Protracted diarrhoea in infancy

Analysis of 82 cases with particular reference to diagnosis and management

V. F. LARCHER,* R. SHEPHERD,† D. E. M. FRANCIS, AND J. T. HARRIES

From the Institute of Child Health and The Hospital for Sick Children, London

SUMMARY Eighty-two cases of protracted diarrhoea in infancy presenting over a 6-year period have been analysed, with particular reference to diagnosis and management. The patients fell into 1 of 2 categories according to whether a specific diagnosis was established or not. A diagnosis (category 1) was established in 59 (72%), the commonest diagnoses being coeliac disease (33.2%), secondary disaccharide intolerance (12.2%), and cows' milk protein intolerance (11.3%). Other diagnoses included primary sucrase-isomaltase deficiency, Shwachman's syndrome, ulcerative colitis, ganglioneuroma, defective opsonization, staphylococcal pneumonia, and Hirschsprung's disease.

Despite intensive investigation a diagnosis could not be established in 23 (28%) infants (category 2). Age of onset of symptoms in this group tended to be earlier than in category 1 patients, and 6 (7%) presented with diarrhoea dating from birth. Of particular interest in these 6 patients was the high incidence of associated extraintestinal anomalies, and of sibs who had died after protracted diarrhoea dating from birth. 4 of these 6 infants died, accounting for a mortality of 5% for the whole series. The remaining 17 (21%) patients in category 2 presented at a mean age of 4.9 weeks with a range of 1-18 weeks. All these 17 patients made an excellent response after institution of a chicken-based dietary formula, the details of which are presented. The pathophysiological mechanisms which may be operating in infants with protracted diarrhoea are discussed.

An infant presenting with protracted diarrhoea and failure to thrive often presents major problems in diagnosis and management, particularly if the patient's general condition precludes intensive investigation. There have been very few reported series of protracted diarrhoea in infancy, and in each report the numbers of patients have been small, varying from 10 to 20 cases (Avery *et al.*, 1968; Hyman *et al.*, 1971; Lloyd-Still *et al.*, 1973). Mortality rates of 45% (Avery *et al.*, 1968) and 70% (Hyman *et al.*, 1971) reflect the difficulties in management which these infants pose, and the nonresponsiveness to dietary treatment in patients in whom a specific diagnosis cannot be established has been emphasized.

We report 82 infants with protracted diarrhoea, paying particular attention to the differential diagnoses, and to the management of those patients in whom a specific diagnosis could not be established.

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Present addresses: *Department of Child Health, King's College Hospital, Denmark Hill, SE5 8RX.

†Division of Gastroenterology, the Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada.

Patients and methods

An infant (less than 1 year old) is defined as having protracted diarrhoea in infancy if he has four or more loose stools per day for longer than 2 weeks, and either loses or fails to gain body weight during this period. The patients presented to The Hospital for Sick Children during the 6-year period 1970-1975, and detailed analysis was confined to those infants in whom a specific diagnosis could not be established. Patients whose symptoms occurred after surgery of the gastrointestinal tract, and those with cystic fibrosis, were excluded from the study. Clinical and laboratory methods used for assessment and diagnosis are outlined in Appendix A.

A diagnosis of coeliac disease was made on the basis of a clinical response to a gluten-free diet (and a jejunal biopsy which had the appearance of subtotal villous atrophy when the patient's condition permitted the investigation), and a subsequent gluten challenge (Packer *et al.*, 1974). The criteria for a diagnosis of cows' milk protein intolerance were as previously described (Harries, 1975).

Results

The patients fell into one of two categories according to whether a specific diagnosis was established or not. Category 1 consisted of 59 (70%) patients in whom a diagnosis was established, and category 2 the remaining 23 (28%) infants in whom no cause for the diarrhoea could be established.

