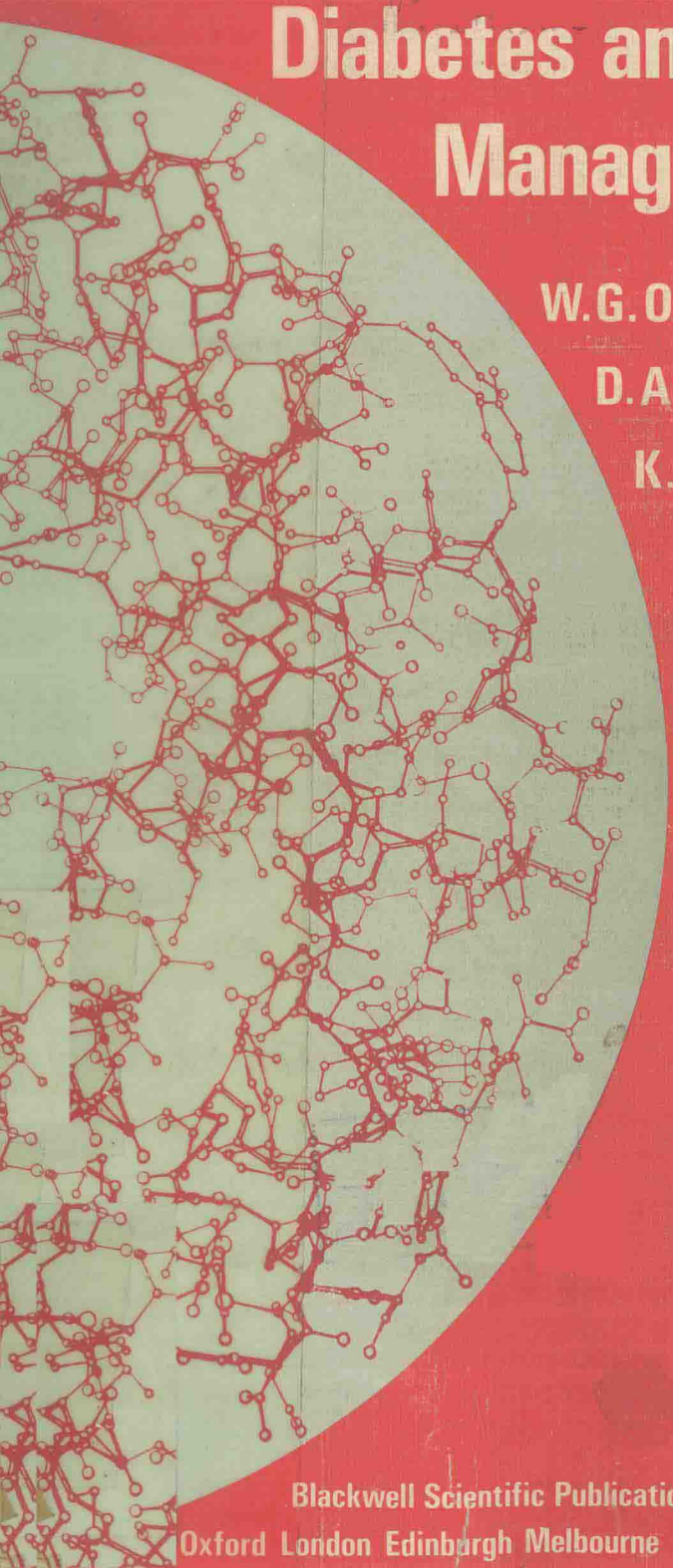
# Diabetes and its Management



W. G. OAKLEY
D. A. PYKE
K. W. TAYLOR

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W. G. OAKLEY
MD, FRCP

D. A. PYKE
MB, FRCP

K. W. TAYLOR
MB, PhD

King's College Hospital
London

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# DIABETES AND ITS MANAGEMENT

# PREFACE

This book has been written as a practical guide to the management of diabetes for the benefit, we hope, of clinicians. It is based on our larger book, *Clinical Diabetes and its Biochemical Basis*, but whereas that was a detailed review of the present state of knowledge concerning all aspects of diabetes, this book is an expression of our own clinical practice. We hope it will be helpful to those with charge of diabetics and also that it will be valuable, either in general practice, or in hospital. We hope also that it will be valuable for students who want to know rather more about diabetes than is usually found in general medical textbooks.

