College Hospital for their co-operation in this trial. We wish to thank the Lund Research Fund of the British Diabetic Association for a grant towards the work done at University College Hospital.

REFERENCES

- Colwell, A. R. (1954). *Diabetes*, 3, 162.
 FitzGerald, M. G., Thorn, P. A., and Malins, J. M. (1954). *Lancet*, 1, 187.
 Hallas-Møller, K., Jersild, M., Petersen, K., and Schlichtkrull, J. (1952). *J. Amer. med. Ass.*, 150, 1667.
 Lawrence, R. D., and Oakley, W. (1953). *British Medical Journal*, 1, 242.
 Murray, I., and Wilson, R. B. (1953). *Ibid.*, 2, 1023.
 Nabarro, J. D. N., and Stowers, J. M. (1953a). *Proc. roy. Soc. Med.*, 46, 864.
 — (1953b). *British Medical Journal*, 2, 1027.
 Oakley, W. (1953). *Ibid.*, 2, 1021.
 Venning, G. R. (1954). *Lancet*, 1, 480.

TREATMENT OF DIABETES MELLITUS WITH INSULIN ZINC SUSPENSION

A CLINICAL STUDY BASED ON 479 CASES

BY

K. J. GURLING, M.D., M.R.C.P.

Senior Medical Registrar

J. A. ROBERTSON, M.B., M.R.C.P.

Clinical Assistant

HERMON WHITTAKER, M.R.C.P.

First Assistant

WILFRID OAKLEY, M.D., F.R.C.P.

Physician

AND

R. D. LAWRENCE, M.D., F.R.C.P.

Physician in charge of Diabetic Department

(From the Diabetic Department, King's College Hospital)

The clinical assessment of the new insulin zinc preparations introduced by Hallas-Møller *et al.* (1952a, 1952b) has necessarily been divided into two stages. The first, in which detailed observations were made on a small number of diabetic patients in hospital under controlled conditions, was necessary to verify their metabolic activity and provide familiarity with their clinical potentialities. Our own initial observations (Lawrence and Oakley, 1953; Oakley, 1953) have been confirmed by those of Drury (1953), Murray and Wilson (1953), Nabarro and Stowers (1953), and Venning (1954), all of whom obtained satisfactory results. From this preliminary work it was evident that in carefully selected and well-treated groups of patients a considerable measure of success could be obtained using insulin zinc suspension ("insulin lente"; I.Z.S.) in a single daily injection.

The second and equally important stage in its evaluation was the study of a large number of diabetics in conditions of everyday life. Variations in diet and activity, exposure to intercurrent disease, and the inevitable spontaneous day-to-day fluctuation in the diabetic state might lead to results at variance with those obtained in the earlier studies.

Present Study

This paper is based on our observations on 479 patients seen in the Diabetic Department of King's College Hospital, treated with I.Z.S. in the period July, 1953, to June, 1954. The length of treatment ranged from three months to one year, the majority having been maintained on I.Z.S. for over six months. When out-patients were changed to the

new insulin, reattendance was demanded during the first six weeks at intervals of a week or a fortnight. Special notes were kept with records of the night and morning urine tests for sugar and ketone bodies, blood sugar, weight, hypoglycaemia, local reactions, the patient's subjective observations, and alterations in diet. Some degree of selection was inevitable, as cases already on insulin tended to be chosen because they were judged likely to do well on I.Z.S., and those with insulin requirements of over 80 units a day were usually excluded. A relatively larger proportion of patients were, for instance, on protamine zinc (P.Z.I.) rather than soluble insulin (S.I.). Almost all new patients seen during this period were tried on a single injection of I.Z.S., those with severe ketosis being first treated with S.I. We must emphasize that at this time it was our policy not to alter the treatment of well-controlled diabetics, and only about 10% of insulin cases attending the clinic were changed to I.Z.S. The frequency of visits also made big demands on the patient's co-operation, and those who could not attend as often as we required were not permitted to change. The total of patients treated at King's College Hospital on I.Z.S., I.Z.S. amorphous ("semilente"), or mixtures of the latter with I.Z.S. crystalline ("ultralente") is now well over 700, and we think that enough clinical experience has been gained to justify a definite decision on their value.

Criteria of Control

There are no clear-cut criteria by which the clinical superiority of any type of insulin can be assessed. We have analysed our results so as to take into account both subjective and objective factors, and have compared these with the degree of control previously achieved using other types of insulin.