Category 1 patients. The age of referral to us and the diagnoses in category 1 patients are shown in Table 1. The commonest diagnoses were coeliac disease

Table 1 *Diagnosis and age of referral of category 1 patients with protracted diarrhoea*

Diagnosis	Age of referral (m) (mean and range)	No. of patients	% of total 82 patients
Coeliac disease	8.2 (4.1-12.0)	27	33
Secondary disaccharide intolerance	6.4 (0.5-12.0)	10	12
Cows' milk protein intolerance	2.1 (0.1-5.0)	9	11
Primary sucrase-isomaltase deficiency	6.1 (5.2-7.0)	2	2
Shwachman's syndrome	5.2 (4.5-6.0)	2	2
Acrodermatitis enteropathica	2.0 (1.5-2.6)	2	2
Hirschsprung's disease	4.1 (3.0-5.2)	2	2
Ulcerative colitis	6.0	1	1
Ganglioneuroma	8.0	1	1
Defective opsonization	4.0	1	1
Staphylococcal pneumonia	3.0	1	1
Malrotation	4.5	1	2

(33%), secondary disaccharide intolerance (12%), and cows' milk protein intolerance (11%). Other causes of protracted diarrhoea included conditions such as primary sucrase-isomaltase deficiency, Shwachman's syndrome, ulcerative colitis, ganglioneuroma, defective opsonization, and staphylococcal pneumonia. Of particular importance was the finding of a surgical cause for the protracted diarrhoea in 3 patients.

Category 2 patients. In the 23 patients in whom a firm diagnosis could not be established, the age of onset of symptoms tended to be earlier than in category 1 patients, and 6 presented with diarrhoea dating from birth (see Table 2). These 6 infants

Table 2 *Age of onset of symptoms in category 2 patients with protracted diarrhoea*

Age of onset of symptoms (w) (mean and range)	No. of patients	% of total 82 patients
From birth	6	7
4.9 (1-18)	17	21

present a particularly interesting group and despite exhaustive investigations no known cause for their severe diarrhoea could be found. 2 sibs had agenesis of the corpus callosum and both died, as did one infant with recurrent acidosis and hyperammonaemia of undetermined cause. One patient had protracted diarrhoea in association with glycogen deposition in mitochondria of skeletal muscle cells, and recovered. The remaining 2 patients had sibs who had died after protracted diarrhoea. In one of these patients profuse watery diarrhoea was associated with hypoplastic villous atrophy of the small intestinal mucosa possibly due to an as yet unrecognized genetically determined abnormality of vitamin B12 metabolism; this patient also died and will be reported in detail elsewhere.

Category 2 patients presenting after birth. The majority of infants in category 2 (17 cases) presented at varying intervals after birth having previously been in good health.

Clinical features. All 17 were referred from other hospitals where a variety of therapeutic dietary manipulations had been unsuccessful, and most had required intravenous fluids before referral. The mean age of onset of the diarrhoea was 4.9 weeks, range 1-18 weeks, and the mode of onset was usually acute diarrhoea with or without vomiting. In 2 cases enteropathogenic serotype strains of *E. coli* were cultured from the stools during the initial illness. None of the patients had been breast fed and only 3 had received gluten-containing foods before their presenting symptoms. The mean duration of diarrhoea before referral to us was 5 weeks, range 3-12 weeks. The perinatal histories were uneventful, a family history of allergy was recorded in 4 cases and one patient had a sib who had died of an undefined diarrhoeal illness at the age of 5 months.

On arrival at this hospital all infants weighed less than the 3rd centile for age and 15 were clinically marasmic; 8 weighed less than their birthweight and these developed symptoms at a mean age of 3 weeks and were referred to us at a mean age of 7 weeks. 4 patients were clinically dehydrated on arrival, and 11 were referred on intravenous fluids. The typical clinical appearance of these patients is illustrated by the 2 infants in the Fig.

