Blood Sugar and the Complications of Diabetes

Sugar itself may damage cells

Diabetes seems to be a grab bag of different disorders. Some diabetics produce too little or no insulin. Some produce a great deal of insulin but release it at the wrong times or fail to respond to it. Some have symptoms of diabetes, such as frequent urination, thirst, or hunger. Some are symptomless. But all of these patients have one thing in common: abnormally high sugar concentration in blood. And nearly all seem to be subject to the complications of diabetes, including heart disease, blindness, cataracts, blood vessel damage, nerve disorders, and kidney damage.

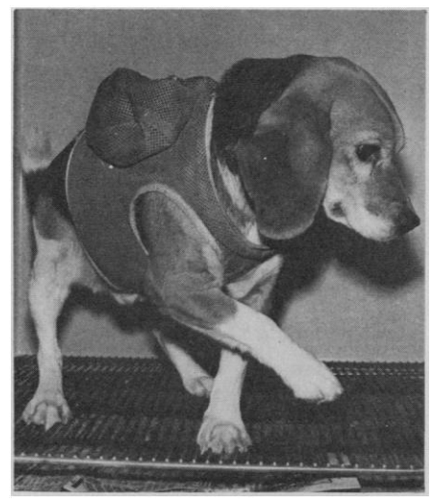
Many physicians believe that they should try their utmost to make their diabetic patients' blood sugar as normal as possible. If the patients developed diabetes as adults and if they are overweight, as most adult-onset diabetics are, doctors urge them to diet. Weight loss alone can eliminate the diabetic state in many of these people. But since most obese patients fail at dieting, many doctors say they should be given oral drugs or insulin to lower their blood sugar, regardless of whether they have any symptoms of diabetes. The argument is that to eliminate the overt physiological abnormality is to prevent the complications of the disease.

Another group of physicians has a different view of blood sugar control. They usually urge strict control of blood sugar for juvenile diabetic patients but not for those with the adult-onset disorder. Although they encourage overweight adult-onset patients to diet, they reserve the use of drugs for their symptomatic patients. These physicians point out that it is clearly hard for patients to maintain so-called strict control of blood sugar. And it has never been proved that strict control prevents the complications of diabetes.

Twenty years ago, there was some hope that the disagreement over how to treat adult-onset diabetics might be resolved. A trial, known as the University Group Diabetes Project (UGDP), was designed to determine whether lowering blood sugar prevents the complications of diabetes (see page 986, 9 March). The trial was carried out in the 1960's. Its results seem to show that treatment does not help adult-onset diabetics, but this conclusion is hotly contested. Most investigators agree that a consensus on how to treat adult-onset diabetics, if it comes at all, will come not from resolving the UGDP controversy, but from basic clinical research.

The question of blood sugar control has been approached from two directions. First are the studies of what high blood sugar does to tissues and organs. Investigators hope to prove that high blood sugar by itself is the cause of diabetic complications and that tight control of blood sugar can prevent, arrest, and possibly even reverse the progress of these complications.

The second type of clinical research is the development of ways to perfectly control blood sugar—that is, to keep sugar concentrations within normal bounds, as in nondiabetic individuals. As yet, no drugs can give perfect control, but perhaps pancreas transplants (the pancreas secretes insulin in response to high blood sugar) or artificial pancreases can. Once blood sugar can be perfectly controlled, it should become obvious whether the complications of diabetes can be prevented. As long as it is only imperfectly regulated, however, the question will remain whether the complications are due to the imperfect control or whether they are correlated with but not caused by the excess sugar in the blood.



