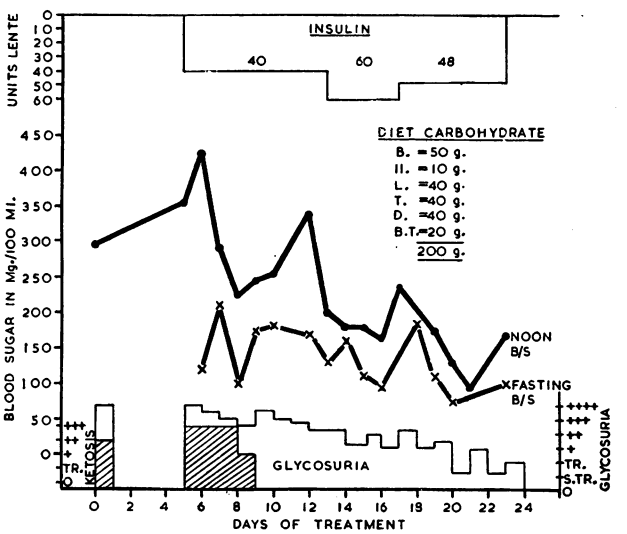

FIG. 2.—Fasting and noon blood sugars, glycosuria, ketosis, and dosage of lente insulin in a male patient aged 40. New case; control good.

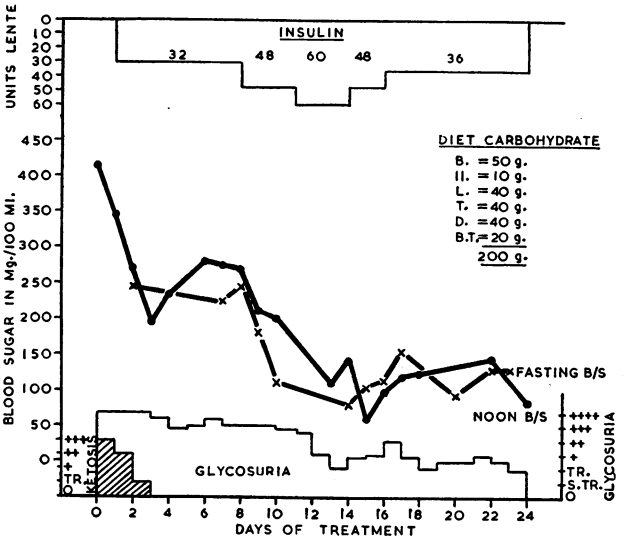

FIG. 3.—Fasting and noon blood sugars, glycosuria, ketosis, and dosage of lente insulin in a female patient aged 20. New case; control good.

There have been remarkably few hypoglycaemic reactions either in the in-patients or in the out-patients. Such reactions as have occurred have been quite typical and relatively mild, except in one or two instances in which the dose given has been clearly too large and had to be greatly reduced.

Reactions have been observed at 10 a.m., three hours after injection, and at noon in the same patient, but not on the same day. The commonest times at which patients on lente insulin before breakfast are liable to have hypoglycaemic reactions appear to be during the morning or afternoon. Nocturnal reactions are uncommon in our experience, and hypoglycaemia rarely occurs in the early hours of the morning.

Conclusion

The reason why we have concentrated on lente insulin is that we think it is the most generally useful of the three preparations and the one which, if any, should be put on the market in the near future. We feel that further knowledge is required to determine whether or not ultralente has, for practical purposes, the same action as P.Z.I. and semilente the same action as globin insulin; if this is shown to be the case then it would seem reasonable to suggest that, if and when these two insulins of the lente series are put on the market, P.Z.I. and globin insulin should be simultaneously withdrawn so as to lessen the confusion which would inevitably result from having seven insulin preparations available to doctors and patients at one and the same time.