Laboratory features. The laboratory investigations performed on these 17 patients are outlined in Appendix A. No pathogenic bacteria or parasites were recovered from stools, and viral studies were not performed. Urine microscopies and cultures were normal, and when performed, blood cultures

Fig. Typical clinical appearance of category 2 patients with protracted diarrhoea who presented after birth. (a) Aged 6 weeks, weight 1.9 kg; (b) aged 9 weeks, weight 2.7 kg.

were sterile. 6 patients had haemoglobins of <10 g/dl, and 4 had total white cell counts of $>15\,000/\text{mm}^3$ ($15.0 \times 10^9/\text{l}$), the predominant cells being neutrophil polymorphs. 4 infants were hyponatraemic (plasma sodium <130 mmol/l; <130 mEq/l), one was hypernatraemic (sodium >160 mmol/l), and 5 had a metabolic acidosis on referral. 3 were hypoalbuminaemic (plasma albumin <3.0 g/l). Hypocalcaemia was not a feature in any of the 17 infants. Plasma zinc level was low in 1 of 5 infants in whom it was determined, whereas plasma copper was normal in all 5.

Serum IgA and IgM levels were raised in 3 patients, and 4 had low levels of IgA; in 1 patient IgM was raised, in another IgG was raised. None of the patients had low serum concentrations of IgG or IgM.

Peroral jejunal biopsy performed in one case showed subtotal villous atrophy; this infant had received gluten (1–2 g daily) for 3 weeks before biopsy, but after a formal gluten challenge has been proved not to have coeliac disease.

Comparison of clinical and laboratory features between category 1 and category 2 patients. On the basis of the clinical and laboratory features it was sometimes not possible to clearly differentiate category 1 patients from category 2 patients at the time of referral. In a small proportion of infants, however, the diagnosis was almost immediately apparent (e.g. acrodermatitis enteropathica, ulcerative colitis, staphylococcal pneumonia). Diagnosis in category 1 patients was established either after more extensive investigation, or in retrospect (e.g. cows' milk protein intolerance). None of the infants in category 1 subsequently proven to have coeliac disease presented the typical clinical appearances of the 2 patients in category 2 shown in the Fig. Some patients in category 1 (e.g. secondary disaccharide intolerance, cows' milk protein intolerance), however, presented identical clinical features to the category 2 patients.

Management. The management of category 1 patients was according to the specific diagnoses which were

made. Correction of water and electrolyte imbalances was necessary in a number of these patients, and a few required a period of parenteral nutrition.

In the category 2 patients with diarrhoea dating from birth, long-term parenteral nutrition for periods varying from 1 to 9 months was necessary in all 6. None responded to the dietary regimen outlined in Appendix B, nor to any other artificial food formulae (e.g. elemental diets) or drugs (e.g. cholestyramine, corticosteroids, prostaglandin synthetase inhibitors, oral antibiotics).

After investigation and unsuccessful attempts to treat with a variety of the commercially available dietary formulae, the 17 patients in category 2 who presented after birth were treated with a diet which excluded all protein sources except for chicken, and the disaccharides lactose and sucrose. Total parenteral nutrition was not considered necessary in any of this group, but oral feeding was temporarily supplemented by intravenous nutrition in one case. In some of this group the infant's condition precluded detailed investigation. The mean duration of hospitalization and weight gain was 29 weeks and 29 g per day respectively.

Details of the chicken-based diet, duration of treatment, and the scheme for reintroducing a normal diet are outlined in Appendix B.

Discussion

It is our experience and that of others (Avery *et al.*, 1968; Hyman *et al.*, 1971) that infants with protracted diarrhoea often present major problems in diagnosis and management. Because of delays in referral to experienced centres, the condition of the patients often precludes intensive investigation and an empirical approach based on theoretically possible diagnoses is necessary. Nevertheless, it should be stressed that every attempt to exclude medical and surgically remediable causes (see Table 3) should be made. In our series 3.6% of patients had an underlying surgical cause for their protracted diarrhoea, compared with 10% in the reported series of Avery *et al.* (1968).

