Drug Treatment of Disease**TREATMENT OF DIABETES MELLITUS****HYPOGLYCAEMIC AGENTS OTHER THAN INSULIN**

BY

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Less than 50% of patients with diabetes mellitus need insulin for the control of their condition. Evidence is accumulating to show that the remainder have no true deficiency of this hormone. It has long been recognized on clinical grounds that diabetics may be divided into two groups: on the one hand the thin patients who quickly become ketotic in the absence of insulin treatment, and on the other those who are or have been obese and, although they have hyperglycaemia, show no tendency to develop ketosis. It has been suggested that the former are insulin-deficient whereas the latter have become resistant to the action of insulin. Confirmation of this differentiation has been obtained from estimations of plasma-insulin activity and from study of the amount of insulin that can be extracted from the pancreas removed at necropsy in suitable cases.

Dietary Treatment of Diabetes Mellitus

Insulin resistance of the overweight diabetic is apparently related to the obesity, and if reduction in weight can be achieved by a suitable diet low in calories and carbohydrates the symptoms usually disappear and blood-sugar levels often return to normal. The diets used provide 1,000 to 1,750 calories a day and contain 100 to 120 g. carbohydrate. Some patients co-operate well in their treatment, but many find it difficult to keep to a restricted diet. This may be for economic reasons, because diets of this type are expensive if they are to be satisfying. In other cases the patients' personalities or environment may make it difficult for them to keep to the prescribed diet. In selected cases drugs like dexamphetamine or "preludin" (phenmetrazine hydrochloride) may help the patient to control the appetite; thyroid preparations cannot be recommended for weight reduction. In most cases the symptoms improve within a week or two of starting the diet, and as the weight comes down the post-prandial or random blood sugar estimation will be less than 200 mg./100 ml. Despite this the diabetes is not cured, the glucose tolerance curve usually remains of a diabetic type, though the blood-sugar levels will be lower than those obtained before treatment started; if the patient's weight goes up again overt diabetes will reappear.

About 15% of these obese diabetics will continue to have a high blood sugar despite getting their weight down to an average level or even below. These patients seldom have any diabetic symptoms, the only abnormalities being glycosuria and raised blood-sugar. Unfortunately there is evidence to suggest that this hyperglycaemia may lead to the development of diabetic complications like retinitis, impaired renal function, or arterial disease. Until recently the only way to lower the blood sugar was by giving insulin, and it was not easy to explain to a symptomless middle-aged or elderly diabetic that daily injections were necessary. It is in just this group of patients that tablets of the hypoglycaemic sulphonamide derivatives are indicated.

Hypoglycaemic Sulphonamide Derivatives

These compounds lower the blood sugar in normal subjects and in some diabetics. How they do it is uncertain, but they are not to be regarded as "oral insulin preparations," because unlike insulin they have no direct effect on utilization of carbohydrate by the peripheral tissues. It has been established that they lower the blood sugar only if the patient's pancreas is capable of secreting some insulin, and one way in which they act is apparently to increase the pancreatic output of insulin (Loubatières, 1957). There is also some evidence suggesting that they influence the enzyme systems of the liver, potentiating the action of insulin on them and reducing output of hepatic glucose. One result of the studies of the pharmacology of these drugs has been to underline our ignorance of the mode of action of insulin itself and to cause a reinvestigation of this problem. It should also be pointed out that the metabolic disturbance in diabetes is not simply an increase of sugar in the blood. These drugs will lower the blood sugar, but there is no evidence that they will correct the other biochemical abnormalities in diabetes mellitus. It is appropriate therefore to refer to them as hypoglycaemic drugs but not to describe them as antidiabetic.

There are three compounds to be considered:

Carbutamide

Tolbutamide

Chlorpropamide

Carbutamide.—This was the first of the hypoglycaemic sulphonamide derivatives to be given extensive trial. Its excretion is slow, so that satisfactory blood levels were achieved with doses of about 1 g. a day, and a single daily dose was all that was needed. Unfortunately, however, a number of serious and some fatal toxic reactions occurred. The commonest was a sulphonamide sensitivity reaction with widespread arterial damage; a few patients developed agranulocytosis, and thrombocytopenia was not uncommon (Kirtley, 1957). Because of these toxic effects this drug is no longer made in this country or in the United States.

Tolbutamide.—This compound is the one most widely used at the present time. The *p*-amino group of carbutamide has been replaced by a methyl group with loss of antibacterial action and marked reduction of toxicity. Tolbutamide is excreted more quickly than carbutamide and must be given in divided doses two or three times a day (Baird and Duncan, 1957). The total daily dose is usually 1–3 g. Side-effects include indigestion, occasionally pain suggestive of peptic ulcer, and irritating rashes.

