A case of subdural effusion complicating sagittal sinus thrombosis is also described. On the basis of this case and of those of other workers it is concluded that certain types of subdural effusion complicating purulent meningitis may be due to a leakage of blood from the necrotic wall of a vein involved in thrombophlebitis.

It is a pleasure to acknowledge the co-operation of all the paediatricians in the Manchester Region in collecting the material for this paper. I am also indebted to Mr. L. P. Lassman and Mr. A. Jolleys, and to many residents at the Royal Manchester Children's Hospital, for help in the documentation and management of the cases, and to Sister N. Kewley for devoted nursing care. There is no doubt that the credit for the low operative mortality recorded in this paper belongs very largely to Dr. Tom Dinsdale, who gave the anaesthetics for almost all the operations.

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THE TREATMENT OF STEATORRHOEA IN CROHN'S DISEASE

BY

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During recent years it has been recognized that Crohn's disease, or regional ileitis, is not always confined to the terminal ileum, but may be widespread, involving the proximal ileum, jejunum, colon, and even the duodenum. Surgery is definitely indicated for the relief of intestinal obstruction, and possibly for treatment of localized forms of the disease, when the affected portion of bowel may be excised. Patients with widespread disease present a difficult therapeutic problem. Surgery has proved disappointing, as complete extirpation of the affected bowel is seldom possible and recurrence after operation is common. In such circumstances therapy is directed towards improving the general nutrition of the patient and correcting deficiencies of vitamins and minerals. The main purpose of this paper is to describe the effects of a high-protein diet and intravenous iron, observed in three patients suffering from Crohn's disease with steatorrhoea, and to draw attention to the beneficial result that may accrue from a carefully planned diet.

Case 1

A schoolboy aged 12 was admitted to hospital on April 4, 1948, complaining of diarrhoea and of colicky pain in the right iliac fossa. Intermittent slight pyrexia was present, but otherwise his general condition was good. He passed several loose green stools daily, from which no pathogenic organisms were isolated. Agglutination reactions to the

typhoid and dysentery groups were negative. A barium enema revealed nothing abnormal. After treatment with sulphonamides and penicillin he was discharged home on May 27. His symptoms persisted and his weight fell from 7 st. 3 lb. (45.8 kg.) to 4 st. 10½ lb. (30.2 kg.). He was readmitted to hospital on July 2. Apart from his wasted appearance clinical examination was negative. A hypochromic anaemia was present: Hb, 13.6 g. per 100 ml.; red cells, 4,300,000 per c.mm. The E.S.R. was 28 mm. in one hour (Westergren). Agglutination reactions were again negative, including those to *Brucella abortus*. The diagnosis of Crohn's disease was considered at this time, but attempts to demonstrate the terminal ileum radiologically failed. A low-residue diet was prescribed and his weight had risen to 5 st. 1 lb. (32.2 kg.) when he returned home on August 19. He remained under observation until March, 1949, when he weighed 6 st. 11½ lb. (43.3 kg.), and although his stools were still loose he was free from pain and attending school regularly.

In September the diarrhoea became worse and colicky abdominal pain returned, accompanied by vomiting. In April, 1950, examination by barium enema and sigmoidoscopy was normal. His condition deteriorated steadily until he was admitted to hospital on February 7, 1951, weighing 4 st. 3 lb. (26.8 kg.). He was passing about 10 loose offensive stools daily and vomiting most of his food shortly after it was eaten. He also complained of numbness and paraesthesiae in the extremities. Clinical examination revealed gross emaciation and faint brown pigmentation of the skin. The blood pressure was 110/75. No mass could be felt in the abdomen.

The results of laboratory investigations at this time are summarized briefly: E.S.R., 40 mm. in one hour (Westergren); Hb, 63% (9.3 g. per 100 ml.); red cells, 3,350,000 per c.mm.; C.I., 0.95; M.C.D., 7.2 µ; white cells, 12,000 per c.mm. The iliac marrow showed a marked normoblastic reaction of iron-deficiency type; macronormoblasts were also present, but no megaloblasts were seen. Microscopy of the stools showed no exudate; a few undigested meat fibres were seen. No faecal pathogens were isolated. Blood culture was negative. The titre of serum agglutinating *Br. abortus* was 1:640 ± 1:1,280, and *Br. melitensis* 1:320 ± 1:640. The total serum proteins were 5.4 g. per 100 ml. (albumin 3 g., globulin 2.4 g.). The average daily output of fat in the faeces was 7 g.; full details are given in the Table.