In category 1 patients the three commonest diagnoses were coeliac disease, secondary disaccharide intolerance, and cows' milk protein intolerance. In 5 patients the latter diagnosis was made retrospectively when milk was reintroduced after a 2- to 3-month period of treatment with the chicken-based formula. The general condition of many of these infants on referral was so poor that the possibility of precipitating severe crises by cows' milk challenges was not considered to be justified. A variety of other diagnoses was established such as primary sucrase-isomaltase deficiency, Shwach-

Table 3 *Differential diagnosis of protracted diarrhoea in infancy*

<i>Causes</i>	<i>Examples</i>
Coeliac disease	
Acquired sugar intolerance	Lactose intolerance
Acquired protein intolerance	Cows' milk protein intolerance Soy bean protein intolerance
Enterocolitis	
Surgical	Malrotation Hirschsprung's disease Blind loops After intestinal resection and other surgical procedures to gastrointestinal tract
Selective inborn errors of absorption	Congenital chloridorrhea Glucose-galactose malabsorption Sucrase-isomaltase deficiency
Extraintestinal infection	Urinary tract infections Staphylococcal pneumonia or lung abscesses
Immune deficiency states	Combined immune deficiency Defective opsonization
Cystic fibrosis	
Chronic inflammatory bowel disease	Ulcerative colitis
Tumours	Neuroblastoma Ganglioneuroma Carcinoid Lymphoma
Antibiotics	Ampicillin Clindamycin
Miscellaneous	Adrenal insufficiency Histiocytosis X Intestinal lymphangiectasis Intrauterine infections

man's syndrome, acrodermatitis enteropathica, ulcerative colitis, ganglioneuroma, defective opsonization (Soothill and Harvey, 1976), and staphylococcal pneumonia (Harries and Francis, 1968). The opsonizing capacity of the serum of infants with protracted diarrhoea in whom a specific diagnosis is not immediately apparent should be assessed, since therapy with plasma infusions may result in prompt and complete control of the diarrhoea; defective opsonization may be a commoner cause of protracted diarrhoea than has been hitherto supposed, particularly when the diarrhoea is associated with frequent infections and eczema.

The most severely affected patients were those in category 2 who presented from birth. 4 of these 6 infants died, a mortality rate of 5% for the total series of 82 patients. Of particular interest in this group was the high incidence of sibs being similarly affected with protracted diarrhoea dating from birth, and the associated extraintestinal anomalies. 2 of the patients who died were sibs and both had absent corpora callosa. 2 others had sibs who had died at 1 week and 8 months after birth; 1 of these had a right dysplastic kidney and the other a 'tissue paper' like skin which exfoliated at intervals of 2 to

3 weeks. The latter patient was the infant with hypoplastic villous atrophy of the small gut as described in the results section. None of the 6 infants in this group had any of the currently recognized inborn errors of absorption, but the familial pattern of severe watery diarrhoea dating from birth may indicate a genetically determined disorder of fluid and electrolyte absorption. There was no clinical or laboratory evidence of intrauterine infection, and no history of intestinal disease in the parents.

Finally there were the 17 infants in category 2 who had remained perfectly well until a mean age of 4.9 weeks, presenting usually with acute diarrhoea with or without vomiting. These were all extremely ill and marasmic on referral, and had previously been unsuccessfully treated with a variety of dietary formulae on the assumption of diagnoses such as cows' milk protein intolerance and/or disaccharide intolerance. All responded promptly to our protocol using a chicken-based feed (details in Appendix B), and were able to return to a diet containing cows' milk approximately 3 months later. 5 infants who originally fell into category 2 were subsequently proved to have cows' milk protein intolerance after a period of successful treatment on the chicken-based diet, and were therefore transferred to the diagnostic category 1. Intolerance to cows' milk protein may result in acute or more insidious and chronic symptoms (Kuitunen *et al.*, 1975), and for this reason it is our policy to delay reintroducing dietary gluten until after the successful reintroduction of cows' milk protein (see Appendix B). In this series a delayed response to cows' milk protein was not seen in any infant, and all are currently receiving a normal diet except for 1 patient who remains on a gluten-free diet awaiting a gluten challenge. From our series and those of Avery *et al.* (1968), Hyman *et al.* (1971), and Lloyd-Still *et al.* (1973), a comprehensive differential diagnosis can be formulated for infants with protracted diarrhoea, as shown in Table 3, which also lists conditions not included in the present series that we have encountered in the past.

