oldest and largest class of oral agents for the treatment of type 2 diabetes are the sulfonylureas, which have been standard therapy for more than 30 years. These drugs, also called oral hypoglycemics, work by stimulating insulin production by the patient's own pancreatic islets. Dosage must be individualized; overdose can lead to hypoglycemia, though seldom as severe as with insulin overdose.

Table 2 lists the sulfonylureas in current use. By and large these are all equally effective. However, newer agents that permit once-daily dosing for some patients are preferable from the standpoint of compliance, and seem less likely to induce hypoglycemia. Sulfonylureas tend to cause weight gain, and in one study their use in type 2 diabetes was associated with a statistically significant increase in the risk of death due to cardiovascular disease.

Table 2. Sulfonylureas (Oral Hypoglycemics)

chlorpropamide (Diabinese)
glimepiride (Amaryl)
glipizide (Glucotrol)
glyburide (Diabeta, Glynase, Micronase)
tolazamide (Tolinase)
tolbutamide (Orinase)

Another class of oral agents useful in type 2 diabetes, currently represented by a single drug, are the biguanides. Because these drugs do not stimulate insulin release, they are referred to as antihyperglycemics rather than hypoglycemics. The biguanides work by increasing the sensitivity of cells to insulin, by decreasing the absorption of glucose from the digestive system, and by inhibiting glucose production in the liver. Unlike the sulfonylureas, they cannot produce hyperinsulinemia or hypoglycemia, and tend to cause weight loss rather than weight gain.

Some readers may remember phenformin (DBI), a biguanide that was taken off the market in 1977 because of the risk of lactic acidosis, a metabolic disorder with a mortality rate of about 50%. The risk of this complication is considerably less with metformin (Glucophage), the biguanide released in this country in 1995, but it still exists, particularly for patients with impaired renal function.

For the many type 2 diabetics in whom insulin resistance is a major problem, a newly released oral agent offers the promise of better control. Troglitazone, marketed as Rezulin, improves glucose tolerance by enhancing the sensitivity of skeletal muscle cells and adipose tissue to the glucose-transporting effect of insulin. Improbable as it may seem, the drug apparently works by binding to receptors in cell nuclei and

changing the genetics of those cells so as to restore their normal sensitivity to insulin. Troglitazone also decreases glucose production by the liver.

Troglitazone does not lower blood glucose directly and has no effect in the absence of insulin. It is therefore indicated principally in the type 2 diabetic with insulin resistance, as manifested by unsatisfactorily high glycosylated hemoglobin levels despite daily insulin doses of 30 U or more. It can be used in combination with other oral agents, insulin, or both. For most patients, troglitazone must be taken for several weeks before its full effects are noted. Blood glucose must therefore be monitored closely to detect decreasing need for other agents. Troglitazone also tends to lower blood pressure and triglycerides. In addition, it is virtually free of side-effects, and the dose need not be reduced in patients with renal failure.

A number of patients taking troglitazone have developed hepatic necrosis, which in a few cases proved fatal. For this reason, in November 1997 the drug was withdrawn in the UK. In this country the manufacturer, with FDA approval, has recommended monitoring of liver function before starting treatment with troglitazone and frequently thereafter. A related agent, rosiglitazone, has not caused hepatic necrosis in limited clinical trials, but has not yet been approved for marketing in this country.

Yet another type of pharmacologic intervention in diabetes is the administration of an oral agent that delays the absorption of glucose from the digestive system. One such drug, acarbose (Precose), has recently been released. Biologically this product is an alpha-glucosidase inhibitor. It blocks the function of enzymes in the lining cells of the proximal small bowel that are concerned with the breakdown of complex dietary carbohydrates into simple sugars, including glucose. The advantage of this blockage is that postprandial rises in blood glucose occur much more gradually. Administered before meals, acarbose can reduce peak postprandial glucose levels by as much as 75 mg/dL. Hence it permits reduction in the dose of oral agents or insulin.

The drug itself is not absorbed into the circulation but acts topically on intestinal lining cells. By itself it cannot induce hypoglycemia, but by reducing the need for insulin, it can increase the risk of hypoglycemia for a given dose of a sulfonylurea or insulin. Its use in conjunction with lispro insulin is not recommended. It is quite safe, but may cause annoying flatulence, bloating, and diarrhea as complex carbohydrates reach the colon instead of being digested and absorbed.

In December 1997 the Food and Drug Administration approved marketing of an oral agent unrelated to previous therapies for diabetes. Like the sulfonylureas, repaglinide (Prandin) induces a release of insulin from the patient's own pancreas. The onset of its action is much more rapid, however, and its duration briefer. Hence it is administered before meals in type 2 diabetes to prevent postprandial hyperglycemia, in much the same fashion as regular and lispro insulins are currently used.

Type 2 diabetes is typically a progressive disorder, in which the endogenous insulin supply tends to wane steadily. Many patients initially managed with diet alone eventually require a sulfonylurea or a biguanide for control, and as their disease progresses many of these will experience secondary failure on an oral agent and require insulin. Currently as many as 40% of persons with type 2 diabetes are taking insulin.

Although pharmacologic treatment is essential to the management of most cases of diabetes mellitus, it is only part of the overall program of care. Education, establishment of clear-cut goals for blood glucose control, and encouragement to follow strict guidelines for diet, exercise, and weight control are also essential. Because of the risk of peripheral vascular disease, persons with diabetes are instructed to maintain rigorous foot hygiene and to report any foot trauma, infection, or ulceration immediately.

Periodic assessment by the physician includes a survey of general health and well-being, a review of blood glucose monitoring and insulin doses, determination of glycosylated hemoglobin, assessment of lipid levels and kidney function, and surveillance for hypertension, cardiac disease, peripheral circulatory disorders, retinal changes, and cutaneous abnormalities.

The frequency of such evaluations depends on the type and severity of diabetes and the preceding history of control and complications. All persons with diabetes are advised to have their eyes examined by an ophthalmologist at least once a year. Testing of urine for microalbuminuria is performed at least once a year to detect the onset of diabetic nephropathy.

The Future

Diabetes mellitus is a common and complicated disease entity with enormous medical, psychological, social, and economic consequences. Whereas, one hundred years ago, a diagnosis of what we now call type 1 diabetes mellitus was tantamount to a death sentence, the disease can now be controlled with minimal impact on lifestyle and restoration of near-normal life expectancy. But diabetics still face a lifetime of rigid dietary control, and many must look forward to several needle sticks a day for blood glucose monitoring and insulin administration.

Current research is pursuing a number of promising leads, such as islet transplants, insulin that can be administered nasally or as eye drops, insulin analogs that can be administered orally, agents to block the autoimmune damage that is responsible for type 1 diabetes, and enzyme inhibitors that can protect blood vessels from elevated blood glucose levels. When one considers the remarkable gains of the past 25 years in the understanding, diagnosis, and therapy of diabetes mellitus, such goals seem eminently attainable.

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