FURTHER EXPERIENCE WITH THE "LENTE" INSULINS

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The initial investigation into the use of insulin-zinc suspensions in the diabetic clinic of the Victoria Infirmary, Glasgow, suggested that these insulins possessed certain advantages over protamine-zinc and globin insulins (Murray and Wilson, 1953), an opinion which coincided with that of other workers in this country (Lawrence and Oakley, 1953; Nabarro and Stowers, 1953; Oakley, 1953; Venning, 1954). Since insulin zinc suspensions became generally available late in 1953 they have been widely used, and several reports based on studies extending over prolonged periods have appeared (Gurling *et al.*, 1955; Stowers and Nabarro, 1955; Jersild, 1956; Spencer and Morgans, 1956). These have in general confirmed the original views of their value. The results reported by Jersild were particularly excellent, since he obtained control with a single daily injection in 96% of patients, and in the remainder two doses a day of I.Z.S. proved satisfactory. However, although we have used these insulins extensively for five years and have found them generally satisfactory, our experience has shown that in certain cases they have given poor control, or have failed entirely. It was therefore decided to examine our results in some detail and compare them with those of other workers.

Method of Investigation

A survey of out-patients attending the diabetic clinic during 1956 showed that 335 of these had been treated with insulin zinc suspension for a period of at least six months. Of these, 134 were "new" patients who had never previously taken insulin, and 201 "old" patients all of whom had been treated with some other insulin before receiving I.Z.S. The age and sex distribution is shown in Table I. None was obese; all were of the insulin-deficient

TABLE I.—Age Distribution. (Numbers of female patients are given in parentheses)

Age Groups:	5-20	21-30	31-40	41-50	51-60	61-70	Over 70
New patients ..	14 (5)	15 (7)	21 (7)	15 (11)	29 (12)	22 (20)	18 (9)
Old ..	19 (9)	26 (17)	22 (11)	32 (12)	41 (25)	47 (25)	14 (13)

type liable to ketosis, and 60% of the "old" patients had been diabetic for more than five years. All the patients had been instructed in a prescribed diet with carbohydrate adjusted to individual requirements. Frequent urine tests were made by patients, generally with "clintest" tablets. Considerable reliance was placed on the patient's own record of these tests, carried out from time to time before each of the main meals of the day, but tests were made at the clinic on each attendance, when frequently blood-sugar estimations were also made.

Since 1953 all new patients requiring insulin have been started with I.Z.S., with the exception of those found on first examination to have considerable ketosis. The latter were generally treated initially with multiple doses of soluble insulin, but as soon as ketosis was overcome I.Z.S. was begun. "Old" patients were normally continued on their existing regime if this appeared to be quite satisfactory, and

were transferred to I.Z.S. only for some definite reason, such as troublesome allergic reaction at the site of insulin injection. Sometimes I.Z.S. was tried in the hope that better control might be established where this was unsatisfactory. Occasionally change to I.Z.S. was made in a patient taking a mixture of soluble and protamine-zinc insulins with a view to eliminating the trouble of making a mixture in the syringe, although this of course could be helpful only when I.Z.S. alone, without admixture with I.Z.S. amorphous or I.Z.S. crystalline, proved effective.

The assessment of the degree of diabetic control in a patient presents difficulties, and no entirely satisfactory method has been devised. Gurling *et al.* (1955) have used as the basis for classification the three factors: (1) degree of night control as judged by early morning urine tests; (2) day control as shown by the blood-sugar level before mid-day; and (3) satisfactory maintenance of weight. We have used similar if perhaps rather stricter criteria, as follows:

1. *Excellent Control.*—Urine tests at all times of day "blue" or occasionally "green," forenoon blood sugar not exceeding 200 mg./100 ml., no insulin reactions, weight constant.
2. *Good Control.*—As above except for occasional "yellow" test, occasional elevated blood sugar, and perhaps the occurrence of mild but infrequent insulin reactions.
3. *Fair Control.*—Urine tests mainly "blue"/"green" but frequently "yellow" at some time or other in the day. Blood sugar before mid-day commonly less than 200 mg./100 ml., but sometimes exceeding this level.
4. *Poor Control.*—Tests generally "yellow" or "red" but "blue"/"green" at times. Blood sugar variable. Liability to insulin reactions, occasionally severe.
5. *Bad Control.*—Urine tests bad. Blood sugar always over 200 mg./100 ml. Readily liable to ketosis or hypoglycaemia.

