INSULIN ZINC SUSPENSION IN CHILDHOOD DIABETES

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In 1951 and 1952 Hallas-Møller and his colleagues described the composition and action of the new insulin zinc suspensions (I.Z.S.) produced by the Novo Laboratories in Copenhagen (Hallas-Møller, Petersen, and Schlichtkrull, 1951, 1952). Several reports have dealt with their use mainly in adults (Hallas-Møller, Jersild, Petersen, and Schlichtkrull, 1951, 1952; Lawrence and Oakley, 1953; Murray and Wilson, 1953; Oakley, 1953; Nabarro and Stowers, 1953; Stowers and Nabarro, 1953; FitzGerald *et al.*, 1954; Melton, 1954; Venning, 1954). Ferguson's (1954) study deals only with children.

Material

The present study deals entirely with I.Z.S. (insulin zinc suspension), which is a 3/7 mixture of I.Z.S. (amorphous)/I.Z.S. (crystalline). We started to use I.Z.S. in October, 1953, and have maintained 20 children on it for periods of from five to thirteen months. We have employed I.Z.S. in every new case (Cases 1-10) as well as in 10 patients (Cases 11-20) who had attended the diabetic clinic for periods of from two to seven years, and in whom the control achieved with either globin insulin (G.I.) or a mixture of protamine zinc insulin (P.Z.I.) and soluble insulin (S.I.) was unsatisfactory. All cases were of the acute variety typical of juvenile diabetes.

Method

The 10 new and 8 old cases were admitted to hospital for stabilization on the new insulin. The remaining two (Cases 16 and 19) were changed to the new insulin as out-patients.

Diet.—The carbohydrate intake was measured. The amount of carbohydrate in the various meals is shown in the Table; one portion is equivalent to 10 g. of carbohydrate (Lawrence, 1952). Because the amount of dietary

protein and fat varies little from day to day (Murray and Wilson, 1953), their intake was not measured.

Insulin.—I.Z.S. was given 20 to 30 minutes before breakfast. In the 10 new cases a rough estimate of the total insulin requirements was obtained during the first two or three days after admission by giving S.I. before the three main meals, the dose depending on the amount of sugar in the urine. On the third or fourth day the S.I. was replaced by a single dose of I.Z.S. In those children who had been under treatment with other insulins the previous dose was replaced abruptly by a single dose of I.Z.S.

Activity.—The nursing staff and occupational therapy staff ensured that the children admitted to hospital took an amount of exercise comparable to that taken at home.

Tests of Diabetic Control

In-Patients.—On an average it was not until three weeks had elapsed that urine passed before meals became sugar-free. At this stage, if the child had no hypoglycaemic attacks and was in good general condition, blood-sugar levels were studied over a 24-hour period. Capillary blood samples were usually taken at midnight, 4 a.m., 8 a.m., 10 a.m., midday, 2 p.m., 4 p.m., and 8 p.m., and the sugar content was estimated by the method of Rappaport and Pistiner (1934). In most cases the results suggested the need for only minor alterations in the diet or insulin dose—for example, in Case 1 (see Table) the insulin was reduced from 24 to 22 units, and the carbohydrate at tea-time was increased by 10 g. to a total of 40 g. It was not considered justifiable to subject these children to a second series of pricks. In a few cases, however, the diurnal blood-sugar curve was so grossly abnormal that it was repeated after the necessary changes in the insulin dose and/or diet.

Out-Patients.—To assess whether control was maintained after discharge the total amount of sugar in a 24-hour specimen of urine, collected in a Winchester bottle containing a small amount of toluene, was estimated. This test was carried out several weeks after discharge, and, when necessary, was repeated until good control had been re-established. The two children who were changed to the new insulin as out-patients had the 24-hour urinary sugar excretion determined when routine urine tests before breakfast and supper, isolated blood-sugar estimations, and freedom from hypoglycaemic attacks suggested that good control had been achieved.

By good control we mean that the child, while leading a normal life, is symptom-free and in good health, gains weight satisfactorily, and passes less than 10 g. of sugar in 24 hours. As the daily carbohydrate intake in every case was at least 200 g., this is equivalent to a sugar loss of less than 5%.