Our results indicate that the chicken-based feeding regimen (see Appendix B) is a highly effective form of dietary treatment in those infants with protracted diarrhoea of undetermined cause who present after birth. It contains a hypoallergenic protein source, essential fatty acids, and excludes the disaccharides lactose and sucrose; carbohydrate is included in the form of a glucose polymer, Gastrocaloreen. In some infants carbohydrate was administered as glucose, or a mixture of fructose and glucose, and was equally effective. The formula provides all the essential nutrients required for optimal growth, is a relatively low osmolar feed, is well tolerated by infants, and is

cheap. After a few teaching sessions with a dietitian before discharge from hospital, the parents of our patients coped extremely well with the diet in their homes. All the children thrived on the chicken-based diet, and a proportion became overweight as a result of their ravenous appetites and parental generosity with regard to food demands. The dietary requirements of marasmic infants with protracted diarrhoea are, of course, greatly in excess of their actual body weight; as they respond to dietary treatment and begin to thrive their nutritional requirements per unit body weight decline and appropriate reductions are necessary to avoid excessive weight gain and obesity.

In infants with protracted diarrhoea, in whom a diagnosis is not readily apparent, we would recommend dietary treatment with the chicken-based formula while awaiting the results of laboratory investigations. Parenteral nutrition may be life saving in marasmic infants and, unless there is a rapid response to dietary treatment, should probably be started at an early stage (Harries, 1971; Hyman *et al.*, 1971; Lloyd-Still *et al.*, 1973). Complications of parenteral nutrition, however, are far more likely to occur in severely malnourished infants, particularly septicaemia and hypophosphataemia (Harries, 1974). Hypophosphataemia may result in haemolytic anaemia, and peripheral hypoxia leading to convulsions and sometimes coma (Jacob and Amsden, 1971; Silvis and Paragas, 1972), and may also result in defective phagocytic function, and thus predispose to sepsis during parenteral nutrition (Craddock *et al.*, 1974). The somewhat traditional concept of 'resting the bowel' of infants with diarrhoeal states continues to be attractive, but there is no good evidence that this approach is therapeutically beneficial. On the contrary, there is now good evidence that intraluminal substrates exert a trophic effect on the small intestinal mucosa and that this effect may be mediated by certain gastrointestinal hormones such as gastrin (Johnson, 1976). For these reasons it is our policy to provide some oral feeds in those infants with protracted diarrhoea who require parenteral nutrition.

A variety of hyperosmolar 'elemental' diets are currently available, and have been advocated in the management of protracted diarrhoea in infancy. These have a number of disadvantages such as their high osmolality, their cost, and the fact that many contain fat in the form of medium-chain triglycerides thereby increasing the risk of essential fatty acid deficiency. In our experience elemental diets are rarely, if ever, indicated in the treatment of protracted diarrhoea.

The pathophysiological mechanisms responsible for the protracted diarrhoea in our patients have

not been defined in the present study, and are probably complex and multifactorial. The turnover of the epithelial absorptive cells of the small intestine is rapid, and a vicious cycle of malabsorption-malnutrition-exacerbation of malabsorption is an acceptable general concept to explain the continuing diarrhoea and malnutrition in many cases. Within this general concept, however, a number of specific pathophysiological mechanisms may act singly or in concert in the genesis of the diarrhoea and these will be briefly considered.

An acute enteric infection can cause damage to the small intestinal mucosa and may render the mucosa sensitive to foreign antigens such as cows' milk protein, and deficiency of IgA may predispose the infant to become sensitive to foreign protein (Harrison *et al.*, 1976). In this context it is of interest that 4 of our 17 patients who presented after birth had reduced levels of serum IgA. As an entity, transient gluten intolerance (Walker-Smith, 1970) has not been unequivocally established, but it is our impression that infants with protracted diarrhoea benefit from temporary withdrawal of dietary gluten. Other foreign proteins such as soy bean protein may also play an aetiological role in some infants (Ament and Rubin, 1972).