Since diabetes affects so many systems, it is the concern of various specialists, for example obstetricians, ophthalmologists, and orthopaedic surgeons, and we trust that they too will find the information they need in this book.

If it is also useful to those taking higher examinations, so much the better.

*Diabetic Department*
*King's College Hospital*
*London SE5 9RS*
*October 1972*

W. G. Oakley
D. A. Pyke
K. W. Taylor

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We are grateful to our colleagues at King's College Hospital, London who contributed to our book *Clinical Diabetes and its Biochemical Basis* (Blackwell Scientific Publications 1968) for allowing us to adapt some of their material in that book for inclusion in this; and to Miss Lily Jacobs and Miss Gwen Gardner for invaluable secretarial help; to Munksgaard, Copenhagen and Dr. Hans-Walther Larsen for allowing us to reproduce colour photographs (Plates 1–5) from *Atlas of the Fundus of the Eye*: and to Dr. J. P. Bingle for allowing us to reproduce the photograph of his patient (Fig. 6.3).

W. G. Oakley
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# CHAPTER 1
# BIOCHEMICAL BASIS OF DIABETES

**Definition of diabetes**

Diabetes is a disorder, whose causes are not fully understood, in which the level of blood glucose is persistently raised above the normal range. It is a common condition, particularly in middle and late life, and occurs in all parts of the world. The diabetic state may occasionally be transient but is usually permanent.

**History**

Although a clinical condition resembling diabetes was known in antiquity, the crucial observation that the urine of diabetics is sweet was not made until the seventeenth century. A hundred years later it was shown that the sweetness was due to sugar.

The metabolic defect in diabetes was unknown until Mering and Minkowski showed that pancreatectomy in dogs gave rise to a state resembling severe diabetes in man. This observation focussed attention on the pancreas as the origin of the disorder.

Many attempts were made between 1890 and 1922 to demonstrate that extracts of the pancreas were effective in relieving the symptoms of diabetes. In 1907, Zuelzer prepared alkaline extracts of the pancreas for which some success was claimed in the treatment of diabetic patients. In 1911, Scott attempted to ligate the pancreatic ducts and so effect acinar degeneration, the technique later used by Banting and Best. In 1921 a number of workers, including Paulesco of Roumania, achieved some success in reducing the blood glucose by the injection of aqueous pancreatic extract, but the first really effective preparation of insulin was made in the same year by Banting and Best. It is a remarkable fact that Gley had, in 1905, injected pancreatic glands with paraffin wax and obtained extracts which caused the disappearance of diabetic symptoms in depancreatised dogs; unfortunately this work was not known until a year after the isolation of insulin by Banting and Best.

Working on the assumption that the active principle of the islets of Langerhans was destroyed by the proteolytic enzymes secreted by the pancreas, Banting and Best ligatured the pancreatic ducts in dogs. The degenerated pancreas gave, on cold extraction, an active solution which, when injected intravenously into depancreatised dogs, produced a rapid fall in blood sugar. Later they made use of the observation that proteolytic enzymes are absent from the foetal calf up to about four months and were able to prepare active extracts from foetal calves' pancreas before the appearance of proteolytic enzymes.

## Control of blood sugar

Normally the level of glucose in the blood varies only within narrow limits; it rarely rises above 120 mg/100 ml or falls below 60 mg/

