TREATMENT OF 90 SEVERE DIABETICS WITH SOLUBLE INSULIN FOR 20-40 YEARS

EFFECT OF DIABETIC CONTROL ON COMPLICATIONS

BY

R. D. LAWRENCE, M.D., F.R.C.P.*Consulting Physician (formerly in Charge), Diabetic Department, King's College Hospital, London*

In 1923, when British insulin became reasonably available in this country, there were, besides a large number of elderly patients with mild long-duration diabetes and some vascular complications, large numbers of younger patients—ketotic and moribund—with uncomplicated diabetes of short duration, cases urgently needing rescue by insulin. These and similar new cases occurring in later years are the material of this study. Of 53 males and 37 females, 33 males and 19 females were under 30 years of age at the beginning of insulin treatment. They were "private" (fee-paying) patients whose treatment and any complications were followed by me personally for 20 years or longer. The majority were treated from the start entirely as "out-patients," and only if they had bad sepsis or some other serious condition (pregnancy, pneumonia, gangrene) or lived too far from London to attend frequently were they admitted for a short time to a private clinic; there was no hospital clinic in those early days.

As 100 units of insulin cost 25s. (no free insulin except to a few employees), this price, and the rather scanty supplies, dominated the therapeutic possibilities, and it was usual at first to continue the low carbohydrate and calorie diets of the Allen period and to add the minimum of insulin that would keep the diabetes under control. There was no problem about the type of insulin as there was only one, the original preparation of Banting and Best in Toronto, later called "soluble" ("regular" in U.S.A.). Though becoming freer of protein impurities, it was very strong but brief in action. It was therefore soon found that at least two doses—morning and evening—were required to maintain health, weight, and strength, and to give anything like control of the diabetes. Even then, when the insulin action was exhausted (8–10 hours) there was a recurrence of glycosuria, hyperglycaemia, and occasionally slight ketosis before and for an hour or two after the two injections—that is, before and after breakfast and supper—with a normal blood-sugar and metabolism and occasional hypoglycaemia four to six hours after both injections.

It was a joy to see how quickly such patients, myself included, were rebuilt—one youth regaining 20 lb. (9 kg.) (mostly water no doubt) in the first week—and how gladly and cleverly most co-operated to keep themselves well and controlled by appropriately timed urine tests or mild hypoglycaemia, with an occasional blood test and general check by myself at least once a year. Indeed, a few "purists," disliking to see any glycosuria before the evening injection, added a small dose at the midday meal.

When the introduction of a long-action insulin made the treatment by one daily injection a possibility, many refused its trial, saying that they were quite happy and understood their treatment—as did their doctors—and its adjustment. If on admission to some hospital after an accident or minor operation they were transferred to a one-dose treatment by an enthusiastic houseman who thought the latest must be the best, they mostly came to me in a few weeks asking to return to their previous treatment because they were showing sugar and having hypoglycaemia at puzzling times. And so they went on year after year with some 150 g. of

carbohydrate and minor adjustments of insulin—the commonest dose being some 20 units morning, 16 units evening—and a full life of work and vigorous play.

The Table shows the age and cause of death of 11 of the 90 diabetics treated in this way.

The series is too small to make it worth while to work out the percentage mortality for comparisons with the results of bigger series of other workers using different types of insulin and treatment, but, like other published post-insulin results, it clearly shows that strictly diabetic deaths from ketosis and coma (only one, and this from a doctor's error) have been replaced by vascular complications common both to long-standing diabetes mellitus and to longevity, which many of the above reached.

Three Complications (Renal, Vascular, Visual) and Their Relation to Diabetic Control

The order of onset and the first manifestation of these complications is difficult to place and may vary from patient to patient. But in this series a faint cloud of proteinuria has usually been the first indication that such a complex has begun. At the same time I usually find in the young that the blood-pressure has risen say from 100/70 to 110–120/80–95, and within a year or so the first retinal changes tend to appear as micro-aneurysms or fleck exudates (thrush breast). These rarely affect vision, and come and go dynamically (Keen and Smith, 1959), but they act as a warning for "better control," the ophthalmologists say. If they see these when fitting glasses some ophthal-

Number and Cause of Deaths

No.	Age at Death	Duration of Diabetes (Years)	Cause of Death	Remarks
<i>Males (6 Deaths in 53 males)</i>				
1	83	32	Senility; no vascular or renal complications	Had a Joslin quarter-century medal
2	71	30	Cerebral softening. Vascular complications	—
3	71	36	Hemiplegia. Vascular complications	—
4	57	37	Heart failure. Vascular complications	Valvular disease of heart on diagnosis
5	50	22	Cerebral thrombosis. Renal and vascular complications	—
6	39	34	Renal and vascular complications	Very careless youth
<i>Females (5 Deaths in 37 females)</i>				
1	74	27	Senility; no complications	—
2	73	24	Diabetic coma; no complications	Given 20 units instead of 80 units soluble insulin by mistake
3	73	21	Senility; only complication blindness	—
4	57	20	Carcinoma of ovary; no complications	—
5	46	38	Uraemia. Kimmelstiel-Wilson syndrome for more than 9 years	—

mologists tell patients that they have haemorrhages which can lead to blindness and should go to their doctor for a check for better control. Some of these patients arrive in extreme agitation—"I'm going blind." If Mr. X has reported only micro-aneurysms, fleck exudates, and no vessel changes—blindness in younger diabetics being caused more by neovascularization and haemorrhages than by straightforward retinal changes (Whittington, 1961)—I am often able truthfully to reassure the patients that I have seen such minor changes off and on for the last five years, and that with care these may not progress and affect their eyesight: not invariably true, but a very proper white lie, in my opinion, to reduce tension in patients already alerted into full care of their diabetes.