Dog wearing an artificial pancreas in a backpack. The apparatus weighs about 1 pound and consists of an insulin pump and a microcomputer which is programmed to control the injection of appropriate amounts of insulin. At present, investigators are substituting these computer-controlled devices for devices that supply insulin in response to an implanted glucose sensor. [Source: A. M. Albisser, Hospital for Sick Children, Toronto]

To understand what high blood sugar does, investigators are asking how, on the molecular level, glucose damages cells. One possible mechanism is that glucose attaches itself to cell proteins, altering their configurations and their functions. A model for how this process may occur was investigated by a number of groups including Anthony Cerami, Ronald Koenig, Charles M. Peterson, and their associates at Rockefeller University and by H. Franklin Bunn, Kenneth Gabbay, and Paul Gallop of Harvard Medical School. These investigators found that glucose attaches, in a process that does not involve enzymes, to the hemoglobin molecules of diabetic patients, thus altering the electrical charges and biochemical properties of the molecules.

The idea that glucose can attach to proteins was nothing new. Food chemists had long known that sugars attach nonenzymatically to proteins in foods, and hematologists had known that about 5 percent of the hemoglobin molecules of normal people contain nonenzymatically attached sugars. But this sort of attachment of sugar molecules to proteins is a slow process, so it normally does not occur to any great degree on proteins that are continually broken down and resynthesized. Even on proteins that, like hemoglobin, are relatively stable, few sugar molecules are expected to attach. Diabetics, however, have so much glucose in their blood that two to three times more hemoglobin molecules than would be expected contain attached glucose.

The discovery of the degree to which glucose attaches to hemoglobin in diabetics has a side benefit that is now being clinically exploited. Red blood cells containing hemoglobin molecules have lifetimes of about 4 months, and once glucose attaches to the hemoglobin molecules it only slowly comes off. Therefore, the proportion of a patient's hemoglobin molecules that have attached sugars is a better index than any-

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thing now available of how well controlled the patient's blood glucose has been for the past few months. This is the first time doctors have been able to assess long-term blood sugar control in an objective way.

Since glucose attaches to hemoglobin, it almost certainly attaches to other proteins in the same way, Gabbay says, and may change these proteins' functions. This alteration of proteins may be the mechanism by which high concentrations of blood glucose damage proteins that are slow to be replaced, such as the lining of blood vessels, and the insulating material around nerve cells.

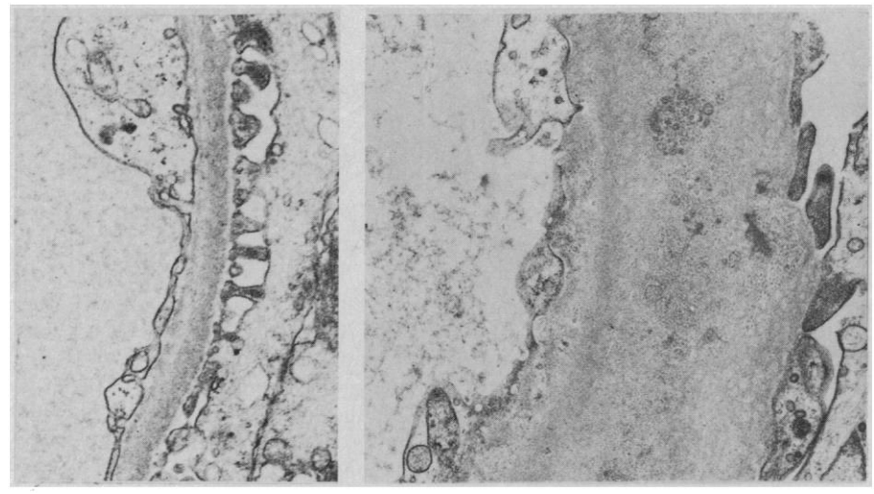
Complications of diabetes may also ensue from an overutilization of glucose by cells. Paradoxically, diabetes was traditionally thought of as a disease characterized by underutilization of glucose. And it is true that certain cells, such as those of fat and muscle, starve for glucose because it cannot enter them unless insulin is present. But the sugar enters many other cells, such as those of nerve and lens, in the absence of insulin. It can be present in such high concentrations in these cells that it damages them.