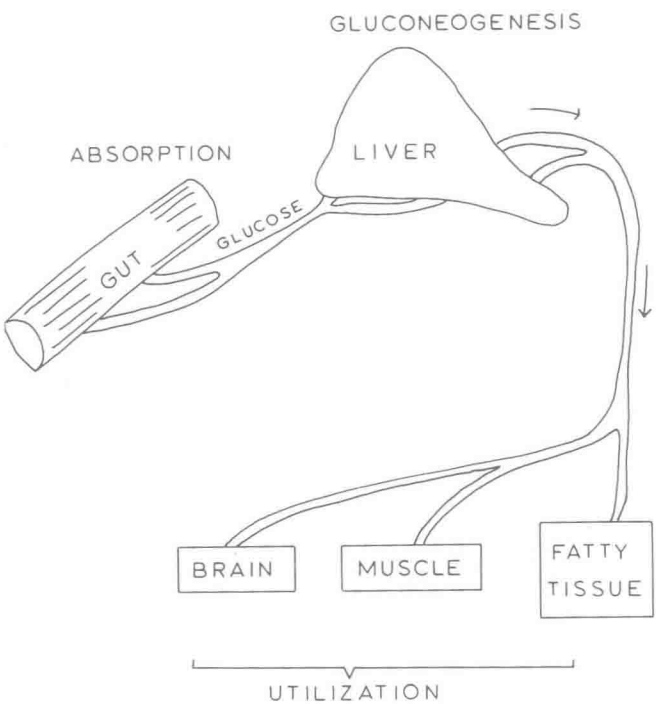


Fig. 1.1. Routes of glucose formation and utilisation; glucose reaches the liver after absorption from the gut and is synthesised from protein (gluconeogenesis); it is utilised mainly by brain, muscle and adipose tissue.

100 ml. Maintenance of a normal blood glucose level is essential because some tissues, for example the brain, rely on glucose for their metabolism. A fall in blood glucose below a level of about 30 mg/100 ml causes serious disturbance of mental function which may culminate in coma. Conversely, a rise in blood glucose produces osmotic diuresis and dehydration. There is a complicated mechanism by which the level of blood glucose is maintained within the normal range both during starvation and after eating carbohydrate food.

The level of blood glucose represents a balance between the inflow of glucose into the blood and its uptake by the tissues. Two factors increase blood glucose, the absorption of glucose from the gut and its production from protein (gluconeogenesis). This important function of the liver is shown diagrammatically in Fig. 1.1.

**Digestion of carbohydrate food**

Blood glucose rises after a meal containing carbohydrate, due principally to the breakdown of starch to glucose. The glucose is then absorbed and carried in the portal vein to the liver.

Starch consists of long chains of glucose molecules joined either in a single chain (amylose) or a branched chain (amylopectin). Digestion of starch begins with the action of ptyalin which breaks down the long chains to smaller units and is completed in the duodenum and ileum by maltase which breaks down the maltose, formed from starch, into glucose. There are also enzyme systems which break down most of the naturally occurring carbohydrates in the diet to their constituent sugars; thus sucrose gives rise to glucose and fructose, and lactose to glucose and galactose. Fructose and glucose are taken to the liver where they are transformed into glucose or glycogen.

**Synthesis and breakdown of glycogen**

In the liver glucose is stored as the polysaccharide glycogen. After an excess of dietary carbohydrate, glucose is synthesised into glycogen. Conversely, in times of shortage of carbohydrate, glycogen is broken down to glucose and released into the blood stream. The transformation of glucose to glycogen is shown diagrammatically in Fig. 1.2. It is first phosphorylated to glucose-6-phosphate and then converted to glucose-1-phosphate. The glucose-1-phosphate adds glucose to the end of existing glycogen molecules, so lengthening the chain.

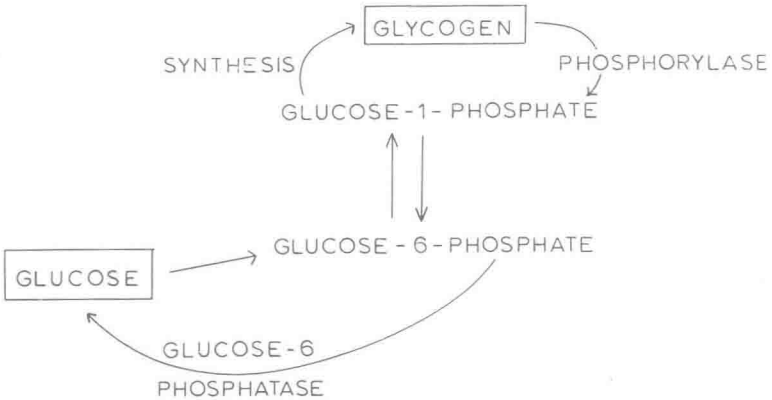


Fig. 1.2. Synthesis and breakdown of glycogen.