Results in New Patients

It is generally recognized that new patients respond well to treatment and that with the older types of insulin they were often well controlled, at least in the early stages. We have not attempted to estimate the relative efficiency of the old and newer insulins in the treatment of new patients, but simply report results obtained in 134 cases. Excellent control was estimated in 36 (26.5%), good in 75 (56%), fair in 15 (11.5%), poor in 7 (5.2%), and bad in 1 (0.8%). Taking the first two degrees of control together, it will be seen that very satisfactory results were obtained in 82.5% of these patients. A single daily injection of unmodified I.Z.S. proved adequate in 121 (90%) cases, while 9 (7%) required relatively more I.Z.S. amorphous, and 4 (3%) relatively less. There was much variation in the size of dose required. In 107 (80%) patients this did not exceed 40 units; but 22 (16%) needed 40-80 units, while 5 (4%) had doses ranging up to 120 units daily. No correlation was found between the degree of control obtained and the individual variations in the proportions of I.Z.S. amorphous ("semilente") and I.Z.S. crystalline ("ultralente"), with the size of the dose, or with the age of the patient.

Results in Old Patients

In Table II the degree of diabetic control existing in 201 old patients prior to transfer to I.Z.S. is contrasted with the state of control thereafter. The number showing excellent or good control was increased from 68 to 130 (64.7%).

TABLE II.—Degree of Control of "Old" Patients with I.Z.S. Contrasted with Degree of Control on Previous Insulin

Previous Control		Control with I.Z.S.				
		Excellent	Good	Fair	Poor	Bad
Excellent ..	8	8	—	—	—	—
Good ..	60	13	40	4	—	1
Fair ..	79	5	37	32	5	—
Poor ..	37	—	20	8	9	—
Bad ..	17	1	6	4	—	6
	201	27	103	48	16	7

TABLE III.—*Dosage of I.Z.S. Relative to that of Previous Insulin*

Diabetic Control	Dose of I.Z.S. Relative to that of Previous Insulin			Total
	Same	Increased	Decreased	
Improved ..	29 (30.8%)	39 (41.6%)	26 (27.6%)	94 (100%)
Equal ..	34 (35.8%)	47 (49.5%)	14 (14.7%)	95 (100%)
Worse ..	2 (16.7%)	10 (83.3%)	—	12 (100%)
Total ..	65 (32.3%)	96 (47.7%)	40 (20%)	201 (100%)

Improvement was noted in 94 patients (46.8%), and in approximately the same number the degree of control was unaltered, although in eight of these control had been so excellent that further improvement could not be expected. Six cases, however, previously bad, continued so with I.Z.S. These were unstable diabetics who had eventually to resume

multiple injections, and were regarded as failures with I.Z.S. It will also be seen that in 12 other patients control is recorded as worse after changing to the newer insulin.

For the 189 patients shown as retaining equally good, or obtaining better, control the dose of I.Z.S. was greater than that of the former insulin in 86 cases, but in 40 a smaller dose sufficed (Table III). Where the dose had to be raised the increase

Type of mixture (expressed as percentage of semilente insulin) used in "old" patients. 0% = ultralente. 30% = lente. 100% = semilente.

was commonly (74% of cases) about 50%. Some, however, required as much as double the former dose. I.Z.S. alone was found suitable in 68% of patients (see Chart), the remainder obtaining the best results on a regime varying from I.Z.S. crystalline alone, through various combinations to I.Z.S. amorphous alone. Such variations in dosage and in the amorphous and crystalline proportions occurred irrespective of the degree of control exerted by the previous insulin, and were noted in patients of all groups. Neither the age of the patient nor the duration of the diabetes appeared to affect the nature of the response to transfer to I.Z.S.

Failures

We have not included in this study a few cases in which immediate deterioration in control after transfer led to abandonment of I.Z.S. at the patient's request, since with persistence and adjustment of dosage satisfactory results might have been obtained. Only patients maintained on I.Z.S. for at least six months are considered. As mentioned above, after transfer to this insulin control was regarded as worse in 12 cases, and these, together with the six unstable diabetics for whom it was found unsuitable, might be regarded as "failures." In three of the former, however, I.Z.S. was not discontinued, as it seemed on the whole preferable.

From Table II it will be seen that, of 60 patients classified as having good control on the previous insulin, seven are shown as having poorer results with I.Z.S. In one of these serious deterioration occurred but was coincident with the development of severe thyrotoxicosis. Of the two whose control became poor, one developed pulmonary tuberculosis soon after the change of insulin was made, while the other suffered from frequent insulin reactions and seemed to be better after changing back to a mixture of protamine-zinc

and soluble insulins. The other four patients showed only slightly inferior control, and are classified as fair. One of these seemed to be more than compensated by the relief from local allergy previously troublesome, but in the other three I.Z.S. had to be abandoned. Great variability in the intensity of the diabetes in one patient rendered a single injection a day unsuitable, while in another case mammary carcinoma and physical deterioration developed after transfer to I.Z.S. A third patient complained of more frequent reactions, and reverted to his former insulin.