Radiological examination of the bowel showed marked narrowing and irregularity of the terminal ileum. There was narrowing in the middle of the transverse colon, with destruction of normal mucosal pattern, continuing to half-way down the descending colon.

As a result of the above findings a clinical diagnosis of chronic ileocolitis due to Crohn's disease was made.

The temperature varied between 99 and 100° F. (37.2 and 37.8° C.) for the first six weeks in hospital. The agglutination reactions to *Br. abortus* and *Br. melitensis* were still at the same high titre a week after admission. Blood cultures for these organisms were negative. A course of aureomycin was given, 60 g. in 21 days. There was little effect on the temperature, but the titres fell to 1:80 to both organisms four days after starting the drug and to 1:20 one month later, and have remained at this level. In view of the rapid fall in titre of agglutinins, it was unlikely that active brucellosis was present.

Feeding presented a great problem at first, owing to vomiting and anorexia. The patient was given a low-residue, high-protein, low-fat diet, containing daily two or three eggs, liberal helpings of meat and fish, and 75 g. of protein in a proprietary preparation. Bread-and-butter, small quantities of sieved vegetables, and boiled potatoes were included. His condition improved rapidly, and at the end of three weeks his weight was 5 st. 5 lb. (34 kg.), a gain of 16 lb. (7.3 kg.). The hypochromic anaemia responded to iron, 30 ml. of "ferrivenin" being given intravenously in the week before he was discharged from hospital.

As his appetite improved, his stools increased greatly in bulk and it was even more evident that steatorrhoea was present than on admission. Estimations in April showed the average daily output of fat in the stools over four days to be 36 g. The fat intake was approximately 90 g. daily during the period of collection (see Table). A glucose-tolerance test was normal.

When the patient returned home on April 27 he weighed 7 st. 6 lb. (47.2 kg.).

Subsequent progress has been excellent. After three weeks' convalescence he returned to school, and has attended regularly for nine months. His activities are not restricted. He plays games, swims, and rides a bicycle for the first time since the start of his illness in 1948. His basic diet consists of an egg for breakfast with bread-and-butter, banana or cheese sandwiches for lunch, and a meal at night of meat or fish, potatoes, and a milk pudding. Milk is not restricted and fats are allowed in moderation. His mother has been advised to add different articles to the diet, one at a time, noting the effect on the stools. It has been found that he can tolerate boiled carrots, stewed apples, and fresh oranges. Most other foods cause an increase in the number of stools. This diet is supplemented by oral iron, vitamins of the B group, and ascorbic acid.

The patient was reassessed in January, 1952. His weight was then 10 st. (63.5 kg.), a gain of 81 lb. (36.7 kg.) in 11 months. He had grown taller and secondary sexual characters had appeared. He was passing two or three semi-formed stools daily, as compared with six stools at the time of discharge from hospital, in spite of the fact that he was taking most of his fat ration. The average daily output of fat in the faeces over three days was 8 g., on a measured intake of 100 g. daily (see Table). A barium enema showed normal haustration and outline as far as the middle of the transverse colon, where persistent narrowing was still present. The proximal part of the transverse colon, ascending colon, and caecum showed a normal outline, as in previous studies. The terminal ileum remained narrowed, with a distorted mucosal pattern. Healing of the lesion in the descending colon and splenic flexure had undoubtedly taken place.