Bacterial overgrowth of the small intestine is now established as a common phenomenon in infants with protracted diarrhoea in both the developing (Gracey and Stone, 1972; Heyworth and Brown, 1975) and developed (Gracey *et al.*, 1969; Challacombe *et al.*, 1974a, b) parts of the world. Both anaerobic (particularly *Bacteroides*) and aerobic (particularly *E. coli* and *Klebsiella pneumoniae*) species have frequently been isolated. These observations may indicate that bacteria, the toxins which they elaborate, or the 'toxic' products which they generate as a result of metabolism of intraluminal substrates may be of pathophysiological importance. For example, a variety of anaerobic bacteria possess enzymes which catalyse the deconjugation and 7- α -dehydroxylation of bile salts resulting in the production of free dihydroxy bile acids such as deoxycholate and chenodeoxycholate. In the experimental animal, deoxycholate inhibits the absorption of fluid and electrolytes in both the small and large bowel and in the jejunum inhibits monosaccharide absorption and mucosal ($\text{Na}^+ - \text{K}^+$)-ATPase activity. At high concentrations this bile acid produces gross structural abnormalities of the jejunal mucosa (Harries and Sladen, 1972; Sladen and Harries, 1972; Guiraldes *et al.*, 1975). Deoxycholate and other free bile acids are present in the duodenal contents of some infants with protracted diarrhoea (Gracey *et al.*, 1969; Challacombe *et al.*, 1974a; Schneider and Viteri, 1974), and may contribute to

the pathogenesis of the diarrhoea. In addition to bile acids, bacterial production of hydroxy fatty acids may also contribute to the diarrhoea (Bright-Asare and Binder, 1973; Ammon *et al.*, 1974). A variety of toxins elaborated by bacteria commonly found in the duodenum of infants with protracted diarrhoea (e.g. *E. coli*, *Kleb. pneumoniae*, *Staph. aureus*, *Clostridium perfringens*) inhibit fluid and electrolyte transport in the small gut of the experimental animal (Sullivan and Asano, 1971; Field, 1974; McDonel, 1974; Elias and Shields, 1976; Klipstein *et al.*, 1976).

Further studies are required to clarify the pathophysiological mechanisms which operate in infants with protracted diarrhoea. We speculate that in a proportion of affected patients an acute infective insult renders the small intestine susceptible to intolerance of foreign proteins and/or bacterial colonization, and that this sequence of events is important in the pathogenesis of the diarrhoea and malnutrition. Malnutrition, whether primary or secondary to infection, probably plays an important pathophysiological role.

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Correspondence to Dr. J. T. Harries, Institute of Child Health, 30 Guilford St., London WC1N 1EH.

Appendix A

Clinical and laboratory methods used for assessment and diagnosis of infants with protracted diarrhoea

Initial assessment

(i) *Clinical*. Historical evaluation of onset and duration of symptoms; relationship between withdrawal and/or introduction of different dietary constituents; family history of gastrointestinal disease; presence of blood and/or bile in vomit; presence of blood and character of stools; frequency of extra-intestinal infections; details of pregnancy and birth with regard to intrauterine infections and asphyxia; clinical assessment of degree of dehydration and nutritional status, and careful examination of the abdomen and anorectal region.

(ii) *Laboratory*. Haemoglobin, white blood cell and platelet counts; blood urea, plasma electrolytes, and acid-base status; plasma glucose, calcium, and magnesium, and serum proteins; blood cultures and clotting studies as indicated; stools for microscopy, culture, and reducing substances; urine for microscopy and culture, and amino acid chromatography. Erect and supine plain films of chest and abdomen.

Subsequent assessment

When a specific diagnosis was not immediately apparent, and when the infant's general condition had stabilized the following investigations were performed in all cases: serum immunoglobulins, folate, cholesterol, and iron; plasma amino acids and organic acids; plasma and urinary catecholamines; 11-oxygenation index of urine; barium meal and follow through; sweat test; opsonizing capacity of serum. Serum trace metal levels (particularly zinc and copper) were determined in patients referred during the past 6 months.