Subjective.—By this we mean the opinion of the patient concerning his well-being and freedom from hypoglycaemia and diabetic symptoms, as compared with his condition either before any form of insulin was started in new cases or on his previous regimen. Since the patient's attitude to any new form of therapy is likely to be biased this information is of limited value.

Objective.—To assess *absolute control* we have taken into account (A) the degree of night control as indicated by the early morning urine tests; (B) day control, judged by the blood sugar before the midday meal; and (C) alterations in weight. Night control was regarded as good when on at least 75% of examinations the early morning Benedict's test was blue or green ($\frac{1}{2}\%$; one plus). Day control was accepted as satisfactory if the capillary blood sugar was under 200 mg. per 100 ml. (Folin and Wu). Changes in weight of ± 2 lb. (0.9 kg.) were ignored, and only larger variations were deemed significant. When both night (A) and day control (B) were good, and when weight was static or had increased (C), control was considered excellent and the A B C classification applied. As in many patients a slight loss of weight was desirable, we have grouped those with A B C and A B classifications together and described the control as good. When only one or two of the criteria were satisfied control was assessed as fair, and if none were satisfactory it was assessed as poor and recorded as O.

Comparative control was assessed in the same way by comparing the results achieved with I.Z.S. with those over a similar retrospective period of treatment with other insulins, and classified as better, the same, or worse.

Analysis of Results

In order to facilitate discussion we have divided our cases into the following groups:

Adults:	{ Old insulin cases	..	..	312
	{ New cases	..	..	122
Children:	{ Old cases	..	..	30
	{ New cases	..	..	15
I.Z.S. abandoned, including adults and children				46

Table I shows that 433 of the 479 cases receiving I.Z.S. remained on it at the close of the trial, and that in only 32 was this form of treatment regarded as a failure.

TABLE I.—Proportion of Successes and Failures in 479 Cases Treated with I.Z.S.

	No. Treated	Maintained	Abandoned	
			Failed	Other Reasons
Old cases	342	299	30	13
New "	137	134	2	1
Total	479	433	32	14

Adult Old Cases

In the 312 adult old cases I.Z.S. was abandoned in 43, of whom only 30 were assessed as failures. The age distribution of the 269 patients who remained on I.Z.S. is shown in Fig. 1. Their previous insulin arrangements were as follows: S.I., 75; S.I. + P.Z.I., 94; P.Z.I. alone, 89; and globin, 11.

FIG. 1.—Age distribution of adult cases.

Subjective assessment (Fig. 2) showed that 43% (117) felt better on I.Z.S. than on their previous treatment, while 55% (147) noticed no change, and only 2% (5) felt worse. In this latter group objective control was, however, not necessarily any poorer. Assessment of control was equally satisfactory from both the *absolute* and the *comparative* point of view. Night control was good in 174 (65%), but bad in 83 (31%), whilst the renal threshold was sufficiently low in 12 to invalidate the urine tests. Day control was good in 179 (67%) and unsatisfactory in 90 (33%), proportions very similar to those for night control, though not necessarily

FIG. 2.—Analysis of results in adult old cases.

in the same patients. The correlation of these factors is mentioned later. There was a weight gain in 108 (40%), no change in 88 (33%), and a loss in 66 (24%), whilst in 7 (3%) the weight was unreliable because of oedema or significant alterations in diet. As shown in Fig. 2, absolute control was good in 53% (143), and bad in only 9% (29). Comparison with the degree of control on their previous insulin arrangements showed that 32% (84) were better, and that in 64% (172) control was the same. There were only 4% (10) in whom control was worse.

Alteration in Insulin Dose.—It is important to know whether this general improvement was in fact due to the superior action of I.Z.S. *per se* or merely to an increase in the total insulin dose compared with that administered

previously. The changes in dose are shown in Table II, an increase of over 10% being made in 61%, whilst in only 28% was no significant alteration ($\pm 10\%$) necessary. Analysis according to the type of insulin previously administered showed that there was a dose increase of 10% or more in approximately the same number of patients on two injections of S.I. as on a mixed dose of S.I. and P.Z.I. It was in the group on P.Z.I. alone that the highest proportion

TABLE II.—Adult Old Cases—Change in Dose on Transfer to I.Z.S.

