ASPECTS OF DISEASE ACTIVITY AND ENTERAL NUTRITION IN CROHN'S DISEASE

by

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DECLARATION

I declare that the work presented in this thesis has been carried out solely by me, except where indicated in the text and below.

The measurements of the hepatic lipid in the animal study, the gastrointestinal protein loss and the alpha$_1$-acid glycoprotein levels in the other studies were performed in collaboration with Dr. A. Duncan, Gastroenterology Unit, Glasgow Royal Infirmary; Dr. A. Shenkin and his staff at the Institute of Biochemistry, Glasgow Royal Infirmary, performed the biochemical nutritional screens; Professor J. McKillop. Nuclear Medicine Dpartment, Glasgow Royal Infirmary, scored the indium scans; Mrs. A. Galloway and other members of the dietetic staff at Glasgow Royal Infirmary provided immense help in assessing patients dietary intake and recording of data during the diet trial.

DEDICATION

To Maureen, Julia and Michael

Some glory in their birth, some in their skill,
Some in their wealth, some in their body's force;
Some in their garments, though new-fangled ill;
Some in their hawks and hounds, some in their horse;
And every humour have his adjunct pleasure,
Wherein it finds a joy above the rest;
But these particulars are not my measure,
All these I better in one general best.
Thy love is better than high birth to me,
Richer than wealth, prouder than garments cost,
Of more delight than hawks and horses be;
And, having thee, of all men's pride I boast.

William Shakespeare

PUBLICATIONS ARISING FROM THE THESIS

PAPERS

Park, R.H.R., McKillop. J.H., Duncan, A., MacKenzie, J.F. & Russell. R.I. (1988) Can ^{111}Indium autologous mixed leucocyte scanning accurately assess disease extent and activity in Crohn's disease ? Gut, 29, 821-825.

Park, R.H.R., Khasawneh, S., Duncan, A., Russell, R.I., Hutchison, A. & Shenkin, A. (1988) Acute phase response in malnourished patients with Crohn's disease. Clinical Nutrition, 7, 207-211.

Park, R.H.R., Galloway, A., Shenkin. A. & Russell, R.I. (1990) Magnesium deficiency in patients on home enteral nutrition. Clinical Nutrition, 9, 147-149.

Park, R.H.R., Danesh, B., Galloway, A. & Russell, R.I. (1991) Double blind controlled trial of elemental and polymeric diets as primary therapy in active Crohn's disease. European Journal of Gastroenterology and Hepatology, 3, 483-490.

ABSTRACTS

Park, R.H.R., Duncan, A., Mitchell, G., Russell, R.I. (1985) A comparison of modular elemental and polymeric liquid diets on growth, nitrogen wastage, faecal residue and hepatic lipids in rats. Gut, 26, A1112.

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SUMMARY

The introductory chapters (Chapters 1, 2) reviewed nutritional problems, methods of nutritional support and methods of assessing disease activity in Crohn's disease. Variable prevalences of macro- and micro-nutrient deficiencies occur in patients with Crohn's disease. Previous studies have concentrated on the role of intravenous nutrition for the correction of nutritional deficiencies.

A spectrum of methods for determining disease activity in Crohn's disease exists : a multinational collection of clinical scores; combination of clinical and laboratory scores; and pure laboratory assessments. The most appropriate routine methods of assessment are clinical score combined with an objective laboratory test, such as the CRP. More sophisticated laboratory methods can be used in special circumstances.

The second section of the thesis summarised the aims and layout of the thesis.

Section III was concerned with special problems relating to disease activity, both in the assessment and in the alteration of disease activity brought about by

malnutrition and blood tranfusion. While previous studies have produced useful clinical indices, the ideal index remains in dispute. Most of the present clinical scores cannot be used for patients with stomas. Ten clinical scores and several laboratory tests were compared in patients with stable chronic disease and also in patients with active disease (Chapter 3). Separate groups of patients with stomas were also assessed by using a modified clinical index.

Interestingly there appeared to be different patterns of correlation between the clinical scores and the laboratory indices in both clinical situations. In acute patients most of the laboratory indices had poor correlation with the clinical indices with the exception of the CRP. In the stable group of patients, most of the laboratory indices correlated with the clinical indices. The CRP appeared to be the most reliable laboratory parameter for all clinical situations. The modified CDI, which was used for patient with stomas, showed significant correlations with other clinical indices and was used in subsequent studies.

Acute phase proteins, in particular CRP, can be useful in assessing disease activity in Crohn's patients, as was found in Chapter 3 of this thesis. However the effect of

malnutrition on the acute phase response has been ignored, and if present, could dramatically alter the assessments of disease activity. From the results of a study described in Chapter 4, which compared the acute phase response in well nourished and malnourished patients, I concluded that malnourished patients were able to mount similar acute phase responses compared with well nourished patients. Acute phase proteins, therefore, can be used in the assessment of disease activity even when the nutritional state of the patient is unknown.

^{111}Indium leucocyte scanning is a new and exciting development in the assessment of activity in Crohn's disease. Previous studies have used sophisticated techniques which are outwith the usual facilities of nuclear medicine department. Indium-oxine mixed leucoctye scanning was compared with other indices of disease activity (Chapter 5). Indium scanning correctly located the extent of disease in only 58% of patients and there was poor correlation between the scan activity and the other indices of disease activity. These results were disappointing as I had hoped that routine Indium scanning would offer a more accurate method of assessing disease extent and activity.

Although blood transfusion is one of the oldest methods

of artificial nutritional support, and is widely used in Crohn's disease, its immunomodulating effect on Crohn's disease has not been studied. This potential effect on disease activity and also relapse rates could have important consequences in therapeutic trials in Crohn's disease. The results from a large group of Crohn's patients (treated both medically and surgically) did not show an advantage in the relapse rates following blood transfusion (Chapter 6). Medical and surgical patients were analysed separately and appeared to have different responses to blood transfusion : the medical patients who did not receive a blood transfusion had better relapse rates; the surgical patients did better if they had received blood transfusions.

Section IV was an animal study (Chapter 7) comparing the new enteral liquid diets which were to be used in the enteral nutrition studies. Both of the diets, Elemental 028 and Enteral 400 (Scientific Hospital Supplies, Liverpool, UK), had similar nutritional efficacy and low faecal residue compared with the established enteral liquid diet, Vivonex HN, which has been used in other diet studies in Crohn's disease. Elemental 028 produced an increase in hepatic lipid, similar to Vivonex HN.

Section V, the clinical application of enteral nutrition in Crohn's disease, was composed of five studies (Chapters 8 - 12). Chapter 8 assessed the role of elemental and polymeric diets, using the new Elemental 028 and Enteral 400 diets, as primary therapy for active Crohn's disease. The results showed that the polymeric diet, Enteral 400, was equally effective in inducing remission in active Crohn's disease, compared with Elemental 028. Polymeric diets could be used more frequently which would reduce the number of patients who are unable to tolerate elemental diets due to poor palatability and also reduce the costs.

Most of Section V involved the assessment of Home Enteral Nutrition (HEN) as a method of providing long-term nutritional support for malnourished patients with Crohn's disease, determining any practical problems and micronutrient deficiencies, and evaluating the usefulness of HEN in correcting growth retardation in adolescents with Crohn's disease. The studies showed that HEN is an effective and easy method of providing long-term enteral nutrition support and can correct growth retardation. Vitamin deficiencies are easily corrected by HEN due to the high vitamin content of the diets. Patients on HEN should be observed for potential magnesium deficiency, which occurred in 44% of patients. Overall the patients clinical disease and well-being improved during their

periods of HEN, and in particular their hospital admission rates fell.

SECTION I

INTRODUCTION

CHAPTER 1

REVIEW OF NUTRITIONAL PROBLEMS AND METHODS OF NUTRITIONAL SUPPORT IN CROHN'S DISEASE

INTRODUCTION

The awareness of nutritional problems in Crohn's disease has evolved slowly from brief comments in early case reports. In 1806 Drs. Charles Coombe and William Saunders recorded their clinical findings from their "singular case of stricture and thickening of the ileum" in which they observed that the patient was "more emaciated than any person witnessed" (Myren,1986). Dalziel (1913) in his series of nine cases recognised that malnutrition was a significant problem, as commented upon by Crohn et al. (1932) twenty years later.

More recent reports have documented the extent of malnutrition in patients with Crohn's disease. Significant weight loss to less than 90% of the ideal body weight (IBW) was found in 20-40% of out-patients with relatively mild disease (Harries et al., 1982; Lanfranchi et al., 1982). The Cleveland Clinic study found up to 18% of patients had lost 20% of their body weight from the onset of their illness (Farmer et al., 1975). Many micronutrient deficiencies have been reported in patients with Crohn's disease (Harries & Heatley, 1983B).

The aetiology of malnutrition in Crohn's disease is

multifactorial : reduced oral intake; inappropriate diets; malabsorption; active inflammation with enteric losses; and the effects of drugs, including cholestyramine and sulphasalazine. Undoubtedly the most important mechanism is reduced oral intake.

Malnutrition from any cause can lead to poor wound healing, increased susceptability to infection due to alteration of the immune system, and numerous vitamin and trace metal deficiencies which may result in alteration of neuromuscular activity (Dowd & Heatley, 1984). However, only a few studies have examined prospectively the benefit of supplemented oral nutrition in malnourished patients with Crohn's disease (Harries et al., 1983A; Brignola et al., 1983; Imes et al., 1986). In the study by Harries et al. (1983A), the disease activity and immune function of 28 patients were measured during a period of supplemented diet by using the liquid diet, Ensure plus (Abbott Laboratories, Maidenhead, UK), and compared to a control period during which they took only ordinary diet. Nutritional parameters, immune function tests and disease activity all improved during the period of supplemented diet. Brignola et al. (1983) used Precision (Wander, USA) and found less impressive gain in weight and reduced improvement in disease activity. Unfortunately very few patients in the study by Imes et al. (1986) were able to

tolerate the liquid diet Ensure, (Abbott Laboratories, Maidenhead, UK) to provide a satisfactory conclusion.In another study by Imes et al. (1988), individualised diet counselling managed to increase patients intakes to achieve the recommended intakes for all nutrients, and also produced an improvement in disease activity and reduction in drug therapy.

INDICATIONS AND METHODS FOR NUTRITIONAL SUPPORT

Correction of Malnutrition

Methods of nutritional support for patients with Crohn's disease are determined by the indications for feeding :correction of malnutrition; treatment of local complications; specific oral diets including lactose free and low residue; and primary therapy. Correction of malnutrition is the most frequent indication and can be achieved by supplements to the patients diet, enteral nutrition in hospital or at home, or by intravenous feeding. Oral supplements can be in the form of nutritionally complete liquid diets taken as sip feeds, or in the form of high calorie glucose mixtures added to the ordinary diet.

Specific Diets

In certain situations specific diets such as lactose-free or low residue can be of considerable benefit. However, it is important to remember that such diets are restrictive and may be nutritionally incomplete thereby further adding to the problem of malnutrition. The diagnosis of lactose intolerance should always be confirmed before embarking on a lactose-free diet which may lead to a negative calcium balance due to reduced intake of dairy produce. Kirschner et al. (1981) found

that 30% of adolescents with Crohn's disease had lactose intolerance and in some ethnic groups the incidence may be as high as 60-95% (Welsh, 1978).

Several patients after small bowel resection for Crohn's disease have fat malabsorption leading to steatorrhoea, which may be helped by a low fat diet. The reduced calorie intake can be increased by providing more carbohydrate or by adding medium chain triglyceride (MCT) supplements. For many years low fibre diets have been advocated for patients with Crohn's disease in an attempt to prevent obstructive symptoms, but in a trial by Levenstein et al. (1985), no benefit was found in using a low fibre diet compared with control diets. Fibre-rich diets, initially thought to be of some value, have been shown over several years to be no better than ordinary diets (Ritchie et al., 1987).