The pathway involved in glycogen breakdown differs, however, from the pathway of glycogen synthesis, different enzymes being involved at two key stages in the process: (1) *phosphorylase*, which produces glucose-1-phosphate from glycogen by adding on phosphate groups and (2) *glucose-6-phosphatase* which hydrolyses glucose-6-phosphate to give free glucose. Both these enzymes are influenced by the activity of hormones; thus glucagon and adrenaline raise blood glucose by activating phosphorylase which depletes liver glycogen. The activation of phosphorylase involves the intervention of the intracellular messenger substance, cyclic AMP (adenosine monophosphate).

Galactose, fructose and a number of other sugars less commonly present in foodstuffs are converted into glucose or glycogen in the liver.

**Protein metabolism and the liver**

Just as complex carbohydrates are broken down into simple sugars in the gut, so proteins are split into amino acids. Amino acids, like sugars, are absorbed into the portal blood stream and carried to the liver; they may also be used to synthesise protein in muscle or kidney.

It has already been indicated that certain amino acids can be metabolised to glucose. This process is especially important in starvation which, if prolonged, may lead to severe loss of body protein by its conversion into glucose in order to maintain the blood sugar level.

### Metabolism of glucose

In all cells there is a common system for the metabolism of glucose. In this process the six-carbon molecule is broken down to three-carbon substances by a series of reactions (glycolysis). Pyruvic acid is the end product of glucose metabolism in mammalian tissues, although under conditions of oxygen lack this may be reduced to lactic acid. The transformation of glucose by this pathway is shown diagrammatically in Fig. 1.3. There are a number of important

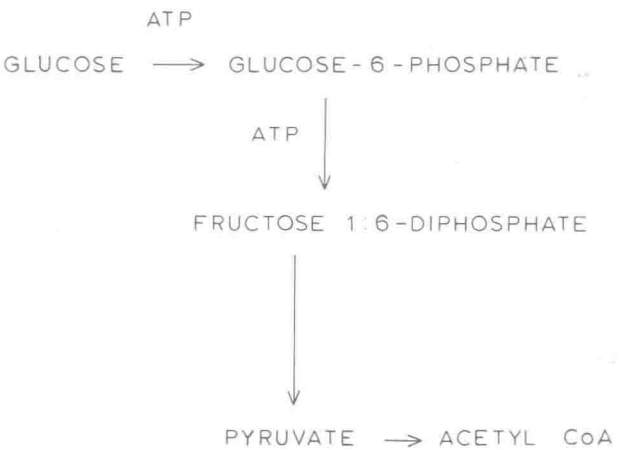


Fig. 1.3. Stages in glycolysis.

points of control of glycolysis, one involves the phosphorylation of glucose to glucose-6-phosphate; another involves the further phosphorylation of fructose-1-phosphate to fructose 1 : 6 diphosphate; these two phosphorylation reactions, as well as the rate of transport of glucose across the cell membrane, determine the rapidity of glucose flow through the glycolytic pathway.

Normally, pyruvic acid is metabolised to give the two-carbon compound, acetyl coenzyme-A, which is then oxidised to carbon dioxide and water. The series of reactions which effect this oxidation was first elucidated by Krebs and is termed the tricarboxylic cycle. The cycle involves the addition of acetyl coenzyme-A to oxaloacetic acid to form citrate which is then transformed into a number of other di- and tri-carboxylic acids (see Fig. 1.4). The tricarboxylic cycle normally takes place in the mitochondria which are small intacellular bodies where most of the energy of living cells is derived

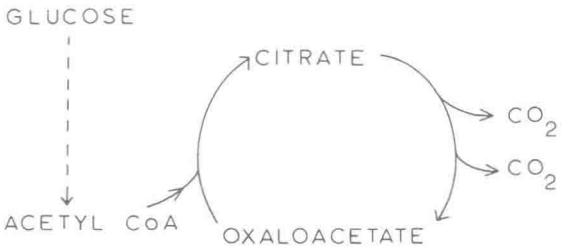


Fig. 1.4. The Krebs cycle.

from oxidative processes. By way of glycolysis and the Krebs cycle there is therefore a complete pathway for the oxidation of glucose to carbon dioxide and water.