Dose Change	Original Insulin				Total	
	Two Injections of S.I.	S.I. + P.Z.I.	P.Z.I.	Globin	No.	%
Less	8	16	5	1	30	11
Same $\pm 10\%$	24	30	17	4	75	28
+25%	17	22	19	3	61	23
+50%	20	18	25	2	65	24
+75%	3	5	6	—	14	5
+100%	3	—	6	1	10	4
+>100%	—	3	11	—	14	5

(75%) needed more insulin, and it was among these patients that the 100% rises occurred. This is probably because the dose of P.Z.I. was limited by the danger of nocturnal hypoglycaemia, control during the day being poorer than that achieved with an increased dose of I.Z.S., with which there is less risk of insulin reactions at night. From these

FIG. 3.—Absolute control on I.Z.S. in relation to previous types of insulin.

FIG. 4.—Comparative control on I.Z.S. in relation to previous types of insulin.

figures it can be seen that most patients needed a larger dose of I.Z.S. than of other types of insulin. In order to decide which patients could best be changed to I.Z.S. the results were analysed according to their previous insulin arrangements (Figs. 3 and 4). Our figures show that the proportion of patients in whom better control was achieved was remarkably similar in all groups. There was no evidence that improvement was directly related to increase in insulin dosage. It is, however, true that patients on very large doses of S.I. were rarely changed, and the highest dose of I.Z.S. that was used with success was 104 units.

Hypoglycaemia in Adults.—I.Z.S., like any other insulin may produce hypoglycaemia. The symptoms and signs are of the usual type, palpitations, sweating, and tremor being

Local Reactions

Local reactions were never bad enough to cause cessation of treatment, but in one case the injections were thought to be more painful than the previous mixed dose of S.I. and P.Z.I. Erythema and pain are often troublesome for a few weeks in any newly treated diabetic, and the impression has been gained that I.Z.S. is less irritating than the more acid soluble insulin. There were five patients in whom local reactions appeared to be worse on British preparations of I.Z.S. than on the original insulin lente, but to all intents and purposes there is nothing to choose between either preparation. It is too early to draw any conclusions about the incidence of fat atrophy or insulin tumour formation.

Discussion

These observations, coupled with a general clinical appreciation, have left us in no doubt that I.Z.S. is a valuable preparation. We can also confirm the opinion of Hallas-Møller that the proportion of I.Z.S. amorphous to I.Z.S. crystalline of 3 to 7 is a satisfactory one for routine use. It has not been possible to predict which cases are most likely to need significantly more of the new insulin, but some increase is usually found to be necessary, especially in patients changed from a single dose of P.Z.I. No patient should be changed to I.Z.S. without adequate supervision. An increase in glycosuria is very common for the first three or four days, until the prolonged action of the crystalline component is fully available, and patients should be warned of the possibility of this. When thirst or polyuria is troublesome a small additional evening dose of S.I. may be advisable for a few days. If after a week the urine tests are still bad, an increase of at least 10% should be made, with still further additions in the following week if necessary. We now usually prescribe a 10% larger dose of I.Z.S. from the start, and the patient is warned not to be disappointed at having to take more insulin.

Progress can be adequately followed by the usual tests provided the renal threshold is normal. For routine purposes the urine should be tested before breakfast and again before lunch, tea, or the evening meal, whichever gives the best result. Clearly it is unsafe to increase the dose of insulin if the urine is sugar-free at any of these times, and in this respect treatment with a single mixed preparation, such as I.Z.S., allows rather less latitude than varying mixtures of S.I. and P.Z.I., or I.Z.S. amorphous and crystalline. It is helpful to modify the dietary arrangements at the time of the change, or in new cases to give at least 160 g. of carbohydrate daily without restriction of fat or protein. A suitable distribution is as follows: Breakfast, 30 g. carbohydrate; mid-morning, 10 g.; midday meal, 40 g.; tea, 30 g.; supper, 30 g.; bedtime, 20 g.

Such a basic diet can usually be increased by the addition of more carbohydrate, especially at breakfast and the evening meal. Since I.Z.S. amorphous comes into action about half an hour later than S.I., it is wise, when convenient, to give the injection one-half to three-quarters of an hour before breakfast; the risk of hypoglycaemia is slight, and the immediate postprandial rise in blood sugar is controlled better.