Case 2

A man aged 20 began to have attacks of right-sided abdominal pain and occasional diarrhoea in 1945. Three months after the onset of symptoms appendicectomy was performed, but no report on the condition of the bowel is available. He was in bed for six weeks after the operation and then returned to work. Symptoms recurred two years later. The pain increased in severity, and was accompanied by abdominal distension and the passage of flatus. Four loose stools were passed daily. He lost 3 st. (19 kg.) in weight before admission to hospital in May, 1948. A tender mass was palpable in the right iliac fossa. The blood count was normal. A diagnosis of regional ileitis was made. This was confirmed at laparotomy in August, 1948, and was treated by resection of 4 ft. (1.2 metres) of terminal ileum, ileo-colostomy, and right hemicolectomy. The histological appearance of the diseased ileum was that of Crohn's disease. He was discharged from hospital in October, 1948, and was well until February, 1950, although he continued to pass loose stools three or four times daily. Abdominal pain then returned and the diarrhoea became worse. A barium meal in February, 1950, showed recurrence of the disease, just distal to the anastomosis. In September, 1950, a fistula appeared at the upper end of the abdominal scar and discharged intermittently.

He was readmitted to hospital on May 1, 1951. Examination revealed a pale, wasted young man, with early finger-clubbing. A tender mass was palpable in the right iliac fossa, deep to the discharging fistula. He was passing three or four bulky offensive stools daily. The results of laboratory investigations are summarized as follows: Hb, 63% (9.3 g. per 100 ml.); red cells, 3,750,000 per c.mm.; C.I., 0.88; M.C.D., 7.2 μ ; white cells, 15,000 per c.mm. The blood film showed a simple polymorphonuclear leucocytosis. Two types of red cells were seen: (1) microcytic and slightly

hypochromic, and (2) macrocytic and normochromic. The iliac marrow showed a normoblastic reaction of iron-deficiency type, along with megaloid cells and macro-granulocytes which suggest liver-factor deficiency. Free hydrochloric acid was present in the stomach. The urine was normal. Microscopy of the stools showed scanty leucocytes only. No faecal pathogens were cultured. The total serum proteins were 7 g. per 100 ml. (albumin 3.4 g., globulin 3.6 g.) Culture of the pus from the fistula grew *Staph. pyogenes*, sensitive to penicillin. The average daily output of fat in the stools was 38 g. measured over three days, while the intake was approximately 70 g. daily (see Table).

There was continuous pyrexia for the first four weeks in hospital, the temperature varying between 99 and 101° F. (37.2 and 38.3° C.). Sulphadimidine, penicillin, and chloramphenicol were prescribed in turn. The abdominal mass finally became fluctuant. It was incised, and approximately 500 ml. of thick pus drained. Thereafter he was afebrile.

A diet similar to that given to Case 1 was prescribed. He also received iron intravenously—90 ml. of "ferrivenin" being given in 10 days—and folic acid, 15 mg. daily by mouth. When he left hospital on June 20 his weight was 8 st. 8 lb. (54.4 kg.). The abdominal fistula had closed by August and he returned to work. In November he weighed 10 st. 2 lb. (64.4 kg.), a total gain of 23 lb. (10.4 kg.). His haemoglobin was 110% (16.3 g. per 100 ml.), and the red blood cells numbered 5,200,000 per c.mm.

A full assessment was made in February, 1952. By this time he had worked regularly for six months, had married, and was feeling extremely fit. His weight was stationary and the fistula had remained healed. For the first time since the start of his illness in 1945 he was passing only one stool daily, and this was usually formed. His basic diet resembled that of Case 1. He said that as fats precipitated diarrhoea he avoided them, but he tolerated fruit and vegetables quite well so long as they were taken with meals. He continued to take ascorbic acid, yeast tablets, and small doses of iron by mouth. Folic acid had been discontinued four months previously.

The average daily output of fat in the stools, on a fat intake of 100 g. daily, was 32 g. (see Table). A glucose-tolerance test was normal. The blood count was as follows: Hb, 95% (14.1 g. per 100 ml.); red cells, 4,100,000 per c.mm.; C.I., 1.15; M.C.D., 7.4 μ ; white cells, 11,000 per c.mm. Slight macrocytosis persisted and megaloid cells were still present on examination of the iliac marrow. Folic acid, 15 mg. daily for 21 days, failed to correct this abnormality.