Details of Cases

Case No.	Age	Sex	As In-patient									As Out-patient							
			Blood Sugar (mg./100 ml.)								I.Z.S. on Discharge from Hospital (Units)	Present Carbohydrate Diet in Portions (1 Portion = 10 g.)					I.Z.S. Present Dosage (Units)	Urinary Sugar Excretion (g. in 24-hour Specimen)	
			M.N.	4 a.m.	8 a.m.	10 a.m.	Noon	2 p.m.	4 p.m.	8 p.m.		Break-fast	Mid-morning	Dinner	Tea	Supper			
1	8	M	127	64	78	92	64	110	64	157	22	4	2	7	4	5	22	0.72	
2	11	M	176	124	108	78	87	147	125	69	48	6	3	7	6	6	44	3.3	
3	11	F	89	82	169	117	111	103	101	155	44	5	4	7	6	6	44	9.2	
4	12	M	184	108	125	85	85	122	113	97	24	6	3	8	7	6	40	7.8	
5	7	M	116	73	82	153	63	118	77	131	20	7	3	8	4	4	34	0.85	
6	7	M	127	137	71	68	59	94	117	143	34	5	3	6	4	4	22	0.62	
7	12	M	71	87	91	132	87	87	94	165	32	6	4	7	5	6	32	1.2	
8	12	F	125	155	169	155	97	122	104	117	36	6	3	7	4	6	36	8.5	
9	9	M	186	237	111	—	132	—	49	221	32	4	3	7	3	5	32	3.9	
10	11	F	146	143	186	162	113	122	183	177	50	7	3	7	5	5	64	2.1	
11	9	F	237	207	89	134	117	162	137	310	48	5	2	5	4	5	48	2.5	
12	13	M	311	275	211	235	143	146	99	188	92	7	4	8	6	5	92	1.6	
13	9	F	143	75	87	77	68	162	89	101	44	5	3	5	4	4	48	8.6	
14	12	F	38	77	127	—	66	—	52	77	46	5	2	4	4	5	46	24.0	
15	8	F	153	84	87	138	66	104	111	273	88	4	2	7	4	5	88	4.8	
16	13	M	Changed as an out-patient									—	5	4	7	4	6	50	0.63
17	10	F	110	73	97	150	89	179	144	177	44	4	2	6	3	6	48	7.8	
18	9	M	134	63	125	216	108	124	59	64	48	5	4	8	6	4	52	0.75	
19	11	F	Changed as an out-patient									—	5	3	5	5	3	72	8.0
20	9	M	106	63	144	167	111	156	89	129	48	6	3	7	4	5	44	31.0	

Results

The Table shows the results. In nine children, even though control had been achieved in hospital, the insulin dose had to be changed after discharge. In four (Cases 4, 5, 6, 10) the change exceeded 10 units. In a few cases minor alterations had also to be made in the carbohydrate content of the various meals. Ultimately good out-patient control was achieved in all but two children.

Case 14.—This patient was a 12-year-old girl who suffered from petit mal as well as diabetes mellitus. Before the change-over to I.Z.S. she had received a mixture of P.Z.I. and S.I., but it had been impossible, despite anti-convulsion therapy, to keep the urine sugar-free without precipitating numerous attacks of petit mal. This state of affairs remained unaltered with I.Z.S.

Case 20.—A 9-year-old boy, in whom a mixture of P.Z.I. and S.I. had not achieved satisfactory control, was admitted to hospital for restabilization on I.Z.S.; good control was achieved. His attendances at the diabetic clinic had not always been regular and a few weeks later he was readmitted in hypoglycaemic coma brought on by omitting tea and playing cricket. Response to intravenous glucose was immediate. Before discharge from hospital control had been re-established and a 24-hour specimen of urine contained only 4 g. of sugar. However, within a few weeks of discharge two 24-hour specimens of urine contained 56 and 31 g. of sugar respectively. It is our impression that bad parental supervision adds to the difficulty of achieving out-patient control.

Discussion

The evidence that good diabetic control plays an important, if not the most important, part in the prevention or postponement of the late complications of diabetes mellitus is strong (Lawrence, 1950; Joslin *et al.*, 1952; Dunlop, 1954; Engleson, 1954; Matthews, 1954). The problem is to obtain such control with the minimum of inconvenience to the patient. Any method involving only one daily injection has a great advantage in the management of diabetes, particularly in children. In the past it has been possible to control a minority of children whose insulin requirements were low by a single injection of G.I. given before breakfast, but for the majority the action of G.I. was too short and early morning hyperglycaemia occurred. In Priscilla White's (Joslin *et al.*, 1952) experience one-third of juvenile patients can be controlled with a single injection of N.P.H. insulin, which is a suspension of crystalline P.Z.I. We have no experience with this substance. In our hands a single injection of P.Z.I. mixed with S.I. had been the most useful method of achieving good control. However, this method has three disadvantages apart from the trouble involved in making such mixtures (Murray and Wilson, 1953):

1. The varying excess of protamine in P.Z.I. (Nabarro and Stowers, 1953), resulting in varying amounts of S.I. being converted into P.Z.I.
2. The error inherent in any method involving the mixing of two insulins in the same syringe. This disadvantage applies particularly to children, who should be encouraged to give injections at as early an age as possible, but who cannot be relied upon to make an accurate mixture.
3. The danger of early morning hypoglycaemia, which often necessitates a late evening meal or snack. For children such a late meal is undesirable.