When these precautions are taken a high proportion of patients on two doses of S.I. as well as those on a mixed dose of S.I. and P.Z.I. with a total daily dose of up to 80 units a day can be safely changed to I.Z.S. Once the dose has been properly adjusted, and an increase is to be expected, about one-third of the patients ought to secure better control of their diabetes. Provided the dose is increased sufficiently, nearly every patient on P.Z.I. alone does well, and there is no doubt that the blood sugar during the day runs at lower levels. Our experience over the last year has shown that I.Z.S. is a reliable insulin, certainly superior to P.Z.I. alone, and in many cases the equal of a mixed injection, or of S.I. alone, without the necessity of two injections. There is no reason why it should not be widely used in the future. Newly discovered diabetics, both

children and adults, should always be given the benefit of a single injection of I.Z.S. once severe ketosis has been dealt with. S.I. still remains indispensable during surgical operations, pregnancy, periods of severe ketosis, and in the treatment of diabetic coma.

Summary

I.Z.S. has been used in the treatment of 479 diabetic patients. The degree of control has been assessed both subjectively and objectively, the latter both from an absolute standpoint and in comparison with that achieved with previous forms of therapy.

In less than 7% of cases I.Z.S. was a failure, whilst 31% of adults and 37% of children previously treated with insulin were found to be improved.

I.Z.S., as at present constituted, is considered to be a satisfactory preparation which should enable an increasing number of diabetics to be adequately controlled on one injection of insulin a day.

Some practical points in the use of I.Z.S. and in the management of the patients are discussed.

We are indebted to Dr. Hallas-Møller and the Novo Laboratories in Copenhagen, as well as to Evans Medical Supplies Ltd., Liverpool, for generous supplies of Novo lente insulin. We also wish to thank the nursing, laboratory, and clerical staff of the Diabetic Clinic, particularly Sister Maureen Tomlinson, our out-patient sister, Mr. H. R. Millar, our chief technician, and Miss E. P. Comley, secretary to the department.

ADDENDUM.—Since we made the above analysis of our results with I.Z.S. our views on its usefulness and application to the treatment of diabetes have been modified by further experience. We are now convinced that there exists a recognizable group of patients in whom I.Z.S. fails to control hyperglycaemia and prevents ketosis. These cases are relatively insensitive to all the long-acting insulin preparations and cannot successfully be treated for any length of time without the use of S.I. Temporary control may sometimes be achieved with the use of large doses of I.Z.S., but this is poorly maintained, or completely lost, when infection or intercurrent illness further reduces insulin sensitivity. It is now our practice not to attempt to change over such cases to one injection of I.Z.S., but rather to leave them on some arrangement which includes the use of S.I.

REFERENCES

- Drury, M. I. (1953). *J. Irish med. Ass.*, 33, 96.
Engelson, G. (1953). *Nord. Med.*, 50, 1008.
Hallas-Møller, K., Jersild, M., Petersen, K., and Schlichtkrull, J. (1952a). *J. Amer. med. Ass.*, 150, 1667.
— Petersen, K., and Schlichtkrull, J. (1952b). *Science*, 116, 394.
Lawrence, R. D., and Oakley, W. (1953). *British Medical Journal*, 1, 242.
Murray, I., and Wilson, R. B. (1953). *Ibid.*, 2, 1023.
Nabarro, J. D. N., and Stowers, J. M. (1953). *Ibid.*, 2, 1027.
Oakley, W. (1953). *Ibid.*, 2, 1021.
Venning, G. R. (1954). *Lancet*, 1, 480.

At Barrow-in-Furness, as elsewhere in towns which have room to spread, new housing estates have developed on the outskirts. The additional child-welfare clinics which are needed to serve these new estates cannot yet be built, and the medical officer of health, Dr. James MacIachlan, has got over the difficulty by establishing a mobile clinic service in a second-hand single-deck omnibus at a cost of £1,500. The clinic contains three rooms, the rearmost being a waiting-room with accommodation for ten mothers; then comes the nurse's room, containing baby-scales and a weighing machine; and the third room is the doctor's, which has an examination couch, washbasin with gas water-heater, instrument stand, sterilizer, and desk. The rooms are warmed by convection heaters, specially modified for use with calor gas, and there are electric extractor fans in the roof of the vehicle. The water supply is carried on the roof, and waste water is collected in a tank under the floor. The staff consists of a doctor, a health visitor, and an ambulance driver. The usual clinic facilities are provided, including immunization and vaccination.