Case 3

A man aged 39 first complained of colicky pain in the right iliac fossa in 1945. It was relieved by the passage of flatus. Diarrhoea was noticed at the same time and the stools remained loose. In November, 1949, he had to give up work as he was passing up to 20 loose stools daily. His weight had fallen from approximately 10½ st. (66.7 kg.) to 7 st. 10 lb. (49 kg.). He was admitted to hospital in February, 1950, and a diagnosis of Crohn's disease was made, narrowing of the terminal ileum being demonstrated radiologically. At laparotomy the disease was confined to the terminal ileum, but there was a fistula into the upper ileum. Three feet (0.9 metre) of terminal ileum was resected and ileocolostomy and right hemicolectomy were performed. The diagnosis of Crohn's disease was confirmed histologically.

The patient returned to work in May, 1950. He gained weight and remained well until November, 1951, although mild diarrhoea persisted. At that time the number of stools increased to four or five daily and slight abdominal pain had returned.

In January, 1952, he was admitted to hospital. Clinical examination showed obvious recent loss of weight and considerable pallor. His tongue was normal. No abdominal mass was felt. He weighed 8 st. 3 lb. (52.2 kg.). Laboratory findings were as follows: Hb, 48% (7.1 g. per 100 ml.);

red cells, 3,270,000 per c.mm.; C.I., 0.73; M.C.D., 7.3 μ ; white cells, 7,000 per c.mm. The iliac marrow showed a normoblastic reaction of iron-deficiency type, along with macronormoblasts. Scanty leucocytes were seen in the stools; no faecal pathogens were isolated on culture. The glucose-tolerance test was normal. The total serum proteins were 6.2 g. per 100 ml. (albumin 3.5 g., globulin 2.7 g.). No abnormality was found in the urine. The average daily output of fat in the faeces was 41 g., on a measured intake of 100 g. daily (see Table).

He was started on the same diet as the other two patients and received iron intravenously, 100 ml. of "ferrivenin" being given in 14 days. After six weeks he had gained 14 lb. (6.4 kg.) in weight and his haemoglobin had risen to 78% and his red cells to 4,500,000 per c.mm.; C.I., 0.86. He was able to return to work.

Discussion

It is fully appreciated that regional ileitis is characterized by remissions and relapses. During a remission rapid gain in weight is common. Crohn (1949) mentions figures of 15, 25, and even 50 lb. (6.8, 11.3, and 22.7 kg.). Case 2 was undoubtedly benefited by the evacuation of a large abscess, and all three patients were at rest in hospital for several weeks. All received intravenous iron, and two of them were given antibiotics. However, it is believed that the rapid improvement was largely due to the diet, especially in Case 1, this patient having already gained 14 lb. (6.4 kg.) in weight before aureomycin was started. He was well and had gained 38 lb. (17.3 kg.) before intravenous iron was given to correct a persistent hypochromic anaemia. During the year on the high-protein diet he gained 81 lb. (36.7 kg.) in weight. Case 3 did not receive antibiotics. In all three cases diarrhoea was controlled for the first time after institution of the diet.

Steatorrhoea, which was present in the three cases, has been observed previously in regional ileitis (Bockus, 1945; Frazer, 1949), and Crohn (1949) mentions tropical sprue in the differential diagnosis. The high incidence of malnutrition, vitamin deficiencies, and anaemia is well recognized, and the great importance of a high-protein diet, with supplementary minerals and vitamins, is stressed by Brown and Donald (1942), Bockus (1945), Crohn (1949), and Kiefer *et al.* (1950).

In order to obtain the extra meat rations granted to patients with steatorrhoea in this country at the present time the diagnosis must be established by analysis of the stools. It is therefore worth while having this carried out in all patients with regional ileitis who have persistent diarrhoea. Steatorrhoea can easily be overlooked if the stools are inspected shortly after admission to hospital, when the food intake is often reduced, or if only a single specimen of faeces is sent to the laboratory for routine examination. The diagnosis of steatorrhoea is most readily established by investigating the response of the patient to an increase of dietary fat. In normal subjects the fat excretion shows a minimal change even when the intake of fat is raised as high as 200 g. daily. Thus Cooke *et al.* (1946) found that with a 50-g. intake the maximum fat excretion was 4.5 g. daily. Fourman *et al.* (1948) state that the output of fat should not exceed 23 g. in four days on a fat intake of 70 g. daily. Wollaeher *et al.* (1946) gave 13 subjects 208 g. of fat daily, and the average output in the stools was 8.7 g., the range being 5.5 to 13.6 g.