TABLE IV.—*Comparison Between the Hypoglycaemic Action of Different Batches of Lente Insulin.*

Batch No.	Lente Units	Fasting B./S.	Noon B./S.	Batch No.	Lente Units	Fasting B./S.	Noon B./S.
12	40	160	150	12	68	354	313
			160				220
13	40	150	160	13	68	210	280
			162				
14	40	160	170	14	68	309	250
			154				
15	40	115	114	15	68	270	240
			140				
16	40	130	150	16	68	296	255
12	60	198	220	12	60	250	250
		180				233	268
13	60	190	230	13	60	250	260
		176				260	260
14	60	176	—	14	60	260	—
14	68	135	200	15	80	180	260
						135	
15	68	45	136	16	80	140	250
						50	50
16	68	77	166			100	115
		96				120	110

I wish to thank Dr. R. D. Lawrence for his unfailing interest and advice, and the Novo Laboratories of Copenhagen for generous supplies of lente insulin.

REFERENCES

Hallas-Møller, K., Jersild, M., Petersen, K., and Schlichtkrull, J. (1952). *J. Amer. med. Ass.*, **150**, 1667.

—— Petersen, K., and Schlichtkrull, J. (1952). *Science*, **116**, 394.

Lawrence, R. D., and Oakley, W. (1953). *British Medical Journal*, **1**, 242.

THE NEW INSULINS—LENTE, ULTRALENTE, AND SEMILENTE

BY

IAN MURRAY, M.D., F.R.C.P.Ed., F.R.F.P.S.

AND

ROBERT B. WILSON, M.B., B.Sc., M.R.C.P.

From the Department of Metabolic Diseases, Victoria Infirmary, Glasgow

Much interest has been aroused in the new insulin preparations of the Novo Terapeutisk Laboratories in Copenhagen (Hallas-Møller *et al.*, 1952a, 1952b; Lawrence and Oakley, 1953; Nabarro and Stowers, 1953). Through the courtesy of Dr. Hallas-Møller supplies of these insulins were made available to us in October, 1952, and since then we have investigated the effects in 28 patients. We have endeavoured to compare the action of these new insulins with that of insulins in current use, and to consider, in the event of their proving to be superior, whether such superiority was sufficient to warrant their introduction for general usage.

Initially, study was made on in-patients in hospital suffering from diabetes of considerable severity but well controlled with various combinations of soluble insulin and protamine zinc insulin, in order to compare the action of these with that of Novo insulins—"semilente," "lente," and "ultralente." Later we tried the new insulins on some patients in whom control was difficult, in the hope that these might give better results.

The investigation was then extended to include a number of out-patients. We hesitated to ask well-controlled patients to stay off work and come into hospital simply for the purpose of trial of a new insulin, while, on the other hand, we thought that a better comparison might be made with the patient continuing under ordinary working conditions. Those selected could be relied upon to carry out accurately all instructions about diet and urine-testing. Several of these out-patients were chosen either because it had been found that in their cases protamine zinc insulin did not have a sufficiently prolonged action, or because they were particularly subject to local insulin reactions.

All the patients were on a measured intake of carbohydrate in the diet, the amount being regulated by appetite but having regard for the maintenance of proper body weight. The daily allowance of carbohydrate was distributed in three roughly equal portions, at breakfast, lunch, and tea, with snacks between and a small late supper—for example, 285 g., distributed as follows: 8 a.m., 75 g.; 10 a.m., 15 g.; 12.30 p.m., 75 g.; 2.30 p.m., 15 g.; 5 p.m., 75 g.; 9 p.m., 30 g. Protein and fat in the diets were not measured, since the quantity of these consumed varies so little from day to day.

Blood-sugar estimations were carried out by the method of Nelson (1944). Urine tests were done on samples collected before meals and after the bladder had been emptied half to one hour previously. In the case of out-patients, control was estimated largely by the result of urine tests, but in some of these, as in all in-patients, blood-sugar estimations were made.

Results

Details of the 28 patients investigated are summarized in Table I. It will be seen that they varied in age from 14 to 72 years, and that the length of time they had been diabetic varied from a few months to over 20 years. Of these patients 15 were female and 13 male. The results of blood-sugar estimations are shown in Table II. Some of the values were low, but were not associated with hypoglycaemic symptoms.

