with infiltration of the pancreas, and the three cases of regional ileitis mentioned in this paper. These findings suggest that steatorrhoea due to regional ileitis is commoner than is generally appreciated. This may be because estimations of faecal fat are not regularly carried out in these cases, and so steatorrhoea is overlooked. Alternatively, Davidson and Fountain suggest that doctors fail to realize that priority rations are available to all patients with steatorrhoea, whatever the cause.

Anaemia, which may be hypochromic, megalocytic, or dimorphic in type, is a well-recognized complication of steatorrhoea (Barker and Hummel, 1939; Bennett and Hardwick, 1940; Cooke *et al.*, 1948). Hypochromic anaemia was present in the three patients described. The value of intravenous iron in the treatment of refractory hypochromic anaemia has been mentioned by Hawkins *et al.* (1950). It is particularly useful in regional ileitis, in which large doses of oral iron are apt to aggravate the intestinal disturbance. Cases 1 and 2 now tolerate a small maintenance dose of iron by mouth. In Case 2 there was also evidence of liver-factor deficiency, and he received folic acid. No effects were observed on the macrocytosis present in the peripheral blood or on the megaloid changes in the iliac marrow.

The patients found that with the five extra meat rations allowed weekly it was possible to have an appetizing and varied diet, although many articles of food had to be excluded to avoid diarrhoea. Their daily protein intake is estimated to be approximately 130 g. Bread, sugar, bacon, cheese, milk, fish, and eggs were not restricted. Fats were allowed in cooking and bread was thinly buttered. They were advised, however, to avoid fried foods. For the rest they were encouraged to find out for themselves the foods that caused diarrhoea by adding different articles to the basic diet one at a time. In addition, they received vitamins of the B group, ascorbic acid, and small doses of iron by mouth.

It is difficult to say for how long the diet outlined above should be continued, for the cost of the extra meat is considerable. Nevertheless, it would seem advisable to continue the high-protein intake so long as there are signs of activity of the disease or of persisting steatorrhoea. Indeed, one of these patients commented that the extra expense of the diet was repaid many times by his restoration to full earning capacity.

The presence of steatorrhoea in regional ileitis suggests that the disease is widespread, and this is of grave prognostic import, but complete clinical recovery has been recorded with medical treatment alone (Crohn, 1949). The regime outlined above is simple and worth a trial in the type of case described. It is probable that there are many patients with steatorrhoea, malnutrition, and anaemia due to this disease attending the out-patient departments of hospitals in this country. With treatment on the lines indicated, particularly by the provision of extra protein rations, they may be restored to reasonable health and normal activity, and even be spared extensive resection of the bowel.

Summary

Detailed case histories of three patients with Crohn's disease are given. Steatorrhoea, considerable malnutrition, and anaemia were present in all.

A high-protein diet led to great improvement, indicated by a considerable gain in weight and restoration to normal activity. The value of intravenous iron for the correction of hypochromic anaemia in these patients was demonstrated.

Faecal fat estimations are recommended in patients with this disease, as steatorrhoea is often overlooked. If the presence of steatorrhoea can be established patients are eligible for extra meat rations in this country at the present time, and by this means they can obtain an appetizing high-protein diet.

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A NEW LONG-ACTING INSULIN A PRELIMINARY TRIAL OF "LENTE" NOVO INSULIN

BY

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The Novo Laboratories, in Copenhagen, have recently produced a series of three new insulin preparations whose composition and action have been described by Hallas-Møller, Petersen, and Schlichtkrull (1952). The makers have kindly provided us with a supply of these insulins on which to carry out a therapeutic trial, and the results obtained justify the publication of this preliminary report.

New Insulin Preparations

In 1934 Scott, of Toronto, found that various metals were of importance for the formation of insulin crystals. This led to a study of the influence of zinc on the insulin effect. This research resulted in the discovery that small quantities of zinc (1–2 mg. per 1,000 units) fail to retard the action of soluble insulin, whereas large amounts increase its length of action. It was further found that the effect of protamine insulin and similar combinations was substantially protracted by the addition of small quantities of zinc (2 mg. per 1,000 units). The practical outcome of these investigations was protamine zinc insulin.