Exclusion diets are very restrictive and require superhuman effort by patients, dietitians and doctors. Several groups have enthusiastically supported exclusion diets, advocating that the main benefit is the long-term remission rate (Alun Jones et al., 1985).

Local Complications

Crohn's disease is frequently complicated by perianal disease and abscesses, high output fistulas and bile acid induced diarrhoea. Dietary manipulation can play a part in the management of these problems. Bowel rest by using either intravenous feeding or more frequently by enteral nutrition, especially elemental diets, can provoke marked symptomatic improvement (Voitk et al., 1973; Nelson et al., 1977; Russell & Hall, 1979).

Primary Therapy

Patients with Crohn's disease would benefit greatly if nutritional support, in addition to correcting malnutrition, also produced improvement in disease activity without additional drug therapy. This is the concept of "primary therapy" in Crohn's disease. This effect had been recognised in early studies looking at the role of nutritional support and had been attributed to "bowel rest" (Voitk et al.,1973; Fisher,1973; Rocchio et al., 1974; Reilly et al., 1976; Nelson et al.,1977; Russell & Hall,1979). By providing intravenous nutrition or enteral nutrition using elemental diets, it was considered that the bowel rest provided by the reduced intestinal and pancreatico-biliary secretions, gut hormone excretion and bowel motility, would have a beneficial effect on disease activity. However, other important

factors may be relevant: intraluminal antigenic food particles (Alun-Jones et al., 1985); alteration in bowel microflora (Leijonmarck et al., 1988; and improvement in immune function following correction of malnutrition (Harries et al.,1984).

The dramatic increase in the use of nutritional support over the past ten years raises important questions about the ideal method of support. Several studies, although hampered by uncontrolled or retrospective design, have shown encouraging results with bowel rest and intravenous feeding (Fischer et al.,1973; Reilly et al.,1976; Muller et al.,1983; Ostro et al.,1985). Ostro et al. (1985) suggested that disease remission could be achieved in up to 77% of patients who had been previously refractory to medical therapy. Another study found that surgery was avoided in 70% of patients who had failed to respond to medical treatment (Reilly et al., 1976).

However, two well designed studies found no difference between bowel rest by intravenous feeding compared with oral diet in patients with acute Crohn's colitis treated with high dose steroids (Dickinson et al.,1980; McIntyre et al.,1986). In a controlled trial involving 36 patients there were no differences in disease remission between the group treated by intravenous feeding or elemental diet

(Alun-Jones et al., 1987). Greenberg et al. (1988A) randomised 17 patients with Crohn's disease unresponsive to medical therapy to receive intravenous feeding and nil by mouth, 19 similar patients received polymeric diet by nasogastric feeding and 15 patients partial intravenous feeding with oral food. There were no significant differences between the three groups for clinical remission rates (71%, 58%, 60% respectively) or for long-term remission at one year (42%, 55%, 56%).

It is not necessary to provide intravenous nutrition for primary therapy for active Crohn's disease unless the enteral route cannot be used. Similarly for patients whose disease is complicated by fistulas there does not appear to be a specific benefit in using intravenous feeding and bowel rest. In a review of previous studies involving a total of 156 patients, only 35% achieved in-hospital fistula closure and only 17% long-term closure (Greenberg et al.,1988B).

Early reports of the use of elemental diets in correcting nutritional deficiences in Crohn's disease patients found coincidental improvement in disease activity (Stephens & Randall,1969; Voitk et al.,1973; Goode et al.,1976; Axelsson et al.,1977). This was considered to be a similar effect to that of primary

therapy with intravenous feeding. Elemental diets are thought to exert their beneficial effect on disease activity by their hypoallergenicity resulting from their nitrogen source of free amino acids. Antigenic protein would therefore be unavailable to pass through the damaged bowel wall (O'Morain et al.,1984). Elemental diets have also been shown to reduce the protein loss from inflamed small bowel (Logan et al.,1981) and improve abnormal small bowel permeability in Crohn's patients (Sanderson et al.,1987A). Controlled trials have shown elemental diets to be as effective as prednisolone (O'Morain et al.,1984), prednisolone with non-absorbable antibiotics (Saverymuttu et al.,1985) and ACTH/prednisolone/sulphasalazine in children (Sanderson et al., 1987).

All the patients included in these previous studies were established on their diets in hospital and then followed up as out-patients. In the diet groups all other food was excluded except clear fluids and tea without milk. It is impossible to check if the patients were adhering rigidly to their diets at home especially as elemental diets are unpalatable. This problem led several investigators to enquire whether more palatable whole protein (polymeric) diets could also achieve similar clinical results. Although the polymeric diets are not considerd to be hypoallergenic, their effect on patients with active

Crohn's disease may arise from alternative mechanisms. There is some evidence that primary therapy for active Crohn's disease is not unique to elemental diets. Ginsberg & Albert (1988) have reported their experience with the whole protein diet, Ensure plus (Ross Laboratories, USA), in steroid dependent Crohn's patients. Two of four patients with small bowel disease and one of three patients with colitis went into remission. One patient from this study who had severe small bowel disease and who had been steroid dependent for 12 years became asymptomatic after 10 weeks on the diet and steroids were withdrawn.

The mechanisms by which elemental and polymeric diets work may be different. The cost of the treatment would be substantially reduced by using polymeric diets rather than elemental diets and by improving the palatability of the diets the patients' compliance would be increased.

HOME NUTRITIONAL SUPPORT

The management of patients with severe intestinal failure and fistulas secondary to Crohn's disease was revolutionised by home intravenous feeding regimes introduced in the early 1970's (Jeejeebhoy et al.,1976).

Although highly effective, home intravenous feeding places an enormous burden on patients' lifestyle, has potential complications and high treatment costs. Fortunately, most patients requiring long-term feeding can be successfully managed by home enteral nutrition, a much easier method of feeding with fewer complications, and less expensive (Goode et al.,1976; Main et al.,1980; McIntyre et al.,1983; Bastow et al.,1985). Home enteral nutrition, using elemental diets, will improve disease activity, reduce resection requirements (Blair et al.,1986), and reverse both growth retardation and malnutrition (Blair et al.,1986; Belli et al.,1988). However reports to date have involved small numbers, mainly children, and have used elemental diets in the majority of cases.

CHAPTER 2

REVIEW OF ASSESSMENT OF CROHN'S DISEASE ACTIVITY

INTRODUCTION

Crohn, Ginsberg and Oppenheim (1932) recognised different patterns of disease, based on a spectrum of disease severity : " in the milder cases there may be little or no emaciation and no anaemia." During the past 55 years the emphasis has shifted from descriptive assessment of disease severity to quantitative assessment. Nowadays the use of the term " disease activity " implies a measure of the degree of bowel inflammation in Crohn's disease and is not necessarily interchangeable with "disease severity".

Truelove & Witts (1955) attempted to define severity in ulcerative colitis by using several clinical and laboratory indices to grade the illness from mild, moderate to severe.Their classification was the foundation for a cascade of multinational indices for Crohn's disease which have appeared over the past 20 years (Table 2.1).

The main stimulus for the multiple numerical indices was the appearance of controlled trials in Crohn's disease, starting with the azathioprine trial in 1971 (Willoughby et al.,1971). Many investigators considered that the response of therapeutic trials in Crohn's disease could

TABLE 2.1

CROHN'S DISEASE INDICES

CLINICAL	CLINICAL AND LABORATORY	LABORATORY
	Willoughby (1971)	
	De Dombal (1974)	
	Talstad (1976)	
	CDAI (1976)	
	Whittington (1977)	
	O'Donoghue (1978)	
	Lloyd-Still (1979)	
CDI (1980)		
	AI (1980)	
Present (1980)		
	New CDAI (1981)	
	Oxford (1984)	
OMGE (1984)		
		Factor Score (1984)
	MOD AI (1985)	
	Cape Town (1986)	
		Brignola (1986)
	Reibnegger (1986)	
Wright (1987)		
Sandler (1988)		
	CAGS (1988)	

only be assessed by a uniform scoring system, in particular when large trials included many different centres and investigators.

CLINICAL SCORES

Willoughby Index

Willoughby et al. (1971) designed a disease activity score for their controlled trial of azathioprine in Crohn's disease (Appendix 2.1). Each clinical feature was graded 0 - 3, stool frequency graded 0-2, and one point was scored for low haemoglobin, low albumin and a high ESR. The theoretical disease activity maximum score was 38, although in the trial the highest was 20. The disease activity score can be criticised by relying too heavily on subjective indices and complications. It is, however, an easy index to score and involves routine laboratory tests. The score was used as the basis for the O'Donoghue index (1978).

deDombal Index

deDombal et al. (1974) adapted Truelove and Witts's classification (1955) (Appendix 2.2). Disease severity was graded mild to severe depending on three local features, including bowel frequency, abdominal pain and rectal

bleeding, and four systemic features : pulse rate, temperature, haemoglobin and weight loss. This index was semi-quantitative and gave only three levels of disease activity. It was found to be difficult to allocate many patients into one of the three grades. Patients with colonic disease tended to be graded in a more severe category than patients with small bowel disease.

Talstad Index

Talstad & Gjone (1976) attempted to create a disease activity index which could be used for both ulcerative colitis and Crohn's disease. Initially patients were allocated disease categories (mild to severe) based on Truelove & Witts' classification (1955). Patients were subsequently assessed by 6 clinical symptoms and 12 laboratory, radiological or sigmoidoscopic results (Appendix 2.3). The disease activity was expressed as "% disease activity" (of the theoretical maximum score of 38). The results of % disease activity correlated with the ESR results. An estimate of disease activity was made :mild disease (<30% disease activity); moderate (30-70%); and severe (>70%). Although this index was suitable for both Crohn's disease and ulcerative colitis patients it has not been adopted for regular use as it contains too many parameters which appear to have little relevance to

disease activity (Maratka, 1981). It is also impractical for use in routine, repeated assessments. One of Talstad's patients, who had toxic dilatation, had a % disease score < 70%, which placed him in the moderate group (Talstad & Gjone., 1976).

Crohn's Disease Activity Index (CDAI)

A more quantitative method of assessing disease activity was introduced in 1970 for use in the American National Cooperative Crohn's Disease Study (Best et al., 1976).A panel of gastroenterologists identified 18 parameters which could be measured at outpatient clinics. The results were collected for 187 outpatient visits of 112 patients with Crohn's disease along with the physicians' global assessment. The contribution of each parameter to the physicians' global assessment was identified using multiple regression analyses. An index was derived (Appendix 2.4) and values of < 150 were considered to indicate quiescent disease, 150-450 active disease and > 450 extremely active disease.

Three years later Best et al. (1979) revalidated the index using data from 1058 patient visits and concluded that the rederived coefficients were similar to the original ones. The CDAI has been used widely for many drug trials in Crohn's disease either in the original form

(Malchow et al., 1984) or in a slightly altered version (Rosen et al., 1982). The CDAI has been criticised for its cumbersome, complex form (Mee et al., 1978; Best & Becktel, 1981), the necessity for the week-long diary history, the heavy weighting of subjective parameters (Cooke & Prior, 1984), and the use of a score < 150 to define remission (Hodgson, 1982). Six percent of patients defined as "poor" had a CDAI < 150 (Best et al., 1976).