Lente.—From our observations we concluded that lente insulin had an action similar to that of a mixture of soluble and protamine zinc insulins. In every patient formerly controlled on a mixture of these, control was at least equally

TABLE I.—*Details of the 28 Cases.*

Case No.	Sex and Age	Duration of Diabetes (Years)	Control Original	Dietary Carbohydrate (g.)	Insulin (Units)		Local Allergy		Control with Novo
					Original	Novo	With P.Z.	With Novo	
1	F 22	6/12	Good	165	Sol. 24 P.Z. 12	Lente 36	—	—	Improved
2	F 18	6/12	,,	300	Sol. 56 P.Z. 28	,, 84	—	—	Equal
3	F 57	5	Fair	195	Sol. 24 P.Z. 12	,, 36	—	—	Improved
4	M 46	3/12	,,	345	Sol. 40 P.Z. 20	,, 60	—	—	,,
5	F 20	1	Good	225	Sol. 64 P.Z. 32	,, 96	—	—	,,
6	F 47	9/12	,,	210	Sol. 16 P.Z. 8	,, 24	—	—	Equal
7	M 58	9	,,	210	Sol. 20 P.Z. 10	,, 30	—	—	,,
8	F 23	3	Variable	195	Sol. 80 P.Z. 40	,, 120	—	—	,,
9	F 34	2/12	Good	255	Sol. 24 P.Z. 16	,, 40	+	—	,,
10	M 31	10	,,	270	Sol. 36 P.Z. 24	,, 60–68	—	—	Improved
11	F 34	10	,,	300	Sol. 20 P.Z. 16	,, 36	—	—	,,
12	M 40	13	,,	300	Sol. 20 P.Z. 20	,, 40	—	—	Equal
13	M 26	1½	Variable	270	Sol. 24 P.Z. 24	,, 48	+	—	Improved
14	M 23	7	Good	300	Sol. 80 P.Z. 80	,, 120	—	—	Equal
15	F 72	21	Fair	240	a.m. Sol. 28 p.m. Sol. 28	,, 56	—	—	—
16	M 43	6	,,	255	a.m. Sol. 24 p.m. Sol. 24	,, 48 S.L. a.m. 24 S.L. p.m. 24	—	—	Improved
17	M 37	18	Good	210	Globin 40	Lente 40	—	—	Worse
18	F 58	11	,,	240	a.m. Sol. 20 p.m. Sol. 12 P.Z. 6	,, 38	—	—	Improved
19	M 31	4½	,,	315	P.Z. 104	,, 104 U.L. 104	+ +	— —	Worse Improved
20	F 14	1	,,	285	P.Z. 120	Lente 120 U.L. 120	+ +	— —	— —
21	M 58	30	Poor	210	P.Z. 36	Lente 36 U.L. 36	— —	— —	— —
22	M 16	4	Variable	225	P.Z. 100	U.L. 100	—	—	—
23	M 28	11	Good	200	P.Z. 60	U.L. 60	+	—	—
24	F 46	3	,,	120	P.Z. 24	U.L. 24	—	—	—
25	F 44	5	Fair	225	P.Z. 44	U.L. 44	+	—	Worse
26	M 45	4	Poor	310	P.Z. 64	U.L. 64 L. 52 U.L. 32	+ +	— —	Improved ,,
27	F 45	22	Variable	250	P.Z. 44 Sol. 16	U.L. 68 U.L. 48 S.L. 28	+ +	— —	Worse Improved
28	F 46	19	,,	210	Globin a.m. 40 Globin p.m. 20	S.L. a.m. 40 S.L. p.m. 40	—	—	—