**Gluconeogenesis**

In gluconeogenesis, glycolysis is reversed. This, however, is not a simple reversal. At least two of the phosphorylations of glycolysis are bypassed. Gluconeogenesis is closely controlled by insulin, adrenal steroids and other hormones. Gluconeogenesis is very important in diabetes in which, due to insulin lack, it may be accelerated and so lead to overproduction of glucose from non-carbohydrate sources.

## Fat metabolism

Fat consists of a combination of fatty acids with glycerol (see Fig. 1.5). It is stored in adipose tissue cells subcutaneously, in the omentum and around the viscera. The first stage in fat breakdown is the hydrolysis of neutral fat to give free fatty acid and glycerol; this process is regulated by a number of hormones such as growth hormone, glucagon and ACTH In adipose tissue free fatty acids are produced by the action of lipase and transported to other sites where they are further metabolised.

While carbohydrate stores provide a source of energy in case of a short term need, fat provides a store of oxidisable material available in conditions of prolonged carbohydrate shortage. Thus, fat stores are readily broken down in starvation.

**The synthesis of fat**

Long chain fatty acids are synthesised by a pathway which differs from that of their breakdown. The starting point is acetyl

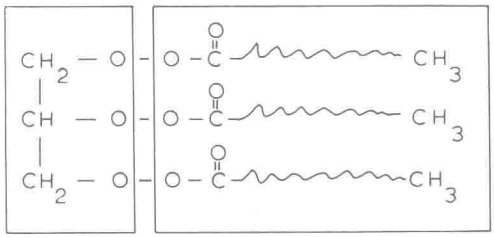


Fig. 1.5. The structure of fat, a combination of fatty acids and glycerol.

coenzyme-A which can readily be formed from glucose by glycolysis; acetyl coenzyme-A molecules combine to form long chain fatty acids which with glycerol form neutral fat.

**Breakdown of fatty acids and formation of ketone bodies**

Normally fatty acids are oxidised in the liver to yield the 2-carbon molecule acetyl coenzyme-A which is metabolised through the tricarboxylic acid cycle to water and carbon dioxide. But, when there is an excessive breakdown of fatty acids, the capacity of the liver to oxidise all the acetyl coenzyme-A is exceeded and the two carbon fragments combine to form acetoacetate whose level in the blood rises rapidly.

Acetoacetate is converted into beta-hydroxybutyrate or decarboxylated to yield acetone (see Fig. 1.6). These three substances, acetoacetate, beta-hydroxybutyrate and acetone, constitute the ketone bodies, and are present in great excess in diabetic coma.

Blood levels of ketone bodies are also elevated in starvation when fat is broken down to provide a source of energy, but the levels are not nearly as high as in diabetic coma.

Acetoacetate is normally metabolised by muscle, where it may be oxidised completely to carbon dioxide and water. In severe ketosis

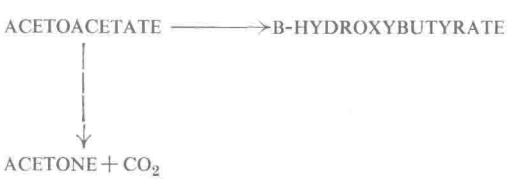


Fig. 1.6. Relationships of ketone bodies.

the capacity for the metabolism of these substances is exceeded so that failure of oxidation contributes to their high circulating levels. All three ketone bodies are excreted in the urine, and acetone, which is volatile, is also excreted in the breath.

**Interaction between carbohydrate and fat metabolism**

There is competition for the intracellular oxidation pathways between glucose and fatty acids. Thus, excessive oxidation of fatty acids leads to an inhibition of glycolysis. Under conditions of excessive fatty acid oxidation by muscle, glucose is less readily metabolised and its level in the blood rises. This inhibition of glucose metabolism may be important in diabetic ketosis, and contributes to the high blood glucose level.

## The action of insulin

The most obvious action of insulin is to lower blood glucose. So much attention has been focused on this aspect of its action that it is sometimes forgotten that it also profoundly affects the metabolism of protein and fat.

It is convenient to divide the actions of insulin into immediate and delayed (Table 1.1).

**Table 1.1.** Mode of action of insulin.

**Rapid effects**

1. Increases glucose uptake and its further metabolism in muscle and adipose tissue.
2. Depresses fatty acid release from adipose tissue.
3. Increases glycogen formation in liver.
4. Increases synthesis of protein, especially in muscle tissue.