The significance of "subjective" and "objective" parameters in forming a Crohn's disease activity score is a recurring theme with every index. The subjective sense of well-being contributes 23% of the final CDAI. The CDAI has only two truely objective parameters, the weight of the patient and the haematocrit (Cooke & Prior, 1984).

Whittington Index

This index was created for a retrospective study of the management of Crohn's disease in children and adolescents (Whittington et al., 1977). One observer performed a retrospective case note review and determined :a) subjective evaluation of patients symptoms; b) physical examination,;c) haematocrit (normal > 35%), ESR (normal < 20 mm/h), and serum albumin (normal range > 3.5 g/dl).

From the data of the retrospective review disease activity rating scales were defined as : I, asymptomatic with normal laboratory tests ; II, asymptomatic with abnormal laboratory tests; III, mild symptoms which did not interfere with activities or new physical findings, laboratory tests usually abnormal; IV, moderate symptoms, occasionally interfering with usual activities; V, severe, requiring symptomatic or antidiarrhoel drugs; VI, incapacitating symptoms. Subjective parameters play a major role in this index.

O'Donoghue Index

This index (O'Donoghue et al., 1978), created for a withdrawal trial of azathioprine maintenance therapy, was based on the Willoughby index (Appendix 2.5). Some clinical parameters were altered : wound sepsis was omitted and recent weight loss and abdominal mass included in this index. One extra laboratory parameter, the white blood count, was added.

Lloyd-Still Index

Lloyd-Still & Green (1979) recognised that the CDAI ignored growth, which is an important indicator of illness in children. Furthermore children are rarely given antidiarrhoeal agents which appear as a parameter in the

CDAI. Therefore the CDAI in the paediatric population tended to result in a lower score than in the adult population, for whom it was devised. Lloyd-Still & Green altered a scoring system which had been used for the assessment of children with cystic fibrosis (Appendix 2.6).

Crohn's Disease Index

Harvey & Bradshaw (1980) eliminated all laboratory parameters and the requirement for a diary card from the the CDAI by producing a much simplified version of a one day scoring system (Appendix 2.7). This index correlated closely with the CDAI (Harvey & Bradshaw, 1980; Gomes et al., 1986) and also the O'Donoghue index (Elliot et al., 1980). Gomes at al. (1986) showed a significant correlation between the CDI and colonoscopic macroscopic score, but not with the histological score. The main criticism of the CDI is the high subjective input (87% of the index comprises 3 symptoms of stool frequency, abdominal pain and well being). Brooke (1980) criticised the CDI for its liquid stool score as post resection patients may have diarrhoea with no other evidence of active disease. Further studies, using the CDI, have reduced the weighting of the liquid stools.

Activty Index

Van Hees et al. (1980) were unhappy about the subjective factors with the CDAI, and devised a more objective clinical score (Appendix 2.8). This score was created using a similar technique of stepwise multiple regression analysis to determine the contribution of 18 variables on the overall assessment. Nine variables were shown to have a good correlation. Index values less than 100 are associated with inactive disease, 100-150 with slight activity and greater than 210 severe activity. However patients who had undergone resection of greater than one metre of small bowel or who had stomas were excluded.

The correlation of the AI with the CDAI was poor (r_S=0.67), mainly because the AI is made up entirely of objective variables of which the serum albumin contributes most to the AI. Poorer correlation has also been seen with other indices (deDombal et al., 1987). The AI is a complex clinical index and is difficult to calculate.

Present Index

Present et al. (1980) described a novel method of attempting to allow for the heterogeneity of the clinical manifestations of Crohn's disease. For each patient specific treatment goals were established. These goals

fell into three categories : reduction of steroid dosage; healing of fistulas ; and improvement in other clinical signs and symptoms. The degree of change in each goal item was scored +3 for excellent improvement to -3 for severe deterioration. This method, although much harder to arrange and more time-consuming, may be more appropriate.

New CDAI

Realising the limitations of the CDAI in relation to the heavy subjective weighting, Prantera et al. (1981) devised an activity index, the New CDAI (NCDAI), using a computerised regression analysis. Sixteen clinical and haematological parameters were compared with three aspects of Crohn's disease : clinical activity, radiological morphology and radiological extent. The NCDAI comprises three clinical and four haematological parameters (Appendix 2.9), and therefore is a more objective index. When validated with 90 subsequent patient visits the index proved to be highly correlated with the physicians' assessment. Prantera et al. (1982) later looked at the correlation of the CDAI and their index (NCDAI) in 57 outpatients with Crohn's disease, and found that the overall correlation was "moderate" ($r = 0.61$). However there was a large discrepancy between the two indices in a large number of patients who had undergone surgery.

Oxford Index

The International Organisation for the Study of Inflammatory Bowel Disease (IOIBD) concluded at their meeting in Oxford in November 1980 that the CDAI was too complex, and devised their own ten point index (Appendix 2.10) (Myren et al., 1984). The advantages of this index are the equal weighting of each variable which allows easy calculation, and the reduced number of subjective variables. There was good correlation with the OMGE index (r = 0.76) but poor correlation with the Activity Index (r = 0.33) (Myren et al., 1984).

OMGE Index

This index, devised by the Organisation Mondiale de Gastroenterologie (OMGE) Research Committee, is based on the CDI (Myren, 1984). This committee considered that the CDAI/CDI were dominated by bowel frequency and therefore their index has changed the scoring for stool frequency to a scale of 0-5, 0 being normal bowel habit, and 5 a bowel habit of 10 or more stools per day. Otherwise the OMGE index is identical to the CDI. This index has good correlation with the Oxford index (r = 0.75), but poor correlation with the Activity Index (AI), r = 0.33.

Factor Score

Cooke & Prior (1984) looked at the contribution of haemoglobin, seromucoids and serum albumin to the assessment of disease activity, using the statistical method of "factor scores". 49 patients with Crohn's disease were investigated during periods when they had been severely ill and when they had completely recovered. A complex equation was generated, which was simplified to : factor score = [1/2 haemoglobin g/dl] + [albumin g/l] - [seromucoids g/l x 4] - [constant 37]. Positive values are associated with health and negative values with illness.

Cape Town Index

This is a more complicated version of the Oxford index, allowing four degrees of severity for each of the 10 items, thus obtaining a score of between 0-30 (Wright et al., 1986). The index provided heavier weighting to complications other than diarrhoea (Appendix 2.11). There was good correlation with the CDAI (r = 0.76), CDI (r = 0.81) and poor with the Dutch AI (r = 0.37). The addition of the ESR to the Cape Town Index did not improve its overall correlation with the other indices.

Modified Activity Index (MAI)

Pettit et al. (1985) found that the Dutch AI was not entirely applicable to their study of the value of acute phase proteins in determining sepsis in Crohn's disease patients. 50% of their patients were excluded from the clinical score as they had either undergone small bowel resection, had stomas or took drugs to control diarrhoea.

A simple alteration to the Dutch AI was instituted to allow for their study patients. As a result, the stool consistency was changed to for patients without stomas : 1 = well formed ; 2 = soft or variable ; 3 = watery, and for patients with stomas 1 = semisolid solid effluent; 2 = watery effluent. The coefficient constant was changed from - 209 to - 261 to allow for different reference range for serum albumin. There was good correlation of the MAI score with the CRP ($r = 0.63$) and orosomucoid ($r = 0.59$).

Brignola Prognostic Index

Previous indices had not provided prognostic information. Brignola et al. (1986) measured multiple laboratory indices of disease activity in 41 patients who were in remission (CDAI < 150), and were followed up for 18 months. Discrimanent analysis was performed on the indices and a prognostic index created : - 3.5 + [ESR x 0.03] + [$alpha_1$- acid glycoprotein x 0.013] + [$alpha_2$- globulin

x 2].The discrimanent threshold for relapse was 0.35 and the index was highly accurate (88 %) for outcome at 18 months.

3-CDAI

An index created along similar lines to the CDAI (Reibnegger et al., 1986). Multiple regression analysis was applied to 9 clinical and laboratory parameters, including the urinary excretion of neopterin, an immune marker mediated by human monocyte/macrophages induced by gamma interferon, derived from activated T cells. The derived index, the 3-CDAI, is : 5 x (50 - haematocrit) + stool frequency + neopterin/10. There was good correlation with the CDAI (r = 0.84) on subsequent follow-up visits. The authors state that their index is an improvement on the CDAI as it contains no subjective variables and is easy to calculate. However the measurement of urinary neopterin is not routinely available and is the major handicap with this index.

Wright Simple Index

Thirty three Crohn's disease patients were followed up for at least nine months in an attempt to identify clinical and laboratory parameters which would predict an acute relapse (Wright et al., 1987). A simple index

(Appendix 2.12) was devised by the authors and compared with the CDAI, the AI and 10 laboratory parameters. Although the "simple index" correlated well with the CDAI ($r = 0.72$) and to a lesser degree with the AI ($r = 0.42$), the CDAI was the most sensitive of the three clinical indices as a predictor of an acute attack. The CDAI three months before an attack rose by an average of 203% compared with a rise of the simple index of only 36% and the AI of only 13%. Of the laboratory indices only the CRP, orosomucoids and $alpha_1$-antitrypsin rose within the three months before an acute attack, and were no better as predictors of an acute attack compared with the clinical indices.

Sandler Index

The present clinical indices for Crohn's disease are unsuitable for epidemiological studies as they rely on laboratory tests and/or results from physical examination. The authors (Sandler et al., 1988) devised an index based on the CDAI and on data collected from the Trial of Adjunctive Sulfasalazine in Crohn's Disease (Singleton et al., 1979), which could be used for large scale epidemiological surveys. Their index comprises : (3 x average number of liquid stools per week) + (10 x sum of abdominal pain ratings) + (3 x sum of daily well-being

ratings). The results, in disease activity quartiles, were compared with the CDAI and produced excellent correlation ($r = 0.87$).

Crohn's Activity Group Scale, CAGS

This complicated study (Pinchbeck et al., 1988) used discriminant function analysis to determine activity groups. 137 patients involved in a diet counselling study (Imes et al., 1988) were followed up for 12 months and the CDAI measured during visits. 31 laboratory tests were used as predictive variables. Patients were classified as having active or inactive disease on the basis of the CDAI results. A rather complicated equation was devised to calculate the activity group scales (Appendix 2.13).

Patients were followed longitudinally to determine the change in the group activity scales. Once a patient's CAGS suggested inactive disease there appeared to be a 82.1% chance that the patient would remain well over the next year. The authors claim that the main advantages of this method include objectivity and its predictive value. It may be of benefit in future drug trials by allowing pre-randomisation of patients with low or high probability of future recurrences. The calculation is quite formidable.

RADIOLOGICAL, ENDOSCOPIC, HISTOLOGICAL AND LABORATORY INDICES OF DISEASE ACTIVITY

Radiology

Radiological examination of the gastrointestinal tract was one of the main methods of assessing disease activity in the early studies of Crohn's patients (Crohn et al., 1932). There is now evidence of an erratic and unpredictable correlation between radiological and clinical features (Goldberg et al., 1979). This method also introduces radiation risk to the patient and is therefore unsuitable for repeated assessments. There is also poor inter-observer agreement. Radiological examination of the GI tract is now considered to be a cumbersome and ineffective method of assessing disease activity.

Colonoscopy

Unlike ulcerative colitis where the rectal mucosa is readily available for easy sigmoidoscopic access, areas affected by Crohn's disease are usually inaccessible to routine endoscopic techniques. Colonoscopy is safe in the majority of patients with Crohn's colitis and has been used to assess disease activity (Gomes et al., 1986; Saverymuttu et al., 1986). Modigliani & May (1987) have shown that there is good reproducibility of colonoscopic

findings in Crohn's disease and could be used in controlled trials.