Cells that have too much glucose start to use minor metabolic pathways to break down the sugar. One of these pathways results in the accumulation of the sugar alcohol sorbitol.

Sorbitol is unique in that it is not metabolized rapidly and cannot leak out of cells. It accumulates in high concentrations in lens cells of diabetic rodents, according to Jin Kinoshita of the National Eye Institute and Shambhu Varma of the University of Maryland. They found that the accumulation of sorbitol causes an osmotic swelling of the lens cells which is characteristic of cataracts. In diabetic rodents cataracts can be prevented with drugs that inhibit aldose reductase, an enzyme that converts glucose to sorbitol. Kinoshita points out that it is not known whether a similar process occurs in humans, but human lens cells contain aldose reductase and swell when they form cataracts.

Sorbitol may also contribute to the damage to peripheral nerve functions that is typical of diabetes. Gabbay and others have shown that sorbitol concentrations increase in cells lining the peripheral nerves of diabetic animals, that these cells swell and become defective in conducting nerve impulses, and that inhibitors of aldose reductase can prevent this swelling and this conduction defect.

Although there is still some question about whether nerve damage is caused entirely by overutilization of glucose, it now seems likely that damage to peripheral nerves is a direct effect of high blood sugar. Conduction of impulses is slowed in both the motor and sensory nerves of diabetic patients because the insulation around the nerve cells has deteriorated. Daniel Porte and his associates at the Veterans Administration Hospital in Seattle find that the amount by which motor nerve impulses are slowed is directly related to the elevation in blood sugar. Moreover, in their preliminary studies, Porte and his associates find that when patients lower their blood sugar, their motor nerve functions improve.



Electron micrograph of basement membrane from normal (left) and diabetic patient (right) showing marked thickening that can occur in diabetics. [*Courtesy: J. Churg, Mount Sinai School of Medicine*]

Porte has not been able to show that sensory nerve damage is also corrected by better blood sugar control. He does not know whether his failure to show this is due to the fact that it is so difficult to accurately measure speeds of nerve impulses in these very small nerves or because sensory nerve damage does not improve when blood sugar is lowered.

In addition to nerve damage and cataract formation, diabetes is also associated with damage to small blood vessels. The lining of these vessels, called the basement membrane, thickens, and at the same time the vessels become more porous. These membrane changes seem to underlie kidney damage in diabetics, for example. In the kidney glomeruli, blood courses through a coil of capillaries from which waste material is filtered into the urine. When the lining of these capillaries becomes more porous, proteins spill out into the urine.

A number of investigators believe that high blood sugar is directly responsible for basement membrane changes in small blood vessels. For example, Robert Spiro and his associates at the Joslin Clinic in Boston find that the membrane proteins have excess sugar added to them and believe that this sugar changes the proteins' configuration. This work is controversial, however, in part because the experiments with the basement membranes are so difficult.

The final answer to the question of whether blood sugar control prevents the complications of diabetes will probably come from the development of a technique for achieving perfect control of blood sugar. Some researchers are trying to develop artificial pancreases to automatically inject insulin in response to fluctuations in patients' blood sugar. Others are studying ways to transplant the islets of Langerhans, the portion of the pancreas that secretes insulin (*Science*, 26 December 1975, p. 1281).

Work on artificial pancreases has gone slowly, mainly because of the problems of developing an appropriate sensor of blood glucose concentration. Work on pancreas transplants has also gone slowly because of the problem of immunological rejection. But the consensus among diabetologists is that one or the other of these techniques will eventually work out.

At the present time, then, there is only suggestive evidence that strict blood sugar control is worthwhile. Many physicians agree with Spiro that it is important to urge young patients, "who have their whole lives in front of them," to strictly control their blood sugar. With older patients, it is not so clear that strict control is necessary, since the patients already have degenerative disorders and strict control may not reverse the complications of their diabetes. So the argument goes on. But the clinical research now being conducted at least holds out the hope that the issue may be resolved.

—GINA BARI KOLATA