Subsequent research has been largely directed towards the discovery of new and more suitable preparations, new substances being tried to replace protamine. The idea of increasing the zinc content alone was regarded as impracticable, because of the local reactions produced when sufficient zinc is added to prolong the action of insulin.

Novo Laboratories were, however, aware that different anions influenced the reaction between insulin and zinc. Hallas-Møller and his co-workers in Copenhagen found that insulin, in the presence of a very small quantity of zinc (1 mg. per 1,000 units) was less soluble at the pH of the blood than protamine insulin, provided that anions such as phosphate and citrate were not present. Phosphate buffer has been thought the most suitable at pH 7, and is normally

used to adjust insulin preparations to that figure. This may explain why more than 15 years of research failed to lead to the simple discovery that if a different buffer is used it is wholly unnecessary to add such materials as protamine, globin, surfene, etc., to make insulin insoluble at the pH of the blood.

With the use of acetate buffer, Hallas-Møller was able to prepare a suspension of pure insulin in media at the pH of the blood in the presence of very small quantities of zinc. Further work led to the discovery that the length of action of such preparations varied with the form of the insulin, whether pure amorphous, amorphous and crystalline, or pure crystalline. This apparently minor difference in the form of insulin would seem to determine the range of activity of the preparations, varying from 12 to 36 hours. The action of amorphous insulin is shorter than that of crystalline, the larger the size of the crystal the greater being the length of activity. Three such insulins have been produced and given the names of "semi-lente," "lente," and "ultra-lente," the first having the shortest and the last the longest range of activity, lente being intermediate in duration. These insulins are miscible to produce preparations of intermediate ranges of activity. They cannot, however, be mixed with the present soluble insulin.

Our present trial has been carried out mainly on lente insulin, the intermediate preparation, and the one which seems the most promising of the three for treatment. The number of diabetics to whom lente has so far been given is very small—some 11 cases—and before briefly describing

the results obtained the conditions necessary for the therapeutic trial of any insulin preparation will be considered:

(1) In view of the variability of diabetes at the onset of the disease only those patients whose diabetes has been controlled for a reasonable period of time can be considered suitable.

(2) The diabetes should be of the severe type which relapses heavily when insulin action is finished.

(3) There must be no intercurrent complicating disease.

(4) The patient must be in hospital long enough for good control on existing methods to be compared with that obtained with a new type of insulin in similar dosage.

These essential requirements are often forgotten and explain, in the present shortage of our hospital beds, so occupied by acute work, the few cases on which we have so far been able to carry out therapeutic trials.

Clinical Material

The therapeutic trial of lente insulin was carried out on 11 adult diabetics, 6 of whom were men and 5 women, their ages varying between 25 and 92. They all fulfilled the conditions of suitability described above, and were in-patients in the diabetic department of King's College Hospital.

The patient's diabetes was controlled on two injections of S.I., P.Z.I. alone, a combination of the two given as a single mixed injection before breakfast, or a single injection of globin insulin. When adequate control was established,

FIG. 1.—Case 1. Comparison between equal doses of a mixed injection of S.I. and P.Z.I., and lente insulin.

FIG. 2.—Case 2. Comparison between equal doses of a mixed injection of S.I. and P.Z.I., and lente insulin.

FIG. 3.—Case 7. Comparison between two doses of S.I. and a single dose of lente insulin of same total amount.

FIG. 4.—Case 8. Comparison between two doses of lente insulin of slightly different sizes to show regularity of action. The noon blood sugar on 76 units of S.I. to be compared with that on 76 units of lente insulin.

FIG. 5.—Case 9. Comparison between a single dose of P.Z.I. and the same dose of lente insulin given on two occasions. Note the regularity of action of lente insulin.

blood-sugar determinations were made before breakfast, at noon, at 6 p.m., and at 9 p.m.; the patient was then changed over to a single dose of lente insulin, given before breakfast, and equal in amount to the total quantity of insulin required to stabilize the diabetes. When the patient had been on lente insulin for not less than two days the blood-sugar estimations were repeated at the same times and the results plotted in the form of graphs (Figs. 1 to 5). In addition to blood-sugar determinations, seven daily urine sugar tests were made at informative times. In two cases the blood-sugar estimations on lente insulin were repeated in order to see whether consistent results could be obtained with this insulin.