Histology

Subtle histological abnormalities can arise in GI tract tissue taken from sites distant from macroscopic Crohn's disease : usually sophisticated histological techniques are required (Goodman et al., 1976; Dunne et al., 1977). The National Cooperative Crohn's Disease Study looked at the clinical usefulness of rectal biopsies in Crohn's disease (Hill et al., 1979). Biopsies from only 15% of the total patient group had histological changes characteristic of Crohn's disease and all but one of these were known to have colonic involvement. There was no correlation found between the rectal biopsy histological grade for disease activity and the CDAI (Hill et al., 1979). Gomes et al. (1986) also found no correlation between colonoscopic biopsy grading for activity and several laboratory indices including CRP, ESR, platelet count and WBC.

LABORATORY INDICES

Haemoglobin

The haemoglobin (or haematocrit) has been shown to be useful in detecting disease activity (Kaufman et al., 1979) and appears in many clinical scores - CDAI (Best et al., 1976), Lloyd-Still Index (1979), Oxford index (Myren

et al., 1984), Cooke & Prior (1984), and the Cape Town Index (Wright et al., 1985). The haemoglobin accounts for 14% of the total CDAI score (Best et al., 1976). Nutritional status, blood loss, iron and vitamin supplements all affect the haemoglobin without necessarily reflecting the disease activity, which limits its usefulness in the assessment of disease activity (Van Hees et al., 1980).

Platelet Count

Thrombocytosis is often seen in Crohn's disease and may represent a non-specific response to inflammation. There is good correlation between the platelet count and other indices of disease activity (Talstad & GJone., 1973; Harries et al., 1983C). Talstad & GJone (1973) found that thrombocytosis was more common in patients with large bowel disease than with small bowel disease.

Serum Albumin

Hypoalbuminaemia commonly occurs in Crohn's disease (Weeke et al., 1971; Beeken et al., 1972), and can arise from various factors : nutritional deficiency, malabsorption, gastrointestinal protein loss, and increased catabolism. There is evidence to suggest that albumin synthesis is increased but unable to compensate

for excess enteric protein loss (Steinfeld et al., 1960). Surprisingly there is poor correlation between the serum albumin and gastrointestinal protein loss (Beeken et al., 1972; Kaufman et al., 1979; Sategna-Guidetti et al., 1982; Karbach et al., 1985), although this was not found in the study by van Tongeren et al. (1976). Several authors strongly advocate the use of serum albumin as a laboratory index for activity (Van Hees et al., 1980; Cooke & Prior, 1984) although most clinical scores do not include it (Best et al., 1976; Andre et al., 1981; Brignola et al., 1986).

Erythrocyte Sedimentation Rate (ESR)

Several studies have shown a good correlation between elevated ESR and disease activity (Talstad et al., 1973; Talstad & Gjone, 1976; Whittington et al., 1977; Mee et al., 1979; van Hees et al., 1980), and van Hees et al (1980) also included it in their index (Appendix 2.8).

However other studies have not confirmed the usefulness of the ESR (Werlin & Grand, 1977; Fagan et al., 1982; Cooke & Prior, 1984; Wright et al., 1986). Even Talstad & Gjone (1976), who had advocated the use of ESR as a useful parameter, found that it was normal in 10% of patients with severe disease. Whittington et al. (1976) found it to

be useful as a predictor of relapse in their paediatric patients. Harvey & Bradshaw (1980) in a reassessment of their clinical index advised that patients who have had previous bowel resections and who have high clinical scores with a normal ESR should not be regarded as having active disease. Brignola et al. (1986) found a highly significant difference in the elevation of ESR in patients who subsequently relapsed.

C-Reactive Protein

C-reactive protein (CRP), one of the acute phase reactants, has been shown to be useful in the management of many aspects of Crohn's disease. Firstly, a random measurement may help to distinguish between inflammatory bowel disease and functional bowel disease (Shine et al., 1985). Secondly, CRP has been shown to correlate closely with disease activity (Mee et al., 1978; Campbell et al., 1979; Prantera et al., 1981; Fagan et al., 1982; Andre et al., 1985; Saverymuttu et al., 1986). Thirdly, an elevated CRP in combination with normal clinical disease activity scores can help in predicting relapses (Campbell et al., 1979; Andre et al., 1983; Boirvant et al., 1988), although Brignola et al. (1986B) found it less sensitive than the ESR or $alpha_1$-acid glycoprotein. Lastly, Pettit et al. (1985) have shown that a CRP level > 33 mg/l may indicate

intra-abdominal sepsis.

There is not a close correlation of CRP with the other laboratory indices (Prantera et al., 1984), nor was there any correlation with the extent of the disease.

Orosomucoid (Alpha$_1$-Acid Glycoprotein)

On fractionation of the seromucoids, more than 90% is the glycoprotein orosomucoid (alpha$_1$-acid glycoprotein), which has been shown to closely relate to disease activity (Andre et al., 1981; Cooke & Prior, 1984; Gomes et al., 1986; Brignola et al., 1986). In fact Andre et al. (1981) found that alpha$_1$-acid glycoprotein compared with the other serum proteins and ESR correlated best with a clinical score. Cooke & Prior (1984) and Brignola et al (1986) incorporated alpha$_1$ acid glycoprotein into their laboratory indices.

Other Acute Phase Proteins

Weeke et al. (1971) found that any other acute phase proteins, including alpha$_1$-acid glycoprotein, alpha$_1$-antichymotrypsin, haemopexin and haptoglobin were elevated in active disease. Other studies have confirmed that alpha$_1$-antitrypsin can be elevated in active Crohn's disease and the alpha$_1$-antitrypsin clearance can be used

as a marker (see later in this chapter). Summers et al. (1979) found that a pronounced elevation of serum haptoglobin was often associated with fistulas and sepsis.

Protein Losing Enteropathy

Early investigators of the methodology of intestinal protein loss used a variety of different radiolabelled proteins : ^{131}Iodine-albumin (Steinfeld et al., 1960); ^{131}Iodine-polyvinylpyrrolidone (PVP) (Dawson et al., 1961); and radio-iodinated human serum albumin (Jeejeebhoy & Coghill, 1961). All these studies found elevated gastrointestinal protein loss in patients with active Crohn's disease. Albumin synthesis was increased but unable to compensate for excessive protein loss (Steinfeld et al., 1960).

Although plasma proteins labelled with radioiodine are suitable for studying plasma protein kinetics, they are not ideal for studying enteric protein loss as the free radioiodine can be concentrated in the salivary glands and then secreted, and can also be reabsorbed in the intestine.These problems can be overcome by using ^{51}Chromium which is not secreted nor absorbed by the intestine. Using $^{51}CrCl_3$ Beeken et al. (1972) found a close correlation between intestinal protein loss and the extent and severity of Crohn's disease.

Crossley & Elliott (1979) first used alpha$_1$-antitrypsin as a method of detecting intestinal protein loss . Alpha$_1$-antitrypsin is a protease inhibitor synthesised in the liver and is not degraded by pancreatic enzymes.Random faecal alpha$_1$-antitrypsin measurement was used at first (Crossley & Elliott, 1977) and subsequently a clearance method was introduced (Berbier et al., (1978). There is good correlation between alpha$_1$-antitrypsin clearance and $CrCl_3$ clearance (Florent et al., 1981; Sategna-Guidetti et al., 1982; Karbach et al., 1983). Most studies have not found a close correlation between alpha$_1$-antitrypsin and disease activity scores (Sategna-Guidetti et al., 1982; Karbach et al., 1983; Karbach et al., 1985). The clearance method requires a stool collection over several days, which is a disadvantage. Random faecal alpha$_1$- antitrypsin concentration has been shown to correlate with disease activity (Thomas et al., 1981; Meyers et al., 1985).

Indium Scanning

In Crohn's disease there is mucosal leucocyte infiltration and also faecal excretion of leucocytes. Autologous leucocytes can be labelled with ^{111}Indium and when re-injected will accumulate within any part of inflammed bowel (Saverymuttu et al., 1983). (See Chapter 5 of this thesis).

Ethylenediaminetetraacetate

Twenty-four hour urinary excretion after oral ingestion of ^{51}Chromium-labelled ethylenendiaminetetraacetate (EDTA) can be used to assess small bowel permeability and hence small bowel involvement in patients with Crohn's disease (Bjarnson et al., 1983; O'Morain et al., 1986). Results have shown a higher excretion of ^{51}CrEDTA in patients with active small bowel disease. As yet the main use for this test lies in screening for Crohn's disease.

Other Laboratory Parameters

Many other laboratory parameters have been used in an attempt to define an easy method of assessing disease activity : serum amyloid A (Chambers et al., 1987);beta$_2$-microglobulin (Descos et al., 1982); serum lysozyme (Peeters et al., 1976); plasma fibrinopeptide A (Edwards et al., 1987); post-heparin plasma diamine oxidase (D'Agnostica et al., 1988); plasma human leucocyte elastase (Adeyemi et al., 1985); leucocyte function (Waddell et al., 1982); circulating immune complexes (Fiasse et al., 1978); urinary neopterin (Prior et al., 1986); activated T lymphocytes (Raedler et al., 1985).

Correlation of Indices

The correlation of many of the clinically based indices, involving mainly subjective items, is on the whole good (Hodgson, 1982). This is not entirely surprising as most of them have evolved from the CDAI and are measuring similar variables. Correspondingly the correlation between the subjective clinical indices and the more objective, laboratory based indices, such as the AI, is weaker. However the Italian New CDAI, based on several laboratory items, had a reasonably good correlation with the CDAI (Prantera et al, 1981).

Several laboratory indices correlate well with the clinical indices - in particular the CRP, ESR and alpha$_1$-acid glycoprotein (Andre et al., 1985). Gomes et al. (1986) found poor correlation between the colonoscopic and histological findings and other disease activity indices. Intestinal protein loss (Karbach et al., 1983) and indium scanning and excretion (Saverymuttu et al., 1983) show good correlation with clinical scores and other laboratory indices.

Two studies have looked at the relationship between the length of the lesion in Crohn's disease and the clinical and laboratory indices (Prantera et al., 1984; Karbach et al., 1985). Surprisingly both have found poor correlation.

Quiescent disease could still show impressive radiological changes and normal macroscopic appearances do not exclude histological involvement.

Prognostic Indices

The prognostic function of the clinical and laboratory scores has not been fully investigated. Brignola et al. (1986) considered that patients in clinical remission who had abnormal laboratory tests might have a greater risk of relapse. They used discriminant analysis to derive their prognostic index (see earlier in this chapter). The accuracy of this index was 88% after 18 months follow up. Pinchbeck et al. (1988) used a different statistical method to determine their Crohn's Activity Group Scale (CAGS). Once the patient's CAGS suggests inactive disease there is a 82.1% chance that the patient will remain well for the next 12 months. Possibly the prognostic indices will become more relevant in future if patients are categorised into prognostic groups.

Deficiencies In Indices of Disease Activity

Ideally measuring disease activity in Crohn's disease should involve patients with similar disease sites, identical surgical complications, in normal nutritional

state and with active mucosal inflammation (Hodgson, 1981). The protean nature of Crohn's disease does not allow for an ideal index of disease activity. Moreover, even using the same clinical data for the same indices, there is considerable inter-observer variation (De Dombal., 1987).

SECTION II

AIMS AND LAYOUT OF THESIS

AIMS AND LAYOUT OF THESIS

The principle aims of this thesis were to investigate the relationship between nutritional deficiencies and disease activity in patients with Crohn's disease, and to determine if artificial nutritional support, in particular enteral nutrition, could alter disease activity.