Fair control existed before changing to the new insulin in 79 patients, but in five this subsequently became poor. One of these was found to have contracted pulmonary tuberculosis. In two cases insulin reactions appeared to be more frequent and more severe, and the previous regime was preferred. The other two patients, however, were emotionally unstable individuals in whom the poorer state of control did not seem attributable to the change in the type of insulin, and in these the use of I.Z.S. has been continued. In this series of 201 old patients, therefore, the use of I.Z.S. has been continued in all except 15.

Insulin Reactions

It is difficult to make a comparison of hypoglycaemic attacks before and after transfer to I.Z.S., as other causative factors may be operative. Some patients, however, did complain that such attacks became altered in character, tending to come on with little or no premonitory symptom, and this led to reversion to their previous type of insulin in the four cases mentioned above. Local allergy at the site of injection was much less. It was on account of this trouble that 27 of the old patients previously treated with protamine-zinc insulin, alone or in combination with soluble insulin, were changed to I.Z.S., and 23 of these obtained complete relief, while improvement was noted in the remaining cases. Nevertheless, in three patients fat atrophy at the site of injection occurred.

Lapse from Control with I.Z.S.

The appearance of intercurrent disease is, of course, likely to upset diabetic control, and, as recorded above, the development of tuberculosis and thyrotoxicosis resulted in such disturbance that I.Z.S. had to be abandoned. However, even minor infections with which the experienced diabetic was accustomed to deal by temporarily increasing the dose of insulin appeared to cause more trouble to patients taking I.Z.S. Larger increases of dose seemed necessary, but, even with this, diabetic control was often difficult to re-establish, and this disturbance was apt to persist for a longer period. In cases of any severity additional doses of soluble insulin were required, but after recovery it was generally possible to return to approximately the same dose of I.Z.S. as previously. When insulin requirements rose with the onset of menstruation this could be met usually by increasing the dose of I.Z.S. by from 10% to 20% for a few days.

Discussion

Examination of the results obtained with insulin-zinc suspensions show that very satisfactory control was obtained in 82.5% of new patients but only in 64.7% of patients previously treated with some other type. There is little to be deduced from this apart from the well-recognized fact that in the initial stages diabetes is generally less difficult to control. On the other hand, a large number of the old patients were transferred to I.Z.S. because of some dissatisfaction with the control obtained with the previous regime, and the high proportion of these who did respond well thereafter may be regarded as satisfactory. Other workers in this country have selected the patients to be changed to I.Z.S., and, since the proportion of "difficult diabetics" in various series studied must vary to some extent, exact comparison between our results and those of others may well be inaccurate. The good results we obtained in 64.7%, however, are to be compared with those of Gurling *et al.* (1955), who obtained good control in 53% of 269 adult old patients,

and of Spencer and Morgans (1956), who obtained satisfactory control in 83% of cases.

Jersild (1956), reviewing 1,000 patients, found satisfactory control in 96% with a single injection daily of I.Z.S. and with two injections in the remainder. His patients, however, did not form a group comparable to those of our series or those of the other workers we have cited. Of the 1,000 patients studied the proportion of women aged 50-70 was relatively high and most of these patients were overweight. Spencer and Morgans pointed out that in the assessment of a new form of treatment of diabetes long and varied experience is necessary, but, in addition, it would seem essential, in comparing the results of different observers, that the type of patient, the duration of diabetes, and the criteria of diabetic control should be defined. Improvement in diabetic control might in fact be due to other factors after transfer to the new insulin, since, knowing that in the assessment of the value of the new insulin study would be made of his record of urine tests, the patient might take better care with diet. As, however, observations were made in each case for a minimum of six months, and in many cases much longer, it seems probable that improvement can generally be credited to the insulin. Improved control was noted in 46.8% of our cases. Other workers have reported improvement—Gurling *et al.* in 32% of cases, Spencer and Morgans in 36%, and Stowers and Nabarro in 80%.

The dose of I.Z.S. required was much larger than that of the previous insulin in 47.7% of cases. The explanation of this increase in some patients taking protamine zinc insulin was that the occurrence of hypoglycaemia in the early morning limited the dose despite relatively poor diurnal control, while the more even effect of I.Z.S. permitted a larger dose, with resultant improvement throughout 24 hours. A smaller dose sufficed in 20% of patients. In many cases this was accounted for by lessening local allergy, with diminished tendency to "insulin lumps" and consequently improved absorption. I.Z.S., with its proportion 3:7 amorphous/crystalline I.Z.S., proved satisfactory in 76% of our cases (in 90% of new and 68% of old patients). In the remainder better results were obtained with the two components in different proportions or, in a few cases, with one or other of these alone. Both Stowers and Nabarro (1955) and Jersild (1956) also found that alteration in the proportions was sometimes desirable, although the former were satisfied with I.Z.S. in 83.5% of cases, and the latter in 74%.