These disadvantages led us to try the new insulins. In adults I.Z.S. has been found the most useful (Lawrence, 1950; Lawrence and Oakley, 1953; Murray and Wilson, 1953; Oakley, 1953; Melton, 1954). Venning (1954) obtained good results with I.Z.S. alone in 20 out of 29 patients. Ferguson (1954) was able to maintain good control in 12 out of 15 children with I.Z.S. However, in 3 of the 12 he found it necessary to add I.Z.S. (crystalline) to I.Z.S. to prolong the effect; he suggests that some of his earlier cases might have benefited from a similar addition. Two of his cases were stabilized on a mixture of I.Z.S. and I.Z.S. (amorphous). Thus less than half of Ferguson's cases were well controlled with I.Z.S. alone. By contrast we obtained good results with I.Z.S. in 18 out of 20 patients; in the other two there is no reason to believe that the addition or substitution of crystalline or amorphous I.Z.S. would have led

to better control. The reason for this difference between Ferguson's and our findings probably is that Ferguson, in order to be able to compare the control obtainable with two daily injections of S.I. and with one of I.Z.S., used a fixed diet with the four main meals containing roughly equal amounts of carbohydrate and calories, while in our series good control was achieved by redistributing the carbohydrate between the various meals.

Nabarro and Stowers (1953) suggest that though the 3/7 mixture of amorphous/crystalline I.Z.S. in I.Z.S. may be optimal for Danish dietary habits, a ratio of 2/8 would be more suitable for this country. Venning (1954), however, concludes that no single mixture containing different proportions of amorphous and crystalline I.Z.S. would be likely to provide adequate control for a greater proportion of diabetics than the 3/7 mixture of I.Z.S. Our findings agree with Venning's.

In this series the amount and the distribution of carbohydrate between the various meals have been regulated according to the child's appetite and the urine and blood-sugar findings. The ratio of carbohydrate taken at breakfast, mid-morning snack, and dinner to that taken later in the day usually worked out at 3:2. In Ferguson's series this ratio was roughly 1:1, and this probably accounts for several of his cases requiring the addition of I.Z.S. (crystalline).

Nabarro and Stowers found I.Z.S. unsatisfactory in 10 out of 19 patients requiring more than 48 units a day. On the other hand, Venning achieved satisfactory results with I.Z.S. in 8 out of 13 patients who required more than 48 units. Six of our cases required more than 48 units of insulin a day, and each was well controlled with I.Z.S. (see Table). We were often pleasantly surprised at the good 24-hour control finally achieved, even though the results of early urine tests, on a smaller dose of insulin, had suggested that I.Z.S. would not prove capable of controlling glucosuria without causing hypoglycaemia at some time during the 24 hours.

Reports dealing with adults and children agree that hypoglycaemic reactions with I.Z.S. are few, that they occur commonly in the late morning or afternoon, that they tend to be typical but mild and with a gradual onset, and that usually they are easily avoided by minor dietary adjustments (Lawrence and Oakley, 1953; Nabarro and Stowers, 1953; Oakley, 1953; Ferguson, 1954; Venning, 1954). We have encountered few hypoglycaemic reactions, and only one that gave rise to anxiety (see report of Case 20). Like Murray and Wilson (1953) and Melton (1954) we have occasionally found low blood sugars not associated with hypoglycaemic symptoms. Probably the remarkably even hypoglycaemic action of I.Z.S. (Gerritzen, 1953; Murray and Wilson, 1953; Ferguson, 1954; Venning, 1954) accounts for the absence of such symptoms. It is important to be aware of these low blood-sugar levels and to make the necessary alterations in insulin dose and/or carbohydrate intake.

In previous studies local reactions due to sensitivity to I.Z.S. have been absent (Murray and Wilson, 1953; Nabarro and Stowers, 1953; Oakley, 1953; Ferguson, 1954) or infrequent (Melton, 1954; Venning, 1954). We have not encountered local reactions.

Melton suggests that if the dose of the old insulins was large, the transfer to I.Z.S. should be gradual. Venning has not yet decided whether a gradual transfer has an advantage over an abrupt one. In our series, as in Ferguson's, the change has been abrupt in every case, and we have no reason to regret this method.