The following investigations were performed only in those infants where they were considered to be indicated; barium enema, rectal pressure studies, sigmoidoscopy, and rectal biopsy; jejunal biopsy for histology and disaccharidase assays; duodenal intubation for pancreatic enzymes, bile salts, and culture of aerobic and anaerobic bacteria; blood levels of hormones such as vasoactive intestinal peptide, gastrin, and calcitonin; oral sugar loading

tests and appropriate tests to exclude intrauterine infection.

Appendix B

Details of chicken-based diet, duration of treatment, and reintroduction of normal diet in infants with protracted diarrhoea of undetermined cause

Protein is provided as comminuted chicken (which contains some long-chain triglycerides), carbohydrate as Gastrocaloreen (a glucose polymer), and fat as Prosparol (an emulsion of long-chain triglycerides); carbohydrate can also be given as glucose, or as a mixture of glucose and fructose, up to a maximum concentration of 8–10%. The basic constituents of 100 ml of the full strength feed are shown in Table 4. Comminuted chicken 50 g, Gastrocaloreen 5 g, and 0.8 g of the metabolic mineral mixture (Table 5) are made up to 100 ml

Table 4 *Constituents of full-strength feed for treatment of protracted infantile diarrhoea of undetermined cause*

Constituents	Amount in 100 ml
Protein (contained in comminuted chicken)	3.75 g
Fat (contained in chicken)	1.65 g
Gastrocaloreen*	5.0 g
Sodium†	1.85 mmol
Potassium†	2.32 mmol
Calcium†	1.75 mmol
Other minerals†	—
Total energy provided: approx.	211 kJ

*Gastrocaloreen is a glucose polymer (Scientific Hospital Supplies, England).

†Sodium, potassium, calcium, and other minerals derived from the comminuted chicken and the metabolic mineral mixture.

Conversion: SI to traditional units—Energy: 4.18 kJ ≈ 1 kcal.

Table 5 *Composition of metabolic mineral mixture**

Constituents	Amount (mg) in 1 g
Calcium	82
Potassium	83
Phosphorus	59
Sodium	39.6
Magnesium	9.7
Iron	0.5
Copper	0.063
Zinc	0.11
Manganese	0.057
Iodine	0.007
Aluminium	0.0002
Molybdenum	0.0015

*Scientific Hospital Supplies, England.

with water. Initially this formula is given as a quarter-strength feed with added sugar (5% dextrose), from which the added fat (Prosparol) is omitted, in a suitable volume as small frequent feeds

(e.g. 1- or 2-hourly feeds) together with disaccharide-free complete vitamin supplements (i.e. 3 Ketovite tablets and 5 ml Ketovite liquid (Paines & Byrne, Greenford, Middx.) per day); any drugs must be administered orally free of disaccharides. The feeds are then slowly built up over a period of 10–30 days. This is achieved by first increasing the feeds to full strength, and then by adding Prosparol in 2–5 ml increments; Gastrocaloreen and calcium gluconate are also added to the feeds during this build up period to provide finally the requirements shown in Table 6. If this feeding regimen is tolerated and the

Table 6 *Details of full feeding regimen in treatment of protracted infantile diarrhoea of undetermined cause*

Constituents	Amounts in feeds
Comminuted chicken	Not more than 10 g protein/kg per day*
Gastrocaloreen	10 g/100 ml of feed
Fat (from prosparol† and comminuted chicken)	4 g/100 ml of feed
Metabolic mineral mixture	1.5 g/kg per day* (provided quantities do not exceed 1 g/100 ml of feed, or a total of 8 g/day)
Calcium (from comminuted chicken, metabolic mineral mixture, and added calcium gluconate)	At least 1.25 mmol/100 ml of feed or a minimum of 12.5 mmol/day.
Feed volume	200 ml/kg per day
Total energy provided	750 or more kJ/kg per day

*Units of weight refer to actual not expected body weight. Vitamin supplements are given as Ketovite tablets (×3/day) and liquid (5 ml/day).