Chlorpropamide.—This is a recent addition to the oral hypoglycaemic agents and is now generally available in this country. It is excreted very slowly and therefore need be given only once a day. The blood levels obtained are higher than those of tolbutamide and the hypoglycaemic action consequently greater. The usual daily dose is 0.25 to 0.5 g. a day. If larger doses are given hypoglycaemic attacks may be produced and some peculiar neuropsychiatric side-effects may result—vertigo, confusion, and so on (Murray *et al.*, 1958). A few cases have been reported of cholangiolitic jaundice after small doses of chlorpropamide. The clinical and pathological changes are similar to those seen in chlorpromazine jaundice.

Tolbutamide Therapy

Patients suitable for tolbutamide therapy are those who develop diabetes in middle age or later. It should not be given to patients who have had marked ketonuria or diabetic ketosis. Most of the suitable patients belong to the group of obese diabetics, and before tolbutamide is given body weight should be reduced by a suitable low-calorie, restricted-carbohydrate diet to within 10% of the average weight for a person of similar age and height (Kemsley, 1952). If, despite weight reduction, glycosuria and hyperglycaemia persist, tolbutamide may be started. The initial dose should be 0.5 g. three times a day, and if necessary it may be increased to 0.5 g. four times a day or 1.0 g. three times a day. The response to tolbutamide may be immediate or delayed, and, because of the delayed type of response, trial of tolbutamide therapy should be continued for four to eight weeks before it is abandoned as unsuccessful. It had been hoped that a one-day test with a large dose of tolbutamide and serial blood-sugar estimations would make it possible to decide which cases were suitable for tolbutamide therapy; in practice, however, it has proved unsatisfactory and therapeutic trial is needed (Dolger, 1956). If there is a good response on 0.5 g. three times a day, it may be possible to reduce the dose to 0.5 g. twice a day or 0.25 g. twice a day. Dietary control must be continued, but, if the patient is underweight and the blood-sugar levels are satisfactory on tolbutamide, gradual increase of calorie and carbohydrate intake may be permitted.

Before tolbutamide became available diabetics of the type considered in the last paragraph had to be given insulin to control their hyperglycaemia, and the question of changing to tolbutamide now arises. It is often difficult to recognize the patients who will be suitable for tolbutamide therapy as opposed to the insulin-deficient type who will become ketotic if treatment with insulin is stopped. If the dose of insulin is more than 30 units per day satisfactory control with tolbutamide is unlikely to be achieved. Patients who are overweight should have their obesity corrected by adjustment of the diet and reduction of the dose of insulin before the change is attempted.

There are various methods of effecting the change of treatment. The simplest is to reduce the dose of insulin over a period of a few days, and when hyperglycaemia or glycosuria is observed to start the tolbutamide at 0.5 g. three times a day. This may be necessary before insulin is stopped or a few days or weeks after stopping it. Some patients are found to remain well controlled without insulin; in other words, they were taking it unnecessarily and of course they do not need tolbutamide either. While the insulin dose is being

reduced and for a few days after it is stopped the urine must be tested daily for ketone bodies; if they are found the patient is unsuitable for tolbutamide therapy and insulin must be started again straight away. During this period the doctor should see his patient every day, facilities must be available for getting blood-sugar estimations done at short notice, and in some cases it is advisable for the patient to be admitted to hospital.

Tolbutamide is a comparatively new drug, and all patients on it must be seen regularly, initially at weekly intervals and when well controlled at least every four weeks. Check should be kept on the urine tests and weight; if possible, the blood sugar should be estimated periodically, because many of these patients have a high renal threshold and a high blood sugar without glycosuria. If a skin rash develops, treatment with tolbutamide usually has to be abandoned. Indigestion is sometimes troublesome; it may be minimized by giving the tablets after meals and prescribing an antacid; occasionally it necessitates stopping the treatment. Some patients seem to become resistant to the action of tolbutamide after they have been taking it for 6–18 months. This may result from laxity in diet, when it is associated with an increase of body weight; but in some there is genuine acquired resistance, with heavy glycosuria, weight loss, and often ketonuria. If this happens tolbutamide must be stopped and insulin therapy started.