TABLE II.—*Blood Sugar mg./100 ml.*

Case No.	Insulin (Units)	Fasting	Fore-noon	Noon	After-noon	Before Tea	Evening
1	Sol. 24 / P.Z. 12	165	—	38	170	165	—
	Lente 36	181	—	74	78	70	—
2	Sol. 56 / P.Z. 28	72	—	34	32	120	—
	Lente 84	115	—	48	—	—	—
3	Sol. 24 / P.Z. 12	320	240	131	—	81	—
	Lente 36	99	138	57	—	99	—
	Sol. 24 / P.Z. 12	406	152	28	—	65	244
4	Sol. 40 / P.Z. 20	260	340	270	—	189	—
	Lente 60	168	256	76	—	82	—
	Sol. 40 / P.Z. 20	314	238	147	—	180	—
5	Sol. 64 / P.Z. 32	151	208	144	47	—	120
	Lente 96	47	69	32	35	—	189
8	Sol. 80 / P.Z. 40	96	—	199	152	118	—
	Lente 120	72	—	243	275	300	—
	,, 140	92	—	280	267	162	—
9	,, 40	110	175	110	75	—	98
12	Sol. 20 / P.Z. 20	340	—	225	332	—	—
	Lente 40	166	—	128	195	193	—
13	,, 48	204	—	99	168	218	—
14	Sol. 80 / P.Z. 80	98	84	56	—	129	126
	P.Z. 120	54	175	80	—	161	162
	Lente 120	110	147	41	—	70	128
15	a.m. Sol. 28 / p.m. Sol. 28	272	164	72	165	274	—
	Lente 56	76	30	48	81	201	—
16	a.m. Sol. 24 / p.m. Sol. 24	326	189	97	—	162	240
	Lente 48	125	178	53	—	46	—
	a.m. S.L. 24 / p.m. S.L. 24	110	196	124	—	168	136
20	P.Z. 120	70	176	126	223	165	—
		62	—	310	271	246	—
	U.L. 120	50	—	368	391	429	—
		34	—	290	340	336	264
21	P.Z. 36	378	389	270	318	170	—
	Lente 36	326	221	123	256	298	—
	U.L. 36	140	414	307	302	55	—
22	P.Z. 100	250	48	108	224	206	—
	U.L. 100	85	304	254	358	252	—

good when lente was administered, while in a number of cases rather more even control throughout the 24 hours was noted. There was some advantage in that with the use of lente the trouble of making a mixture of two insulins was avoided.

The results obtained in two of these patients are shown in Figs. 1 and 2. It will be noted that, while they were well controlled with lente, in Case 3 previous control had not

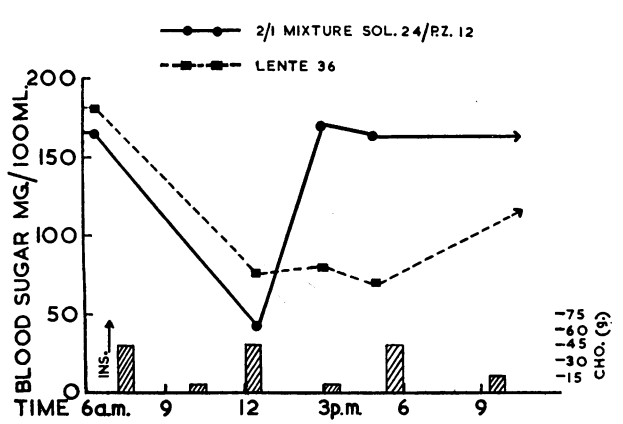

FIG. 1.—Chart of Case 1.

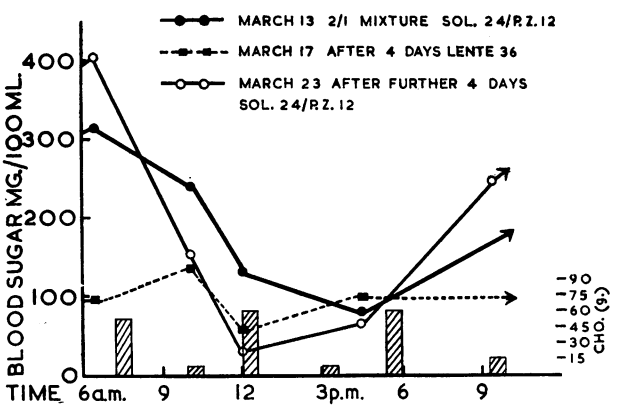

FIG. 2.—Chart of Case 3.

been completely satisfactory. The blood-sugar values given in Table II for Case 8 would seem to show that the results obtained with lente were much inferior to those with a mixture of soluble and protamine zinc insulins. Actually we concluded that control was equal by either method, but this patient showed great variability. Although no other series of blood-sugar estimations was carried out while she was having the mixture, occasional examinations on various days gave values at least as high as those with lente.