Reviews of nutritional problems and methods of nutritional support (Chapter 1) and assessment of disease activity in Crohn's disease (Chapter 2) provided the background for the thesis, supplemented by introductions to each study chapter. Methods, results and discussion sections formulated the rest of the study chapters. Additional information was provided in the appendices.

As there are many methods of assessing activity of Crohn's disease, the initial part of the thesis attempted to determine the most appropriate tests. Two studies looked into this problem : a longitudinal study of clinical scores and acute phase proteins in both inpatient and outpatient groups (Chapter 3); and a study using Indium scanning (Chapter 5). An important aspect of the longitudinal study was to assess the best index for patients with stomas, whom I had anticipated would appear in subsequent clinical studies.

In Chapter 4, malnourished patients were investigated to see if they had an impaired acute phase response which could produce false assessment of disease activity. The immuno-modulating effect of blood transfusion on disease activity was studied in Chapter 6.

The aims of the animal study (Chapter 7) were to compare the nutritional efficacy of new modular enteral liquid diets, which were to be used in the five later studies involving enteral nutritional support.

A major part of the thesis was concerned with the application of enteral nutrition in Crohn's disease : to determine if elemental or polymeric diets are appropriate primary therapy for active Crohn's disease (Chapter 8); to assess the role of home enteral nutrition in providing long-term nutritional support and to document associated problems; to identify micronutrient deficiencies in patients on home enteral nutrition (Chapters 10, 11); and to assess home enteral nutrition as a method of correcting growth retardation in adolescents with Crohn's disease (Chapter 12).

SECTION III

STUDIES ON SPECIAL PROBLEMS OF CROHN'S DISEASE WITH RESPECT TO DISEASE ACTIVITY AND NUTRITION

CHAPTER 3

THE ROLE OF ACUTE PHASE REACTANTS AND CLINICAL INDICES IN THE ASSESSMENT OF DISEASE ACTIVITY IN PATIENTS WITH ACUTE AND STABLE CROHN'S DISEASE

INTRODUCTION

Methods of assessing Crohn's disease activity vary from simple clinical indices to complex indices involving sophisticated laboratory tests, as discussed fully in Chapter 2 of this thesis. The majority of studies have not performed longitudinal follow-up of these methods nor have included patients with intestinal resections resulting in stomas. In fact, Van Hees's index (1980) specifically excludes such patients.

There is also some doubt as to whether all the clinical indices behave similarly in different clinical situations. Brignola et al. (1986) showed that the CDAI appeared to have a better predictive value for relapse than the AI or the new CDAI.

AIMS OF STUDY

The aims of this study were to determine if a simple clinical index correlated with more complex indices and with other laboratory tests; to check if the indices of disease activity had similar correlations in patients

with stable Crohn's disease or with active disease ;and to investigate if a modified clinical index gave accurate assessment of disease activity in patients with stomas.

PATIENTS AND METHODS

Patients

Four groups of patients were investigated : patients admitted with acute relapses (Group I); patients with stomas admitted with acute relapses (Group II); stable patients followed up as outpatients (Group III); and stable stoma patients followed up as outpatients (Group IV). The clinical and demographic details of the patients are shown in Table 3.1 . Eighteen patients appeared in both the acute and stable groups.

Study Design

All the clinical indices used in this study, except the modified Crohn's disease index (MOD CDI), have been discussed in Chapter 2 of this thesis and appear in full in the appendices. The MOD CDI was based on the CDI (Harvey & Bradshaw, 1980) with an alteration to the weighting for stool frequency which allowed it to be used for patients with stomas (Appendix 2.7). The stool frequency score was changed to 0 = normal stools, 1 = < 3 liquid stools per day and 2 = > 3 liquid stools per day for patients without stomas. For patients with stomas the score was 0 = normal stomal output, 1 = slightly increased stomal output and 2 = very loose and increased output. The MOD CDI is similar to the altered CDI suggested by the

	Group I	*Group II*	*Group III*	*Group IV*
Number in each group	24	3	62	12
Gender (M/F)	9/15	1/2	25/37	2/10
Age (years)	34(15-62)	46(28-58)	40(15-68)	44(26-75)
Disease location				
small bowel	6	2	22	11
large bowel	6	-	22	-
small and large bowel	12	1	18	1
Duration of follow up (months)	-	-	15(0-24)	17(0-27)
Total observations	24	3	300	70
Number of visits per patient	-	-	4(1-14)	6(1-12)

(Key : Age in mean(range) years; duration of follow up in median (range) years; number of visits in median (range) years)

TABLE 3.1

Patient Clinical and Demographic Details

OMGE committee (Myren et al., 1984), although this has not been validated in a large group of patients.

On admission all patients in Group I had 10 clinical indices measured including the Crohn's disease index (CDI) (Appendix 2.7), the modified CDI, Sandler's index, Crohn's Disease Activity Index (CDAI) (Appendix 2.4), O'Donoghue index (Appendix 2.5), Talstad's index (Appendix 2.3, with the exception of the result of the barium enema), Cape Town index (Appendix 2.11), Oxford index (Appendix 2.10), van Hees's index (Appendix 2.8), and the modified AI. Seven laboratory tests were performed including the haemoglobin, ESR (Westergreen method), C-reactive protein (nephelometry), $alpha_1$-acid glycoprotein (radial immunodiffusion), protein losing enteropaphy (by $CrCl_3$ method , van Tongeren & Reichert, 1963), serum albumin and platelet count. Group II patients had only 2 clinical indices measured, the modified CDI, and the modified AI and the same laboratory tests as with the Group I patients.

Group III patients had serial measurements of 9 clinical indices, the CDI (Appendix 2.7), the modified CDI, Sandler's index, the CDAI (Appendix 2.4), O'Donoghue's index (Appendix 2.5), Cape Town index (Appendix 2.11), Oxford index (Appendix 2.10), the AI (Appendix 2.8), and

the modified AI. Talstad's index was not measured as several items were not suitable for serial measurements. Six laboratory tests were performed (haemoglobin, platelet count, ESR, CRP, alpha$_1$-acid glycoprotein, and serum albumin). On review of all the results, patients were classified as having either active or inactive disease.

The Group IV patients had serial measurements of two clinical scores (the MOD CDI, and the MOD AI), the six laboratory tests performed on Group III patients, and a global assessment of active/inactive disease.

The correlation between all the clinical indices and laboratory tests were calculated for each group using the Spearman rank correlation coefficient test. Results were considered to be significant if the p value was < 0.05.

RESULTS

Group I

There was good correlation between all the clinical indices except for both the Cape Town and Oxford indices with the AI and the MOD AI (Table 3.2). Interestingly, the AI and the MOD AI, two indices considered to be more objective as they have a large laboratory weighting, did not correlate with the laboratory indices any better than the more subjective indices. Most of the clinical scores correlated best with the CRP.

The CDAI, AI and MOD AI had significant correlations with the protein losing enteropathy test, and the AI and MOD AI also had good correlation with the serum albumin. This is not unexpected as the serum albumin contributes a large part to both indices.

There was generally poor correlation between the laboratory indices. In fact the only significant correlations were between the CRP and $alpha_1$-acid glycoprotein ($r = 0.56$), PLE and albumin ($r = -0.45$) and albumin and haemoglobin ($r = 0.45$). The MOD CDI correlated well with all the clinical indices and also with the CRP ($r = 0.42$).

	CDI	MODCDI	SAND	CDAI	O'DON	TAL	CAPE	OXF	AI	MODAI	ESR	CRP	ALPHA	PLE	ALB	PLAT	Hb
CDI	1	0.89	0.83	0.73	0.83	0.79	0.73	0.63	0.45	0.47	0.01	0.42	-0.01	0.13	-0.36	0.03	-0.27
MODCDI		1	0.85	0.83	0.90	0.72	0.73	0.63	0.51	0.46	0.04	0.39	0.13	0.31	-0.38	0.19	-0.34
SAND			1	0.85	0.86	0.84	0.78	0.60	0.59	0.51	-0.14	0.30	0.02	0.22	-0.44	0.22	-0.41
CDAI				1	0.90	0.81	0.76	0.56	0.53	0.53	-0.06	0.46	0.15	0.44	-0.37	0.26	-0.29
O'DON					1	0.86	0.82	0.63	0.52	0.46	-0.08	0.49	0.20	0.22	-0.36	0.28	-0.35
TAL						1	0.75	0.53	0.59	0.54	-0.05	0.44	0.15	0.09	-0.41	0.22	-0.36
CAPE							1	0.85	0.36	0.19	0.05	0.34	0.01	0.07	-0.06	0.26	-0.23
OXF								1	0.34	0.11	-0.04	0.21	-0.03	0.11	-0.02	0.10	-0.05
AI									1	0.76	-0.35	0.22	0.17	0.46	-0.79	0.37	-0.30
MODAI										1	-0.15	0.25	0.09	0.49	-0.89	0.29	-0.51
ESR											1	0.25	0.13	-0.17	0.28	-0.20	-0.22
CRP												1	0.56	0.31	-0.13	0.29	-0.34
ALPHA													1	0.13	-0.08	0.17	-0.14
PLE														1	-0.45	0.19	-0.12
ALB															1	-0.13	0.45
PLAT																1	-0.12
Hb																	1

[KEY: CDI = Crohn's disease Index, MOD CDI = Modified Crohn's disease Index, SAND = Sandler's Index, CDAI = Crohn's disease Activity Index, O'DON = O'Donoghue's Index, TAL = Talstad's Index, CAPE = Cape Town Index, OXF = Oxford Index, AI = Activity Index, MODAI = Modified Activity Index, ESR = Erythrocyte Sedimentation Rate, CRP = C-reactive Protein, ALPHA = Alpha 1 acid glycoprotein, PLE = Protein losing enteropathy, ALB = Albumin, PLATS = Platelets, Hb = Haemoglobin - All significant values underlined].

Table 3.2 - Correlation Matrix of Indices for Group I

Group II

Unfortunately due to small numbers in this group the significance of these results was difficult to interpret (Table 3.3). However there were a few isolated significant correlations, including the MOD CDI and CRP, and also the MOD AI and ESR. The clinical indices did not appear to correlate closely with one another.

Group III

The majority of correlations showed significant values, with the clinical scores having the closest correlations (Table 3.4). The MOD CDI showed significant correlation with all the other indices except alpha$_1$-acid glycoprotein and haemoglobin. The Oxford index performed least well. Although there were many significant correlations between the laboratory indices, most were not particularly good.

Group IV

Although the MOD AI appeared to show more significant correlation between the laboratory parameters, the MOD CDI was the only index which correlated with the overall global assessment of the patients (Table 3.5). There was not a significant correlation between the two clinical indices.

	MODCDI	MODAI	ESR	CRP	ALPHA 1	PLE	ALBUMIN	PLATS	Hb
MODCDI	1	0.5	0.5	0.96	-0.5	0.5	-0.87	-0.5	0.01
MODAI		1	0.96	0.5	0.5	-0.5	-0.87	0.5	0.87
ESR			1	0.5	0.5	-0.5	0.87	0.5	0.87
CRP				1	-0.5	0.5	-0.87	-0.5	0.01
ALPHA 1					1	0.96	0.01	0.96	0.87
PLE						1	0.96	0.01	0.87
ALBUMIN							1	0.01	-0.5
PLATS								1	0.87
Hb									1

[KEY: See Table 3.2].