Chlorpropamide Therapy

The indications for chlorpropamide are similar to those for tolbutamide, but the initial dose should be 0.25–0.5 g. a day. In small elderly subjects it should not exceed 0.25 g. a day. The dose should be reduced as soon as possible to a maintenance level which may be as low as 100 mg. a day. Because of the high blood levels achieved it is more potent as a hypoglycaemic agent than tolbutamide, and it may work where the latter fails to produce an adequate reduction of blood sugar. On the other hand, it is possible to produce genuine hypoglycaemic attacks with it. Skin sensitization has been reported, and the incidence of jaundice after its use cannot yet be assessed.

Phenethyldiguanide (D.B.I.)

This is an oral hypoglycaemic agent unrelated to the sulphonamide derivatives but in some ways resembling "synthalin," which was used in the treatment of diabetes in the 1920s and abandoned because of toxic effects on the liver (Graham and Linder, 1928). D.B.I. is active in the absence of insulin and has been given with some success to juvenile diabetics (Krall and Camerini-Davalos, 1958). It seems to reduce the blood sugar by increasing anaerobic glycolysis. In practice it has been found that at least half the patients get gastro-intestinal side-effects with therapeutic doses, and for this reason it seems unlikely that D.B.I. will be widely used in the treatment of diabetes (Hall *et al.*, 1958).

Recent reports of a new diguanide, the dimethyl compound, suggest that it may be as effective as D.B.I. although a larger dose is needed, and that it is much less likely to upset the gastro-intestinal tract (Azérad and Lubetski, 1959).

Other Hypoglycaemic Agents

Many other compounds have been used in the treatment of diabetes. There are numerous herbal and vegetable remedies, but they do not seem to have a

consistent hypoglycaemic action (Hugh-Jones, 1955; Sepaha and Bose, 1956). Oestrogenic hormones have been given for diabetes developing at puberty and for the diabetes found in post-menopausal women (Gessler *et al.*, 1939). Dimercaprol has been shown to reduce the blood sugar in a few diabetics, but it is unlikely that it will be used in treatment (Butterfield and Thompson, 1957). The salicylate drugs are of considerable interest. They lower the blood sugar in some diabetics (Reid *et al.*, 1957) and also appear to enhance the hypoglycaemic action of the sulphonamide derivatives (Stowers *et al.*, 1958).

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DR. ELLIOTT JOSLIN: A BIRTHDAY TRIBUTE

Written at the special invitation of the B.M.J. by

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Elliott Proctor Joslin, dean of the American medical profession and authority extraordinary on diabetes to a considerable proportion of the civilized world, will celebrate his ninetieth birthday on June 6. That is, his devoted friends, relatives, associates, and admirers will presumably press some sort of a celebration on him; he will probably spend at least part of the day in his office, attending to business as usual.

Dr. Joslin was born these fourscore and ten years ago in the town of Oxford, Massachusetts. As a boy, it has been reported, he spent his spare hours working in his father's shoe factory putting laces into shoes at six cents per 60 pairs. The inflationary sums thus amassed were not spent riotously, however; his father insisted that they be put into the savings bank, where they still remain. Frugal in his personal life, Dr. Joslin is such a ready giver in good causes that his friends fear his coming to want if old age ever overtakes him. Perhaps the interest on the pennies in the bank will yet serve to rescue him.

From the academy in the neighbouring town of Leicester Elliott went to Yale College and then to Harvard Medical School, then to the Massachusetts General Hospital for an internship. It was here, in 1893, as a student, that he acquired his interest in diabetes through his care of Mary Higgins.

the first case in his series of over 50,000 diabetic patients. A spare person, one of Dr. Joslin's aphorisms is that people who run 10 to the ton are most likely to acquire diabetes. Dr. Joslin was one of the first to recognize the achievement of Banting and Best in Macleod's Canadian laboratory in 1922, and he was the first to use insulin in his own country.

Years ago he started the custom of giving a bronze medal to each of his diabetic patients who exceeded the normal life expectancy (there have been over 2,000 of them) and a gold medal to those who more than doubled it.

A gold medal recipient was George F. Baker, then president of the First National Bank of New York, whose award was bread upon the waters, for he eventually left a quarter million dollars for the Baker Diabetic Clinic at the New England Deaconess Hospital in Boston. The frieze by Malvina Hoffman on the new Joslin Clinic building opened last year at the Deaconess Hospital, representing the history of medicine, starts with Imhotep and ends with the late George Richards Minot, the diabetic physician of Boston who received the Nobel Prize for his part in discovering the liver treatment for pernicious anaemia. He was another of the 50,000 who owed to Dr. Joslin and his associates the renewed capacity to carry on.