†Prosparol is a 50% arachis oil emulsion of long-chain triglycerides (Duncan, Flockhart & Co., London).

patient begins to thrive, then the following modifications are implemented before discharge home. (i) The intervals between feeds are increased (e.g. 4-hourly × 5); (ii) introduction of suitable weaning solids appropriate for age (e.g. Robinsons baby rice mixed with 5% dextrose; milk-free mashed potato, and puree meat). The dietitian then spends two to three sessions with the mother teaching her the diet.

After a period of 2 to 3 months the patient is readmitted and reintroduction of disaccharides and cows' milk protein is attempted according to the following scheme.

Day 1. Lactose replaces the feed carbohydrate, initially in a concentration of 1%. If this is tolerated the concentration of lactose is increased on days 2, 3, and 4 to 3, 5, 7% respectively.

Day 5. If lactose is tolerated, a challenge (5 ml) of fresh pasteurized cows' milk is given.

Day 6. If the milk challenge does not precipitate any symptoms, the volume of a suitable low solute cows' milk formula is slowly increased over the next 4 days

so as to completely replace the chicken feeds. Sucrose is added to the diet (e.g. as fruit puree) before discharge. If lactose is tolerated then invariably sucrose will also be tolerated, since secondary lactose intolerance usually persists for longer periods of time than secondary sucrose intolerance.

Day 10. The patient is discharged home on a gluten-free diet and closely followed-up in the outpatient department.

If there is a family history of coeliac disease or if onset of symptoms followed the introduction of gluten-containing foods into the infant's diet, then it is our policy to perform a small intestinal biopsy

before and after a gluten challenge 1 to 2 years later (Packer *et al.*, 1974). If there is clinical or biochemical evidence of deterioration on a gluten-free diet, a small intestinal biopsy is performed to exclude an enteropathy caused by cows' milk protein, before returning the patient to a cows' milk protein-free diet. If the patient thrives and does not fulfil the diagnostic criteria for gluten challenge as outlined above, gluten is introduced to the diet after approximately 3 to 6 months, and the patient is followed up at regular intervals for 2 years. If during this time there is any clinical or biochemical evidence of coeliac disease a small intestinal biopsy is performed.

Erratum

In the article on 'Controlled trial of continuous positive airway pressure given by face mask for hyaline membrane disease' by Allen *et al.*, May 1977, pp. 373–378, the published values for CPAP and ventilation therapy on pages 374, 375, 376, 377, and in Table 3 (corrected version published below) were incorrect from the decimal point being sited one place to the left, resulting in the figures given being 10 times too small.

Table 3 Values (mean $\pm$ 1 SEM) for mechanical ventilator variables when mean airway pressure was highest in the early-intervention and late-intervention groups. These values were obtained 2–4 hours after starting ventilation. P_{aO_2} was between 6.30 and 8.60 kPa (47 and 67 mmHg), P_{aCO_2} between 4.52 and 9.17 kPa (34 and 69 mmHg), and pH between 7.19 and 7.41

	Group		P
	Early intervention (n=4)	Late intervention (n=7)	
F_{iO_2}	0.85 $\pm$ 0.03	0.89 $\pm$ 0.02	NS
Respiratory frequency (cycles/min)	33.8 $\pm$ 3.7	35.4 $\pm$ 1.6	NS
Peak airway pressure (kPa)	2.0 $\pm$ 0.28	2.6 $\pm$ 0.27	NS
End-expiratory pressure (kPa)	0.3 $\pm$ 0.11	0.27 $\pm$ 0.11	NS
Inspiration : expiration ratio	0.62 $\pm$ 0.12:1	1.79 $\pm$ 0.26:1	<0.02
Mean airway pressure (kPa)	0.91 $\pm$ 0.08	1.76 $\pm$ 0.25	<0.05

Conversion: SI to traditional units—1 kPa $\approx$ 7.5 mmHg and 100 mm H₂O.