In three cases in which lente was used the patient had previously been having morning and evening injections. In one (Case 18) the result was extremely satisfactory. In the other two (Cases 14 and 16), although the fasting blood-sugar level was normal, the levels during the early part of the day were too low.

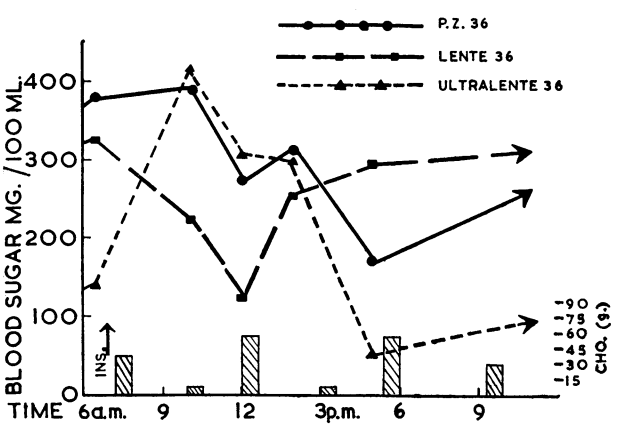

FIG. 3.—Chart of Case 21.

Ultralente.—We found that ultralente had a more prolonged action than protamine zinc insulin, but when used alone it failed to control hyperglycaemia for several hours after injection. It is apparent in Fig. 3 that control on protamine zinc was poor. The explanation is that, although the patient was continued on this insulin, the dose, on account of hypoglycaemic attacks each afternoon, was reduced until these were eliminated.

Semilente.—We have used semilente in an insufficient number of cases to be able to draw definite conclusions, but its action appears to resemble that of soluble insulin.

Local Allergy.—Troublesome local insulin reactions are commonly encountered, as has been pointed out by Paley and Tunbridge (1952). This was a feature in eight of our cases, all of which had been receiving protamine zinc insulin either alone or in a mixture. On changing to lente or ultralente local allergy was immediately eliminated in every case.

Use of a Mixture.—Recently we have tried in one case (Case 26) a mixture of ultralente with lente, and in another (Case 27) ultralente with semilente. In the former, protamine zinc failed to control the man properly, urine tests were bad, and he became thirsty at night. The thirst was relieved on change to ultralente, but the tests still showed considerable glycosuria. He was then given a mixture of 52 units lente with 32 units ultralente, and he is now under better control than ever before. In the other case, a woman who has been diabetic for 22 years, control was very variable. Best control was obtained with separate injections of protamine zinc 44 units and soluble 16 units. She was then given 68 units ultralente. With this she became thirsty in the late afternoon and tests were bad, but in the early morning the urine was almost sugar-free. Eventually she was given a mixture of semilente 28 units with ultralente 48 units. This was a very definite improvement, as judged by urine tests, and she remained symptom-free and without hypoglycaemic attacks, of which she was always afraid.

It will be observed from Table I that no conclusion has been made regarding control with novo insulin of five patients (Cases 15, 20, 21, 23, and 28). In the first four of these the results seemed to suggest that a mixture of lente with ultralente might have proved very satisfactory, and until this has been tried it seems premature to judge the efficacy of novo insulins in these cases. The remaining case showed such fluctuations in control, associated with frequent asthmatic attacks, that comparison between different types of insulin was impossible.

Failures.—In two cases, previously well controlled, change to novo insulin was followed by rapid deterioration. Both were out-patients, and with the reappearance of diabetic symptoms they, on their own initiative, abandoned the new insulin and resumed that which they had been taking before. The first (Case 17) was a very intelligent man, a research chemist, extremely careful about diet and accurate in urine tests. On changing from globin insulin to lente he steadily became worse, and even a considerable increase in the dose of lente failed to correct this. With resumption of globin control was regained. The other patient (Case 25) was tried with ultralente because she was having much trouble with "lumps." All the urine tests very soon became bad and she developed thirst. Within two days of the resumption of protamine zinc control was restored. We have not so far had an opportunity of investigating the cause of the failure of novo insulin in these cases.

Conclusions

We considered that control obtained with the new Novo insulins was rather better in 14 and equally good in 7 of the 28 diabetic patients in whom trials were made. In two cases the results were definitely worse.