Results

In six cases comparison was made with mixed doses of S.I. and P.Z.I., the total dose varying from 36 to 60 units. In two cases the patients were previously stabilized on 68 and 76 units of S.I. respectively, given in divided doses, before breakfast and the evening meal. Two cases received single injections of 52 units of P.Z.I. and one of 28 units of globin. It will be seen that in all 11 cases lente insulin produced fasting blood sugars of the same order as those obtained with the other insulin preparations, the figures varying between 70 and 200, being 150 or less in eight. At noon lente produced a degree of control as good as, or better than, that obtained with the other insulins in all but two cases. At 6 p.m. the blood sugar on lente was comparable with but tended to be slightly higher than that produced by the other insulins, but at 9 p.m. the reverse was seen to be the case in most instances (see Table).

Comparison of Blood Sugars in the Six Cases Not Shown in Figs. 1 to 5

Case No.	Insulin	Blood Sugar in mg /100 ml.			
		8 a.m.	Noon	6 p.m.	9 p.m.
3	44 S.I.+16 P.Z.I.	165	260	140	118
	60 Lente ..	200	375	260	255
4	20 S.I.+16 P.Z.I.	168	238	95	190
	36 Lente ..	105	100	155	155
5	24 S.I.+20 P.Z.I.	110	155	130	195
	44 Lente ..	130	105	110	95
6	24 S.I.+16 P.Z.I.	155	210	170	—
	40 Lente ..	140	180	135	—
10	52 P.Z.I. ..	190	178	195	250
	52 Lente ..	95	140	175	180
11	28 Globin ..	155	245	165	—
	28 Lente ..	165	205	170	250

It would appear, therefore, from this small series of experiments that lente insulin possesses the prolonged action claimed by the manufacturers, and also that it exerts a shorter hypoglycaemic action, comparable with and equal to that of soluble insulin alone or mixed with P.Z.I. Throughout the course of these and other experiments with

lente insulin, hypoglycaemia occurred only two or three times and was never severe. There were no local reactions or undesirable side-effects. In the few cases in which tests were repeated with lente insulin the results obtained were remarkably constant.

We hope to carry out further trials on lente insulin in order to determine: (1) the length of action and time of maximum action of lente insulin in varying dosage; (2) whether there is significant variation between different batches of the same preparation; (3) whether lente insulin produces satisfactory control in ambulatory cases; (4) the arrangement of diet best suited to the action of these insulins; the diet of the cases reported was kept constant, and the carbohydrate content was arranged to suit the insulin or insulins with which comparison was made; (5) the suitability of the new insulins for initial stabilization of severe diabetics.

Summary

A preliminary trial of the new Danish lente insulin supports the claim that it exerts a prolonged hypoglycaemic action, lasting at least 24 hours, which is strong enough to control the blood sugar of moderately severe diabetics throughout the day without causing hypoglycaemia during the night. It has not in our experience produced either local or general reactions and appears to be no more likely to produce hypoglycaemic reactions than the insulin preparations at present in use.

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ACUTE BENIGN PERICARDITIS

A REPORT OF FOUR CASES IN CHILDHOOD

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Acute benign pericarditis has been recognized more often in America than in Europe, and its existence in Britain has even been denied (Andrews *et al.*, 1948). Having recently seen two typical cases, we decided to examine the notes of all children with pericarditis treated at the Birmingham Children's Hospital between 1942 and 1951, and thus discovered two other probable examples of the condition.

Case 1

Both parents of an 8-year-old boy had a feverish illness, one a week before and the other a week after their son was taken ill with shivering and left-sided chest pain. Penicillin and sulphonamides in adequate dosage had no effect on his high temperature or irritating cough. A week later he developed severe abdominal pain and was transferred to hospital. He was then only moderately ill; temperature 103° F. (39.4° C.), pulse 124, and respirations 28. Fine crepitations and distant bronchial breathing were heard at the left base; clinically the heart was normal. Chloramphenicol—40 mg. per lb. (88 mg. per kg.) per day—reduced the temperature, but pain increased and the child developed both a loud pericardial friction rub and an apical systolic murmur. Yet he was not critically ill. The E.C.G. strongly