The renal complication is the most threatening, and when increasing renal and vascular complications with added oedema develop into the dreaded Kimmelstiel-Wilson syndrome I usually hope that a quiet uraemic end takes them before they pass through the depression of blindness. Only one death from Kimmelstiel-Wilson disease occurred in this series, and this woman lived so long and actively as to teach me to be very cautious in my prognosis of the duration and value of life even when the blood urea has been over 100 mg./100 ml.

Control Reduces Complications

Contrary opinions have been expressed about this by different authorities, perhaps because it is difficult to gauge and compare control either by periods in hospital or by a frequent check on out-patients. On the other hand, insulin reactions ("hypos"), confirmed by a blood-sugar test or merely from the story of a trusted patient of its timing with a sugar-free urine, are easy to recognize; and it is certain that, apart from actual symptoms, these patients are often in the normal blood-sugar area of non-diabetic metabolism. I have found that such patients among these 90 cases have had few or milder complications, if any. This has been the experience of Sven Johnsson (1960), whose summary I quote: "8 patients who had hypo-

glycaemic coma on more than 20 occasions were all free from proteinuria after 25 years of diabetes mellitus, and 4 had normal ocular fundi and the remainder normal vision and only a few micro-aneurysms." His findings, like mine, suggest that hypoglycaemia—evidence of control—minimizes complications; but I think, from my experience, that the occurrence of 20 comas is carrying hypoglycaemias unnecessarily far.

To understand how periods of control brought about by hypoglycaemia could prevent retinal complications, it is interesting to examine an aetiological suggestion of Ashton (1959) as a basis for further thought and research. "In the metabolic defect of diabetes the retina, being so particularly dependent upon the breakdown of glucose as an energy source and having a higher glycolytic rate than almost any other tissue, is subject to a chronic metabolic disturbance leading gradually to failure of osmotic regulation with the inhibition of water and an increase in retinal turgescence. The resulting rise in tissue tension impedes the capillary circulation, stagnation and anoxia result, and micro-aneurysms form."

This state of "chronic abnormal metabolism" is abolished, and indeed normalized twice a day, by treatment with soluble insulin, properly used, with greater certainty and with less risk of seriously prolonged hypoglycaemia than by any one-dose-a-day treatment.

However, diabetic control, so far as it is possible, can hardly be the whole answer to visual troubles, as there are exceptions in both directions: some, careless and uncontrolled, retain perfect vision; and one of the best-controlled young diabetics I know—my lab. man—went blind from neovascularization trouble without renal or vascular complications (Whittington, 1961), and his case is one of the major puzzles and disappointments of the first 40 years of my practice.

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DIABETES MELLITUS AND INSIPIDUS IN TWO SISTERS

BY

S. RAITI, M.B., B.S., D.C.H., M.R.C.P.Glasg.

Formerly S.H.O. and now Research Student, Department of Endocrinology

S. PLOTKIN, M.D.

Medical Registrar

G. H. NEWNS, M.D., F.R.C.P.

Consultant

The Hospital for Sick Children, Great Ormond Street, London

The occurrence of diabetes mellitus and diabetes insipidus in the same patient is rare. Only 43 cases have been reported previously in the literature available to us; of these, only five have been in children (Natelson, 1954; Rowntree and Poppiti, 1954; Randall *et al.*, 1959; Riggs and Randall, 1960). The familial occurrence of these two diseases has not previously been reported. This article records the case histories of two sisters, each of whom has been shown to have diabetes caused by disorders of both carbohydrate metabolism and the neurohypophysis.

Case 1

The patient was born on May 7, 1951. Thirst and polyuria were first noticed at 4 months, when her mother had difficulty in maintaining a supply of dry napkins.

She was first admitted to Great Ormond Street at the age of 3 years with the complaints of thirst, polyuria, anorexia,

and constipation. The only previous illness was measles at 18 months. On examination her blood-pressure was 110/80 and no abnormal physical signs were found. Tests of renal function showed nothing abnormal. An intravenous pyelogram showed bilateral hydronephrosis and hydroureters. Cystoscopy revealed hypertrophy of the bladder, normal ureteric orifices, and no hypertrophy of the bladder-neck. Skull x-ray films were normal.

From the results of "pitressin" and water-deprivation tests the patient was considered to have diabetes insipidus. Treatment with intranasal pitressin was begun and improvement of symptoms was striking. Intramuscular aqueous pitressin tannate, 1 unit b.d., was substituted later, and this gave adequate control. A second intravenous pyelogram four months later showed considerably less dilatation of the ureters and no good evidence of hydronephrosis. As the child grew older the pitressin had to be increased to 10 units of pitressin tannate in oil, given every other day.