In four of the remaining five cases we have not felt justified in drawing definite conclusions on the relative merits of the old and new types of insulin, since the possibility of control with a mixture of lente and ultralente has not yet been investigated.

Lente insulin appeared to have an action similar to that of a mixture of soluble and protamine zinc insulins and thus had the advantage of avoiding the trouble of making such a mixture. In some cases it seemed to exert a more even action than such a mixture.

Ultralente was found to have a more prolonged action than that of protamine zinc insulin, but when used alone it rarely effected control in the early part of the day. It has the advantage that a small dose of semilente can be added without losing the effect of the latter, thus avoiding the necessity for separate injections.

Semilente appears to have an action similar to that of soluble insulin.

The Novo insulins available to us were in a strength of 40 units per ml. only, thus necessitating a bulky injection in many cases, but we understand that they may be introduced in double this strength.

The complete absence of local allergic reactions when using the new insulins was striking. In no instance was there any evidence of this, and, even in the eight cases in which insulin "lumps" had previously been troublesome, change to Novo insulin gave immediate and complete relief.

Having due consideration for the necessity of serious reflection before recommending the introduction of any insulin in addition to the series in current use, and admitting that further investigation especially regarding the use of mixtures of lente and ultralente insulins is required, we would nevertheless advise that lente and ultralente insulins be made available for general use. It seems probable that these insulins could control the large majority of diabetics and render unnecessary the use of protamine zinc and globin insulins.

ADDENDUM.—This paper was read at the meeting of the Diabetic Association in Leeds on July 17, 1953. Since that date it has been possible to make further observations on three of the patients (Cases 20, 21, and 23) in whom it was hoped better results might be obtained with the use of a mixture.

Case 20.—On changing from a dose of 120 units lente to a mixture of lente and semilente, 60 units of each, blood-sugar values were: fasting, 175 mg. per 100 ml.; noon, 47 mg.; 4 p.m., 156 mg.; 8.30 p.m., 140 mg. In view of the sharp drop in blood sugar before lunch the dose was altered to semilente 40 units, lente 80 units. Judged by urine tests, control was extremely satisfactory and there have been no hypoglycaemic incidents.

Case 21.—After the trials with lente and with ultralente he was discharged from hospital on his former regime. Later, as an out-patient, he was given lente and ultralente as a mixture, with 20 units of each. With this, control was better than ever before. The tendency to insulin reactions was entirely overcome. Blood-sugar results were: fasting, 64 mg. per 100 ml.; 11.45 a.m., 70 mg.; 4.30 p.m., 57 mg.; 8.30 p.m., 105 mg.

Case 23.—This man has now been taking a mixture—lente 40 units, ultralente 60 units—for six weeks, with satisfactory results.

We are in no doubt that in these three cases the use of a mixture has brought about definite improvement in control.

Investigation of the cause of failure with this insulin in Cases 17 and 25 has not yet been possible.

We are indebted to Messrs. Hendon Laboratories Ltd. and to Evans Medical Supplies Ltd. for supplies of the Novo insulins.

REFERENCES

Hallas-Møller, K, Petersen, K., and Schlichtkrull, J. (1952a). *Science*, **116**, 394.
—— Jersild, M., Petersen, K., and Schlichtkrull, J. (1952b). *J. Amer. med. Ass.*, **150**, 1667.
Lawrence, R. D., and Oakley, W. (1953). *British Medical Journal*, **1**, 242.
Nabarro, J. D. N., and Stowers, J. M. (1953). *Proc. roy. Soc. Med.* In press.
Nelson, N. (1944). *J. biol. Chem.*, **153**, 375.
Paley, R. G., and Tunbridge, R. E. (1952). *Diabetes*, **1**, 22.

A study of European methods of dealing with air and water pollution caused by the chemical industry is being carried out by a technical assistance mission arranged by the Organization for European Economic Co-operation. The mission visited various chemical firms in the United Kingdom during the week October 25–31. The Board of Trade emphasized that the mission is confined to studying the problem of pollution caused by the chemical industry. It is not dealing with the problem of "smog," which is not a special problem of the chemical industry, being caused by the combustion of coal in general.