Table 3.3 - Correlation Matrix of Indices for Group II

	CDI	MODCDI	SAND	CDAI	O'DON	CAPE	OXF	AI	MODAI	ESR	CRP	ALPHA	ALB	PLAT	Hb	REL
CDI	1	0.92	0.88	0.82	0.73	0.82	0.67	0.39	0.33	0.18	0.24	0.11	-0.19	0.20	-0.03	0.50
MODCDI		1	0.87	0.79	0.78	0.85	0.73	0.34	0.30	0.18	0.21	0.09	0.17	0.16	-0.07	0.51
SAND			1	0.88	0.77	0.81	0.66	0.42	0.38	0.27	0.19	0.24	-0.26	0.19	-0.16	0.53
CDAI				1	0.81	0.84	0.64	0.58	0.55	0.41	0.27	0.33	-0.41	0.18	-0.37	0.56
O'DOW					1	0.88	0.67	0.59	0.57	0.55	0.30	0.38	-0.47	0.19	-0.45	0.56
CAPE						1	0.81	0.49	0.46	0.39	0.21	0.23	-0.35	0.13	-0.34	0.54
OXF							1	0.32	0.70	0.19	0.10	0.09	-0.21	0.07	-0.14	0.43
AI								1	0.95	0.59	0.46	0.58	-0.86	0.16	-0.49	0.47
MODAI									1	0.60	0.46	0.63	-0.88	0.13	0.52	0.44
ESR										1	0.46	0.61	-0.55	0.15	-0.69	0.44
CRP											1	0.43	-0.35	0.14	-0.25	0.28
ALPHA												1	-0.56	0.16	-0.51	0.31
ALB													1	-0.13	0.55	0.35
PLAT														1	-0.05	0.12
Hb															1	-0.28
REL																1

[KEY: See Table 3.2. REL = Relapse/Remission].

Table 3.4 - Correlation Matrix of Indices for Group III

	MODCDI	MODAI	ESR	CRP	ALPHA	ALB	PLAT	Hb	REL
MODCDI	1	0.03	0.14	0.17	0.16	0.04	-0.16	-0.16	0.65
MODAI		1	0.35	0.35	0.61	-0.95	0.04	-0.16	0.15
ESR			1	0.24	0.45	-0.17	0.09	-0.68	0.14
CRP				1	0.43	-0.31	-0.18	-0.25	0.09
ALPHA					1	-0.54	0.05	-0.34	0.18
ALB						1	-0.09	0.05	-0.11
PLAT							1	-0.18	-0.22
Hb								1	-0.02
REL									1

[Key - see table 3.2]

Table 3.5 - Correlation Matrix of Indices for Group IV

DISCUSSION

In both the acute and stable groups, all the clinical indices which had a common source (CDAI, Sandler, CDI, MOD CDI, Cape Town), correlated extremely well. As expected there were weaker correlations between these clinical indices and the indices which included more laboratory results (Oxford, AI, MOD AI). In particular there was very poor correlation between the Cape Town/Oxford indices with the AI/MOD AI indices. These results are similar to earlier studies (Myren et al., 1984; Wright et al., 1985). Correlation was not good between the two clinical indices designed for stoma patients. Both are based on different indices, the MOD CDI on the CDAI/CDI and the MOD AI on the AI which has a large laboratory bias.

There appeared to be different patterns of correlation between the clinical indices and the laboratory indices in the acute and stable clinical situations. In acute patients most of the laboratory indices had poor correlation with the clinical indices with the exception of CRP and to a lesser extent with PLE and serum albumin. In the stable group most of the laboratory indices correlated well with the clinical indices, and also the global assessment. Most of the previous studies which have looked at the correlation of multiple clinical and

laboratory indices have been performed on stable outpatients. The CRP appears the most reliable laboratory parameter for both clinical conditions.

There was poor correlation between the MOD AI and the MOD CDI in the stoma patient groups despite good correlation between these indices in Groups I and II. The MOD CDI correlated better than the MOD AI in the overall assessment of patients in Group IV, although it had poorer correlation with the laboratory indices.

SUMMARY

Multiple clinical and laboratory indices were assessed in patients with acute and stable Crohn's disease. In the acute clinical situations there was poor correlation between the clincal indices and the laboratory indices, with the exception of the CRP level. The MOD CDI correlated well with the other indices and appeared to be suitable for use in most assessments.

CHAPTER 4

ACUTE PHASE RESPONSE IN MALNOURISHED PATIENTS WITH CROHN'S DISEASE

INTRODUCTION

Acute phase proteins have been used in the assessment of disease activity of patients with Crohn's disease (Andre et al., 1981; Fagan et al., 1982). Alpha$_1$-acid glycoprotein (orosomucoid) and C-reactive protein are the most frequently used acute phase proteins (Andre et al., 1981; Brignola et al., 1986). In addition to assessing disease activity, the acute phase proteins can help in predicting relapse (Brignola et al., 1986; Boirvant et al., 1988) and in determining the presence of intra-abdominal abscesses (Pettit et al., 1985).

However there is some evidence to suggest that the acute phase response may be altered in malnutrition. Miller & John (1970), using isolated perfused rat livers, found impaired synthesis of alpha$_1$-acid glycoprotein, fibrinogen and haptoglobin in six day fasted rats, with only a small increase in synthesis on refeeding, compared with fed controls. In another study rats fed a protein free diet showed an impaired response of alpha$_2$ and beta glycoproteins when subjected to trauma (Neuhaus et al., 1963). Malnourished patients with gastric cancer who underwent surgery had reduced acute phase response for

alpha$_1$-antitrypsin and alpha$_1$-acid glycoprotein and slightly enhanced C-reactive protein and fibrinogen, compared with well-nourished gastric cancer patients (Domimioni et al., 1983).

The influence of malnutrition on the acute phase response in patients with Crohn's disease has not been studied despite the increasing use of acute phase proteins in the assessment of disease activity and the recognition of the high prevalence of malnutrition in patients with Crohn's disease (Harries & Heatley, 1983B).

AIM OF STUDY

The aim of this study was to compare the acute phase response of well-nourished patients with Crohn's disease with malnourished patients.

PATIENTS AND METHODS

Patients

Twenty-one consecutive patients requiring inpatient treatment for active Crohn's disease were included. Patients were considered to be malnourished if their body weight was less than 80% of their ideal body weight (IBW), as defined by standard tables (Chicago Society of Actuaries, 1959). Ten patients were considered to be malnourished (Group 1) and 11 patients were well nourished (Group 2).

The clinical details of the patients are shown in Table 4.1. The mean age and range (years) of patients in group 1 was 32 (15-54) and for Group 2, 38 (21-61). Disease location was assessed using standard radiology and colonoscopy either during a recent admission or during the study admission. There were slightly more patients with colonic disease in Group 2. More patients in Group 1 (70%) had previous resections than in Group 2 (27%).

Nutritional Assessment

Full anthropometric and biochemical assessment of each patient's nutritional status was performed as soon as possible after each admission and in every case within 2-3 days. Anthropometric measurements were taken to calculate percentage ideal body weight (%IBW), triceps skinfold thickness (TST % standard), and mid - arm muscle

Patients	Sex	Age	Disease Location	Previous resections	Drugs
1	M	54	SB	Colectomy	Vit D
2	M	15	SB + LB	-	-
3	M	36	SB + LB	R.Hemi + SB	-
4	F	24	SB + LB	R.Hemi	Mg
5	F	28	SB	Colectomy	-
6	F	28	SB	R.Hemi	-
7	M	15	LB	-	SSZ
8	F	33	TI	-	-
9	M	28	SB + LB	R.Hemi	SSZ
10	M	41	SB + LB	R.Hemi + SB	Mg,Vit D
Group 2					
11	F	32	SB + LB	R.Hemi	-
12	M	25	LB	-	-
13	M	61	SB + LB	-	-
14	F	33	LB	-	-
15	F	40	SB	-	SSZ
16	F	21	SB + LB	-	-
17	F	60	LB	R.Hemi	-
18	M	34	SB	R.Hemi	-
19	F	58	SB + LB	R.Hemi + Sigmoid Colectomy	Mg
20	F	51	LB		-
21	F	31	SB + LB		-

Key: SB = Small Bowel; LB = Large Bowel; TI = Terminal Ileum, R.Hemi = Right Hemicolectomy; Vit D = Vitamin D; Mg = Magnesium Supplements; SSZ = Sulphasalazine

Table 4.1 - Patients' Clinical Details

circumference (MAMC % standard) (Shenkin & Steele, 1978). Percentage weight loss was also calculated for eight patients who had previously documented weights. Blood samples were taken for analysis of albumin, transferrin, calcium, phosphate, magnesium, zinc, copper, iron, vitamins A, E, B_1, B_2, B_6, B_{12}, red cell folate and 24 hour urine collections for urinary magnesium and zinc excretion. Laboratory methods are described in Appendix 4.1.

Disease Activity

A modified clinical scoring system (the Modified Crohn's Disease Index MOD CDI) was used (see Chapter 3). The modified index allowed the same clinical score to be used for patients with and without stomas. The erythrocyte sedimentation rate (ESR) was measured by the Westergreen method, C-reactive protein (CRP) by nephelometry (Hyland laser Nephelometer) and alpha$_1$-acid glycoprotein by radial immunodiffusion. Gastro-intestinal protein loss was investigated by the $CrCl_3$ method (Van Tongeren & Reichert, 1966).In addition to the CRP and alpha$_1$-acid glycoprotein measurements on admission, eight patients in each group had previously documented outpatient weights and the rise in the acute phase reactants was calculated.

Statistical Analyses

Most of the indices for disease activity were not normally distributed and the Wilcoxon rank sum test was used to compare the disease activity between the two groups. Comparison of the nutritional assessment between the two patient groups was also performed by the Wilcoxon rank sum test. All results with $p < 0.05$ were considered to be significant.

RESULTS

Nutritional assessment

Full nutritional assessment was made on all the patients and the results appear in Table 4.2 The percentage IBW (mean, sem) for Group 1 was 72 (1)% and Group 2, 95 (3)%. The only significant difference in the nutritional status between the two groups was for the triceps skinfold thickness (percentage standard) : Group 1 v Group 2, 62 (5)% v 87 (6)%. Eight patients in each group also had previously documented outpatient weights and the percentage weight loss calculated : Group 1 patients 14.8 (1)% and Group 2, 6.8 (0.8)% ($p<0.01$).

Disease Activity

The results for the indices of disease activity MOD CDI, ESR, CRP and alpha$_1$-acid glycoprotein, and gastrointestinal protein loss are shown in Table 4.3. There are no significant differences between the two patient groups. Eight patients in each group had previous outpatient measurements of the acute phase reactants during quiescent periods of their disease. The rise in the acute phase reactants was similar in both groups and not statistically different.