In all but two cases stabilization on the new insulin took place in hospital, and it is probable that this accounts for the absence during stabilization of episodes of ketosis on the one hand and severe hypoglycaemic reactions on the other. Venning stresses the difficulties of a change-over to I.Z.S. controlled from the out-patient department and suggests certain precautions. In our opinion children

should, in general, be admitted to hospital for stabilization on the new insulins. In the two out-patients frequent attendances over a long period were necessary before good control was achieved.

Like FitzGerald *et al.* (1954) we found that transfer from a mixture of P.Z.I. and S.I. or G.I. to I.Z.S. necessitated an increase in dose. This increase reflects, at least in part, a better 24-hour control, but Venning has shown that even a well-controlled patient may need an increased dose after transfer to the new insulin to maintain a comparable degree of control. Similarly, in Ferguson's series 6 out of 10 well-controlled children required more insulin when changed to I.Z.S., and only one a smaller dose.

We agree with Venning that estimation of the 24-hour urinary sugar excretion is a most useful method of assessing control after discharge from hospital. In several children routine twice-daily urine tests before breakfast and the evening meal showed no sugar or only a trace, but the amount of sugar excreted in 24 hours exceeded 10 g. and indicated the need to increase the dose of insulin.

We adopted this method for the first time in the present study, and it has taught us that, though in the majority of diabetic children it is relatively easy to establish good control in hospital, it is much more difficult to maintain such control over prolonged periods at home.

Summary

A single daily injection of insulin zinc suspension (a 3/7 mixture of amorphous/crystalline I.Z.S.) achieved good diabetic control in 18 out of 20 children.

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ADDENDUM.—While preparing this paper we have had the opportunity of studying a further eight children, in all of whom good control was obtained in hospital with a single daily injection of I.Z.S. It is too early to state whether such control will be maintained as out-patients.

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The first secondary technical school for deaf boys to be opened in Britain will begin the September term with thirty boys over 11 who use speech as their normal means of communication. To be known as Burwood Park School, the school is to train pupils for technical schools, technical colleges, and colleges of art. It will be under voluntary management, and is to be recognized by the Ministry of Education. Lady Patricia Lennox-Boyd and her father, the Earl of Iveagh, have given the freehold of the property to the school.

TRICHOPHYTON SULPHUREUM RINGWORM

INFECTIONS IN AN ADULT SCALP, A NEWBORN INFANT, AND THREE NURSES

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The following cases of ringworm infection are of interest because one of them occurred in an infant 10 days old—possibly the youngest case on record—and because of the light the outbreak throws on the incubation period of the disease.

Case 1

This baby was born on December 19, 1953, three weeks premature, after a normal delivery. On the tenth day he was transferred to an isolation ward because of umbilical sepsis, which was readily controlled by chlortetracycline cream. His mother was definite that a rash was present on his face at this time; it was noted in writing by the resident medical officer on the fourteenth day as of a circinate erythematous nature. This caused little concern at the time and was diagnosed as "mucous burns." Dermatological opinion was not sought until the twenty-sixth day, when Dr. D. I. Williams made a clinical and microscopical diagnosis of ringworm, which he kindly invited me to investigate further on the next day.

The child was small but healthy. Three striking circular lesions were present on the face. They were bright red and scaly, with central clearing, without vesiculation or accentuation at lanugo hair follicles; one of these rings involved the eyebrow area. The scalp appeared entirely normal; the sides of the face, including the affected area, bore a luxuriant lanugo beard 1 cm. long. The limbs and trunk seemed to be normal. There was no fluorescence of scalp or face under Wood's light.

Case 2

The mother, aged 19, was seen at the same time as Case 1. Her menstrual history had been entirely normal, and this was her first child. She had lived in London for two years, and before that in a seaside town in Sussex. Two years previously she had suffered from multiple boils and whitlows; following a whitlow six months later she noticed deformity of her left index nail. For the past year there had been patchy hair loss, which worried her little; it had been diagnosed as alopecia areata, and she had used several local applications with little effect. A younger brother, still resident in Sussex, was said to suffer from boils and inflammation of the neck, but this was not investigated. Her husband was well. No other relative or close contact was known to have suffered hair loss or ringworm.

The nail of her left index finger was seen to be fragmented, but very little thickened or discoloured; there were no scars suggestive of old whitlows. At first sight the scalp was normal, except for some thinning in the left frontal and parietal areas, consisting of irregular patches of incomplete baldness on each side of the parting. Only on the closest inspection could one see broken-off stumps resembling "exclamation mark" hairs, and some black dots; these were present not only in the bald areas but all over the otherwise normal scalp. There was no inflammation or appreciable scaling, perhaps because she had been applying a lotion containing salicylic acid. Her skin was otherwise normal except for a nondescript crusted lesion 5 mm. in diameter above the left eyebrow. Removal of the crust left a shallow pit, which disappeared in ten days without treatment.