Many workers, however, appear to rely on I.Z.S. alone and have encountered difficulty in some cases with hypoglycaemia, particularly in the late afternoon, while at other times glycosuria might be considerable. Marble (1957), for example, has noted this so often that he recommended that patients with I.Z.S. should have an extra meal in the afternoon. It has always been our endeavour to prescribe the meals so far as possible according to the patient's taste and habit and to avoid the necessity of compelling him to eat at unusual hours. By altering the proportions of the more rapidly acting I.Z.S. amorphous and the slower-acting I.Z.S. crystalline it is often possible to obtain satisfactory control while avoiding hypoglycaemic episodes.

I.Z.S. (lente) was discontinued in 15 of the 201 old patients. In four cases the reason for this was that hypoglycaemic episodes became worse and in several instances seemed to occur with less premonitory symptoms. The development of serious intercurrent disease in three patients resulted in the poorer control which might have occurred whatever type of insulin had been used. However, Stowers and Nabarro have drawn attention to the danger, when using I.Z.S., of lapse from control in the presence of intercurrent infection and pointed out that in such circumstances the dose must be increased more boldly than in the case of other insulins. Our experience fully confirms this observation, and we have frequently had to advise patients, on finding diabetic balance upset, to take one or more injections of soluble insulin later in the day in addition to their usual morning dose of I.Z.S., rather than to attempt to obtain

control simply by an increase of dose of the latter insulin. No explanation has been given for this peculiarity with I.Z.S., but we suspect that it concerns the crystalline element rather than the amorphous. The following case report illustrates this.

A man aged 62, diabetic for 14 years, having excellent control with a mixture of 16 units of I.Z.S. amorphous and 24 units of I.Z.S. crystalline, sustained a wound of the arm which became septic. He had had previous experience of upset of control by intercurrent infection, and of his own accord, finding urine tests had become poor, increased his dose to 20 units of I.Z.S. amorphous and 52 units of I.Z.S. crystalline (thereby taking a mixture which is virtually 72 units I.Z.S.), but with no apparent benefit. On changing to 40 units of I.Z.S. amorphous in the morning and 20 units of I.Z.S. amorphous in the evening excellent control was at once re-established. After a few days he tried a single injection, taking 20 units of I.Z.S. amorphous and 48 units of I.Z.S. crystalline, but urine tests immediately became bad, again to become satisfactory on resuming the two doses of I.Z.S. amorphous. One week later, when the arm was healing, he was able to revert to his original mixture.

This case demonstrates a practical feature in the use of the insulin zinc suspensions. When I.Z.S. proves inadequate we prescribe I.Z.S. amorphous and I.Z.S. crystalline, and instruct the patient in the amount of each which he should take mixed in the syringe. Should he lapse from control this mixture taken in the morning can be reinforced by an injection in the evening of I.Z.S. amorphous, which he has available, and on subsequent days he should rely on the latter alone, taken morning and evening, till the emergency has passed. If he is in the habit of taking I.Z.S. he is probably best advised, while continuing his usual morning dose of this, to supplement it with two or more injections of soluble insulin, being guided by urine tests.

Summary

A review has been made of 335 diabetic patients treated for at least six months with I.Z.S. Satisfactory control was obtained in 82.5% of 135 new patients, and in 64.7% of 201 patients previously receiving some other form of insulin. In 94 of the latter I.Z.S. produced a better degree of control. I.Z.S. proved unsatisfactory in 15 patients.

In the presence of intercurrent infection lapse from diabetic control with I.Z.S. appears to occur more readily than with some other insulins. It is suggested that in such circumstances it is I.Z.S. crystalline which becomes relatively ineffective, since transfer temporarily to two injections a day of I.Z.S. amorphous has been shown to re-establish control.

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The Clean Air Act came into force on June 1, making it a punishable offence to emit dark smoke from any chimney in England and Wales. The ban applies to all buildings and also to railway engines and ships, but it will chiefly affect industrial and commercial premises. The Act requires steps to be taken to reduce grit and dust emissions from industrial chimneys. The Ministry of Housing and Local Government has prepared a memorandum on the industrial provisions of the Act and their administration (H.M.S.O., price 1s. net). The memorandum, which has been circulated to local authorities, deals with the following subjects: dark smoke, grit and dust, smoke nuisance, railway engines, and ships. Under each heading the relevant part of the Act, is quoted, followed by comment on its administration.