Measurement	*Group 1*	*Group 2*
Weight (%IBW)	72 (1)	95 (3)
Percentage weight loss *	14.8 (1.0)	6.8 (0.8)
TST (%standard) +	62 (5)	80 (7)
MAMC (%standard)	75 (4)	87 (6)
Haemoglobin (11.5-15.5 g/dl)	10.6 (0.3)	10.5 (0.4)
Albumin (35-50 g/l)	26 (2)	29 (2)
Transferrin (2-4 g/l)	1.9 (0.2)	1.9 (0.2)
Calcium (2.2-2.6 mmol/l)	2.32 (0.18	2.33 (0.15)
Phosphate (0.7-1.4 mmol/l)	1.03 (0.11)	1.13 (0.08)
Serum magnesium (0.7-1.0 mmol/l)	0.72 (0.03)	0.79 (0.02)
Urinary magnesium (2-11 umol/l)	1.4 (0.4)	2.1 (0.3)
Serum zinc (12-18 umol/l)	10.0 (0.7)	10.7 (0.7)
Urinary zinc (4.6-10.6 umol/l)	6.8 (1.5)	11.5 (2.6)
Copper (15-25 umol/l)	19 (1.9)	21 (1.7)
Iron (10-30 umol/l)	3.9 (0.9)	5.4 (0.6)
Vit A (1-2.8 umol/l)	1.1 (0.3)	1.3 (0.1)
" E (14-39 umol/l)	21 (4)	24 (3)
" C (11-114 umol/l)	28 (5)	32 (5)
" B1 (<25% activation)	14 (3)	17 (4)
" B2 (<60% activation)	27 (6)	35 (10)
" B6 (<150% activation)	48 (7)	65 (10)
" B12 (150-730 pg/ml)	669 (269)	759 (195)
Red cell folate (106-614 pg/ml)	272 (66)	295 (68)

[Key : IBW = Ideal body weight; TST = Triceps skinfold thickness; MAMC = mid arm muscle circumference. All values expressed as mean (sem). Normal range in parenthesis.
* $p<0.001$ + $p<0.05$]

TABLE 4.2

Nutritional Assessment

Activity parameter	*Group 1*	*Group2*
MOD CDI (0)	5, 3-9	6, 3-10
ESR (<15 mm/h)	49, 22-80	53, 25-102
CRP (<10mg/l)	42, 15-180	40, 11-97
Alpha1-acid glycoprotein (50-120 mgldl)	288, 156-406	271, 155-416
GI protein loss (<25ml/day)	76, 27-150	61, 11-295
Δ CRP (mg/l)	18, 5-80	28, 5-60

[Key : results expressed as median, range. All results not significant. Normal values or values indicating quiescent disease in parenthesis. CRP = increase in CRP from outpatient values in 8 patient in each group]

TABLE 4.3

Disease Activity

DISCUSSION

There is no ideal method of assessing nutritional status which involves a combination of clinical examination, anthropometric and biological measurements (Shenkin & Steele, 1981). My definition of malnutrition as being less than 80% ideal body weight could be criticised, but does offer a fairly safe criteria which is easy to measure. Bistrian (1981) has suggested that percentage weight loss is more accurate but many patients in this study did not have previous documented weights. Only eight patients in each group had a previous weight recorded, but all the patients with more than 10% weight loss were in the malnourished group.

Dominioni et al. (1983) used serum albumin (less than 32 g/l) as an arbitrary measurement of malnutrition. However hypoalbuminaemia can arise from transcapillary flow as part of the acute phase response (Fleck et al., 1985) or in Crohn's disease from severe protein losing enteropathy, rather than from a primary nutritional problem involving protein intake, absorption and synthesis. Serum albumin was not thought to be suitable as a single parameter of nutritional status in this study. The skinfold thickness was significantly lower in the malnourished group but not the mid arm muscle circumference which can be a less accurate measurement. All the biochemical indices except

for the water soluble vitamins, were lower in the malnourished group, but the differences were not significant.

There were no significant differences in the disese activity as assessed by several indices between the two groups. The use of three different methods of assessing disese activity (clinical score, acute phase response and GI protein loss) should have compensated for any deficiency in using only a single method.

This study has shown that the acute phase response of C-reactive protein and alpha$_1$-acid glycoprotein in patients with Crohn's disease is not impaired in malnourished patients. The acute phase response can be used as a marker of disease activity in Crohn's disease in patients whose nutritional status is unknown.

CHAPTER 5

ASSESSMENT OF AUTOLOGOUS MIXED LEUCOCYTE INDIUM SCANNING IN DETERMINING DISEASE ACTIVITY AND EXTENT

INTRODUCTION

Conventional imaging techniques of the bowel involve invasive procedures. Small and large bowel radiology and colonoscopy have small but recognised complication rates, and may be hazardous, especially in patients who have active disease. Radionuclide scanning of the bowel offers unrestricted use as it is non-invasive and does not require bowel preparation.

^{67}Gallium Scanning

^{67}Gallium citrate , used during the late 1970s in the investigation of occult abcesses and neoplasia, was one of the first radionuclides to be used in the investigation of Crohn's disease. The results were disapointing, as many patients with Crohn's disease had negative scans (Goldenberg et al., 1979; Rheingold et al., 1979). ^{99M}Technetium diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) has a clearance similar to inulin, which has a distribution approximating to the extracellular fluid space (Kadir & Strauss, 1979). It was reasoned that ^{99m}Tc-DTPA may be useful in Crohn's disease in which a localised increase in the extracellular fluid space and an increased tissue permeabilty to the radionuclide could occur (Kadir

& Strauss,1979). Although many patients showed increased ^{99m}Tc-DTPA activity in the diseased bowel, this type of scanning never became popular due to the high false positive rate.

^{111}Indium-Oxine Mixed Leucocyte Scanning

Segal et al. (1976) were the first to use ^{111}Indium labelled white cell scanning for abscesses and subsequently in patients with Crohn's disease (Segal et al., 1981). As a heavy neutrophil infiltrate of the lamina propria is a characteristic microscopic appearance in Crohn's disease, in addition to the large neutrophil excretion in the stools, it was presumed that radiolabelled leucocytes would appear in areas of inflamed bowel. Autologous leucocytes, when exposed to ^{111}Indium, a gamma ray emitting radioisotope, and 8-hydroxyquinolone (oxine), a chelating agent, are stably labelled with the radioisotope (Zakhireth et al.,1979). The lipophillic chelating agent facilitates transport of ^{111}Indium across the white cell membrane. The labelled leucocytes are re-injected and subsequent scanning with a gamma camera identifies areas of inflammation. The faecal excretion of labelled leucocytes has been found to be higher in patients with Crohn's disease, raising the possibility of its use as a marker of disease activity (Segal et al.,1981).

^{111}Indium Scanning - Diagnosis of Crohn's Disease

The application of ^{111}Indium scanning in patients with Crohn's disease includes diagnosis, assessment of disease extent, assessment of disease activity and the investigation of intra-abdominal abscesses. In a large study of 100 consecutive cases of suspected inflammatory bowel disease, 33 cases (24 of Crohn's disease) were confirmed by conventional tests, including radiology colonoscopy, histology and/or surgery (Saverymuttu et al., 1985A). The scan accuracy was 94% compared with radiology of only 79%. The sensitivity of the scan increased to 100% when faecal indium excretion was included. Fotherby et al. (1986) looked at 40 patients with gastrointestinal symptoms and found 2 patients who had inflammatory bowel disease, 2 false postive scans and no false negative scans.

^{111}Indium Scanning - Assessing Extent

A few studies have been performed to assess the accuracy of ^{111}Indium scanning in estimating the extent of diseased bowel. Initial studies found excellent results when scanning was compared with radiology or colonoscopy, with the exception of small bowel disease (Saverymuttu et al., 1982,; Saverymuttu et al., 1983B,; Stein et al., 1983). In addition there was good correlation between the scans' estimation of extent, and colonoscopic and

histological assessment (Saverymuttu et al., 1986C). The less accurate results with small bowel disease were explained by poor imaging due to motility of the small bowel loops. While more recent studies have shown good correlation with disease extent in small bowel disease (Saverymuttu et al., 1983A; Fotherby et al., 1986; Becker et al., 1986), the scans were less accurate compared with scans for colonic disease (Crama-Bohbouth et al., 1988).

^{111}Indium Troponolone Granulocyte Scanning

There have been several reports indicating that ^{111}Indium scanning is less accurate than conventional techniques, resulting in an underestimation of disease extent (Buxton-Thomas et al., 1984; Leddin et al.,1987). The poor results of these studies could be explained by the scanning technique. Initial studies were carried out using a mixed leucocyte preparation, which unavoidably labelled lymphocytes and platelets in addition to granulocytes (Saverymuttu et al., 1983B; Buxton-Thomas et al.,1984). The technique has been modified to replace the mixed leucocyte preparation with pure granulocytes (Saverymuttu et al.,1983C). This provides better scan image by reducing the background to target activity. However preparation of pure granulocytes is time-consuming and expensive, and remains outwith the armamentarium of many nuclear medicine departments (Hesselwood, 1986).

There has also been discussion over the ideal chelating agent. Leucocytes have to be removed from plasma during labelling with ^{111}Indium oxine because of the affinity of this complex for transferrin (Peters et al.,1983), which could interfere with the viability of the leucocytes. Zakhireh et al. (1979) did not find impairment with the *in vitro* locomotion and bactericidal activity of ^{111}Indium - oxine labelled leucocytes.

In 1983 Peters et al. introduced the chelating agent troponolone for ^{111}Indium cell labelling, which offered the advantage of labelling the leucocytes in plasma and thereby reducing any effect on leucocyte function (Peters et al., 1983). Since then several studies on the use of Indium scanning in Crohn's disease have used troponolone as the chelating agent despite its additional cost and the need for a high cell concentration. A study by Datz et al. (1985) found that leucocytes labelled by either chelating agent have similar physiological activity for the detection of occult infections. However, an oxine-like chelating agent, acetylacetone, performed less well compared with troponolone in a large study of patients with mixed clinical conditions (Schauwecker et al., 1986). Whilst the labelling debate continues, oxine remains the agent used for routine scanning.

Assessing Disease Activity

Early investigators realised the value of ^{111}Indium scanning in assessing Crohn's disease activity. There are two methods : assessment of the intensity of the radioactivity of the abdominal scans (Ybern et al., 1986) or the quantification of the faecal Indium excretion (Saverymuttu et al., 1983B). Obviously the assessment of the scans is much easier than a four day stool collection, which is often incomplete and inaccurate.

Measurement of disease activity in Crohn's disease is very difficult (Chapter 2) and there is no objective gold standard. Most studies use a clinical index, most commonly the Crohn's Disease Activity Index (CDAI) (Best et al.,1976). Saverymuttu et al. (1982), using this estimation of disease activity, found that indium scanning could distinguish between active and inactive Crohn's colitis. In a later study Saverymuttu et al. (1983C) found good correlation with ^{111}Indium-tropolone granulocyte scanning and the CDAI. Fifteen patients were looked at pre and post steroid therapy. Surprisingly 6 out of 12 patients who had a CDAI <150 (inactive disease) had scan scores >1. Other studies have found good correlation between scan activity and CDAI (Stein et al., 1983), CDI (Ybern et al., 1986), acute phase proteins (Fotherby et al., 1986), ESR (Fotherby et al., 1986), colonic histology

(Saverymuttu et al., 1983D) and colonoscopic assessment (Saverymuttu et al.,1983D).

Faecal Indium Excretion

Faecal indium excretion has been more widely used than scanning activity for the assessment of disease activity. Several studies have found good correlation with the CDAI(Saverymuttu et al.,1983B; Saverymuttu et al., 1983D; Buxton-Thomas et al.,1984; Saverymuttu et al.,1986C); the Van Hees clinical index (Leddin et al.,1987; Fishbach et al.,1987); ESR (Saverymuttu et al.,1983D;. Fishbach et al.,1987); CRP (Saverymuttu et al.,1983D); $alpha_1$-acid glycoprotein (Fishbach et al., 1987),;$alpha_1$-antitrypsin (Fishbach et al.,1987); albumin (Fishbach et al.,1987); colonic histology (Saverymutttu et al., 1986C) and colonoscopic findings (Saverymuttu et al.,1986C).

Although Saverymuttu et al.(1986C) found good correlation between faecal indium excretion and gastrointestinal protein loss this was not confirmed by Fishbach et al. (1986) using $alpha_1$-antitrypsin stool concentration and clearance. Leddin et al (1983) found that faecal indium excretion had good correlation with the van Hees index, but there was a poor correlation with the CDAI.Several of their patients were classified by the CDAI

as having inactive disease.