**Long term effects**

1. Increases activity of some enzymes involved in glucose metabolism (e.g. liver glucokinase).
2. Depresses activity of enzymes involved in gluconeogenesis.

**Rapid effects of insulin on muscle and adipose tissue**

The lowering of blood glucose by insulin is the result of its immediate effect in increasing glucose uptake in the tissues. This effect was shown by incubating rat diaphragm or rat adipose tissue with small amounts of insulin and studying the rate of disappearance and fate of glucose. In muscle, under the action of insulin, glucose is more readily taken up and either converted to glycogen and lactic

acid or oxidised to carbon dioxide. In adipose tissue, the increased oxidation of glucose leads first to the production of an excessive amount of acetyl coenzyme-A which is then synthesised into long chain fatty acids. In addition, insulin has an immediate effect in preventing lipolysis. The glycerol needed for fresh fat synthesis is derived from an increased rate of glycolysis which readily takes place in adipose tissue under the influence of insulin. Thus insulin also has an immediate effect in increasing the deposition of body fat at the expense of glucose.

**Long term effects of insulin**

Insulin affects a number of important enzymes concerned with metabolism; in particular, it increases the activity of glucokinase, which phosphorylates glucose and by so doing increases the rate of glucose metabolism in liver. Insulin also suppresses gluconeogenesis by depressing the function of liver enzymes which operate the reverse pathway from proteins to glucose.

The overall effect of insulin therefore is to build up complex molecules, such as glycogen and fat, from simpler materials, such as glucose. In the absence of insulin these complex molecules readily break down; this is the reason for the excessive breakdown of fat in the insulin-deficient diabetic.

**Tissue responsiveness to insulin**

Not all tissues of the body are equally sensitive to the effects of insulin. Muscle and adipose tissue respond within minutes and are sensitive to small concentrations of circulating insulin. There has long been a difference of opinion as to whether the liver also responds immediately to the effects of insulin. It is now agreed that insulin has a direct effect within 15 minutes of its administration. Some other tissues, notably brain, do not appear to be responsive to insulin. The early effects of insulin are related mainly to its action on liver, muscle and fatty tissue.

**The mechanism of action of insulin at the cellular level**

The major effect of insulin is to increase the rate of glucose transport across the membranes of insulin–sensitive tissues. In addition, insulin decreases the levels of the intracellular messenger substance cyclic-AMP in adipose tissue which, by inhibiting adipose tissue lipase, depresses fat breakdown. The way in which insulin affects protein

synthesis has been disputed, but it now seems certain that it does so by its effects on ribosomes, the minute intracellular particles which are responsible for protein synthesis.

### Metabolic consequences of insulin lack

The changes in an animal deprived of insulin can now be worked out, and are assumed to be the same as those in acute onset diabetes. Because of lack of insulin, transport of glucose into muscle and adipose tissue is restricted, and blood glucose therefore rises. In addition, the breakdown of neutral fat to free fatty acids and glycerol is increased and there is a rise in the fatty acid content of the blood. The increased catabolism of fatty acids by the liver results in a greater production of ketone bodies which diffuse out from the liver and pass to the muscles for further oxidation. As the diabetic state worsens the ketone body levels increase and, as the capacity for their oxidation is exceeded, ketosis becomes progressively more severe.

Less amino acids are taken up by tissues and protein breakdown is greatly increased. At the same time the enzymes responsible for gluconeogenesis are activated by the absence of insulin with a consequent increase in the production of glucose, mainly from the liver—at the expense of protein. The lack of insulin depresses protein and fat synthesis and, when prolonged, leads to an increase in their breakdown.

These changes can be reversed by insulin, although some, such as the reversal of gluconeogenesis, may take many hours.

### Other hormones and the control of blood sugar

Besides insulin there are other hormones which significantly influence the control of blood glucose. The most important of these are growth hormone, glucagon, adrenaline, ACTH and adrenal steroids.

#### Growth hormone

Growth hormone regulates metabolism in the growth period and probably also in states of carbohydrate deprivation, such as fasting. Growth implies a laying down of protein and this is achieved partly by a direct effect of growth hormone on amino-acid uptake of tissues, and partly by a direct effect on the pancreas leading to