On the other hand, when steatorrhoea is present the total fat excretion is within limits proportional to the fat intake, and defective fat absorption can be made more obvious by increasing the dietary fat (Fourman *et al.*, 1948). It is accordingly suggested that patients be given 70 to 100 g. of fat daily two days before and during the time that the stools are being collected, instead of 50 g. as often recommended (Cooke, 1952). By this means more elaborate balance studies using coloured markers may be avoided. These points are clearly shown in the Table, where the measurements of the faecal fat excretion of the three cases of Crohn's disease are summarized. In addition, for com-

parison, there are included observations on a case of idiopathic steatorrhoea and on four subjects with normal intestinal function.

Details of Fat Intake and Output

Diagnosis	Date of Faecal Fat Estimation	Daily Fat Intake in g.	No. of Days of Stool Collection	Average Daily Wet Weight of Faeces in g.	Total Fat Percentage of Dried Faeces	Average Daily Output of Fat in g.
Crohn's disease (Case 1)	23/2/51	Very small owing to anorexia and vomiting	5	302	32	7
	11/4/51	90	4	820	32	36
	9/1/52	100	3	200	39	8
Crohn's disease (Case 2)	28/5/51	70	3	461	73	38
	18/2/52	100	4	391	48	32
Crohn's disease (Case 3)	12/2/52	100	4	649	67	41
	29/2/52	70	3	264	51	14
	7/3/52	50	3	285	35	9
Idiopathic steatorrhoea	17/10/51	70	3	96	38	10
	29/10/51	150	3	179	56	22
Convalescent pneumonia	12/11/51	100	3	44	58	5
	20/11/51	150	3	60	41	5
Treated Addison's disease	14/3/52	150	3	61	37	2
Normal	14/3/52	150	3	179	24	3
	19/3/52	150	3	55	43	2

It will be seen that when the faecal fat was first estimated in Case 1 the daily output just exceeded the upper limit of normal. However, when the fat intake was increased gross steatorrhoea was evident. When the third estimation was done the daily output of fat was only 8 g., although the intake was 100 g. for two days before and during the time the faeces were being collected. The capacity to absorb fat had clearly increased. In Case 3 the faecal fat was estimated on intakes of 100, 70, and 50 g. during the patient's first admission to hospital. The fat excretion increased with the fat intake. The findings were similar in the case of idiopathic steatorrhoea. In contrast to this the excretion of fat in the normal subjects did not exceed 5 g. a day even when the intake was as high as 150 g. The total fat content of the dried faeces was, however, over 30% in three of the normal subjects, and it is clearly fallacious to base a diagnosis of steatorrhoea on this figure alone.

Davidson and Fountain (1950) reviewed all patients with the sprue syndrome who applied for extra rations between January 1, 1943, and December 31, 1948. These included 1,303 cases of coeliac disease, 311 cases of idiopathic steatorrhoea, and 403 cases of tropical sprue. Among the 58 cases of steatorrhoea due to causes other than the sprue syndrome there were only five cases of regional ileitis. In addition there were 15 in which the diagnosis was uncertain; 12 of these had undergone resection of gut or short-circuiting operations. Even if it is assumed that all these patients had regional ileitis, this only makes a total of 20 applying for extra rations. No information is available regarding the incidence of steatorrhoea in a large series of cases of regional ileitis, though it is probably high, especially if the disease is extensive. It was certainly present in all the three cases of regional ileitis that we have investigated during the last two years. It accordingly seems improbable that steatorrhoea, either due to sprue or of the idiopathic variety, is over 30 times commoner than that due to regional ileitis, as is suggested by the figures of Davidson and Fountain.

In an effort to ascertain the relative frequency of steatorrhoea due to regional ileitis and other causes the records of cases admitted to the Royal Infirmary, Sheffield, have been studied during the two years 1950-1. There were 10 cases of steatorrhoea. These included five cases of idiopathic steatorrhoea, one case following gastro-enterostomy and vagotomy, one due to carcinoma of the suprarenal gland

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