The fault may lie with the clinical scores : they are subjective and rely heavily on stool frequency which could be due to other factors. Saverymuttu et al. (1986B) looked at 48 patients (71 assessments) who had inactive disease as assessed by the CDAI (CDAI < 150) and found that 89% of the patients had elevated faecal excretion compared to a control group of patients with irritable bowel syndrome.

Other Methods of Scanning

Because of the difficulty with ^{111}Indium, other methods of labelling white cells have been developed. ^{99m}Technetium offers several advantages over ^{111}Indium : the cell separation is technically easier and more convenient; it is less expensive; better image resolution; and lower radiation dose. Attempts have been made to "feed" leucocytes radiolabelled particles, usually ^{99m}Technetium colloid (Pullman et al.,1986). The leucocytes are induced to phagocytose and thereby activated, producing poor results and high false positive rates (Peters et al., 1986A), and it is not recommend for routine screening.

Locher et al (1986) used anti-granulocyte antibodies labelled with ^{125}I with some success. However the granulocytes are activated as a result of antibody

attachment and the patients may be immunised. Sucralfate, which is known to bind to ulcerated areas throughout the gastrointestinal tract, has been labelled with ^{99m}Technetium (Dawson et al.,1985).A recent study has failed to confirm the initial promising results (George et al., 1987). A major disadvantage is the necessity to wash out the bowel to recover unbound sucralfate.

Hexamethylpropylene-amineoxine (HMPAO) can form a lipid-soluble neutral complex with ^{99m}Technetium which is rapidly incorporated into leucocytes *in vitro*. Initial results were impressive, despite evidence of leucocyte activation (Peters et al.,1986B). Bowel excretion of technetium makes images taken more than three hours post-injection difficult to interpret.

Summary of introduction

^{111}Indium white cell scanning is a new non- invasive method of assessing disease extent and activity in patients with Crohn's disease. While ^{111}Indium-troponolite labelled pure granulocyte scans appear to give the optimum results, these scans are outwith the armamentarium of a routine nuclear medicine department. ^{111}Indium-oxine mixed leucocyte scanning is the routine method. Other methods of radionuclide labelling to leucocytes have not produced equivalent results due to leucocyte activation.

AIMS OF STUDY

The aims of this study were to compare ^{111}Indium-oxine mixed leucocyte scanning with other indices of Crohn's disease activity and to assess the accuracy of indium scanning in determining the location and extent of disease.

PATIENTS AND METHODS

Patients

Nineteen patients with Crohn's disease (sixteen females, three males, mean age 29, range 16-62) who required hospital admission with active disease were studied. Four patients had two assessments and therefore 23 sets of results are available. Conventional radiology and colonoscopy were used to assess the extent of disease, which was found to be limited to the small bowel in six patients, small and large bowel in four, ileocaecal in three, large bowel in four and ileocolonic anastomosis in two. Two patients had an ileostomy and one a colostomy (Table 5.1). Five patients were on sulphasalazine during the assessment period, three on both sulphasalazine and steroids and four on enteral nutrition.

Indium Scanning

Indium scanning was performed within five days of the conventional imaging techniques and before any change in drug therapy. Fifty millilitres of venous blood were taken from each patient and mixed with 2000 units of heparin and 8 ml of hetastarch. This mixture was gravity separated for one hour. The white cell layer was separated and centrifuged and resuspended in 10 ml saline, and incubated

PATIENT NUMBER	SEX	AGE	DRUGS	PREVIOUS RESECTIONS ENDOSCOPY	EXTENT OF DISEASE		DISEASE ACTIVITY					
					RADIOLOGY/	SCAN	CDAI CDI	MOD mm/h	ESR mg/l	CRP	GI PROTEIN LOSSml/24hr	SCAN
1 a	F	28	-	-	SB, S/R	RC	206	6	38	41	110	3
b			EN				71	0	10	10	90	1
2	F	28	-	R Hemi	SB	SB, TC, DC	269	4	52	30	60	3
3	F	51	SSZ	-	SB, DC	Neg	250	4	29	16	118	0
4	F	53	SSZ	-	DC, S/R	Neg	440	10	65	79	175	0
5	F	28	-	Colectomy	SB	SB	-	4	34	18	23	2
6 a	F	32	-	R Hemi	SB, S/R	SB, S/R	337	6	36	16	295	3
b			EN				196	3	39	35	230	5
7	F	58	-	R Hemi, Colostomy	SB, DC	SB, DC	-	6	35	15	147	2
8	F	28	-	Colectomy	SB	Neg	-	4	23	15	195	0
9	M	20	SSZ, Pred	-	DC, S/R	DC, S/R	299	3	46	24	42	5
10	F	29	SSZ, Pred	-	SB	Neg	243	3	20	58	165	0
11 a	F	42	-	-	TC, DC, S/R	TC, DC, S/R	384	6	55	93	44	6
b			EN				89	0	15	10	40	1
12	F	62	SSZ	-	RC	RC	160	3	16	11	11	1
13	F	23	Pred	R Hemi	Anastomosis, S/R	S/R	402	8	46	61	72	4

Table 5.1 - Patients Clinical Details and Disease activity Assessment

14 a	F	35	-	-	RC	RC	170	3	54	15	23	2
b			EN		RC	RC	203	3	45	10	45	1
15	M	28	SSZ, Pred	R Hemi	Anastomosis, S/R	S/R	290	5	30	51	42	1
16	M	25	-	R Hemi	SB	SB	154	3	34	28	26	2
17	F	16	-	-	RC, TC	RC, TC	70	1	30	62	39	2
18	F	23	SSZ	-	RC	Neg	160	2	40	48	36	0
19	F	32	SSZ	-	SB	RC	223	4	58	47	116	1

[Key

R Hemi - Right Hemicolectomy
SB - Small Bowel
RC - Right colon
TC - Transverse colon
DC - Descending colon
S/R - Sigmoid/rectum
SSZ - Sulphasalazine
PRED- Prednisolone
EN - Enteral Nutrition
Neg - Negative scan]

Table 5.1 Cont.

for 45 minutes with 10-20 MBq ^{111}Indium-oxine. Further centrifugation was done to yield the labelled cell button which was resuspended in 10 ml saline and reinjected intravenously. Gamma camera scans were carried out at four hours, anterior images of the abdomen and pelvis being obtained using a wide field of view gamma camera interfaced to a microcomputer.

The indium scan activity score was calculated by dividing the scanned area into five segments : the small intestine; right colon; transverse colon; descending colon; and sigmoid colon/rectum. For each segment an activity score of 0 = no activity, 1 < marrow activity, 2 < liver activity, 3 < splenic activty , and 4 >splenic activity was allocated and summated to give a theoretical maximum score of 20. Each scan was scored blindly by Professor J. McKillop. Examples of the scoring system are shown in Plates 5.1 - 5.3.

Disease Activity Indices

Disease activity was assessed by two clinical scores : the Crohn's Disease Activity Index (CDAI) (Best et al., 1976), and a modified Crohn's Disease Index (MOD CDI), based on the Bristol simple index (Harvey & Bradshaw, 1980), to allow for a score to be calculated for patients

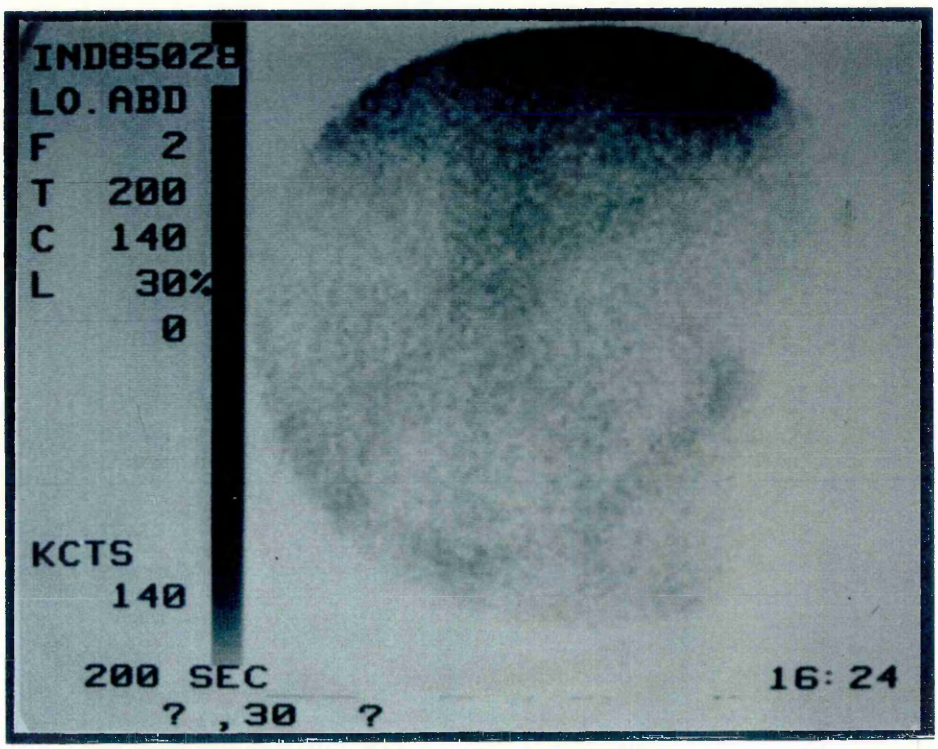


PLATE 5.1 Normal indium scan (scan score 0)

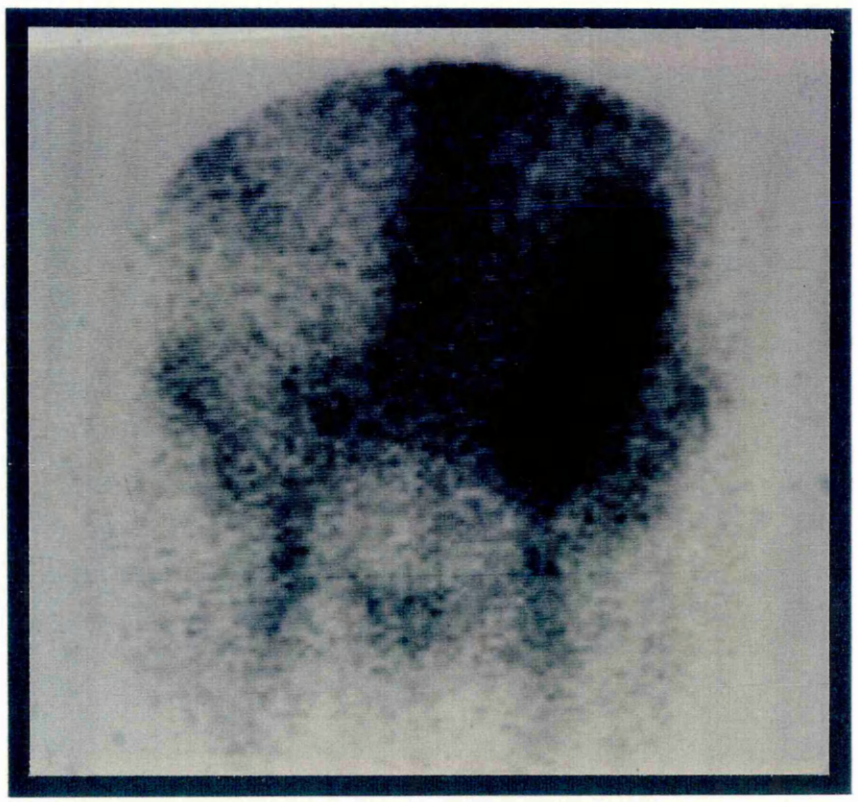


PLATE 5.2 Indium scan showing disease of descending and sigmoid colon (scan score 4)

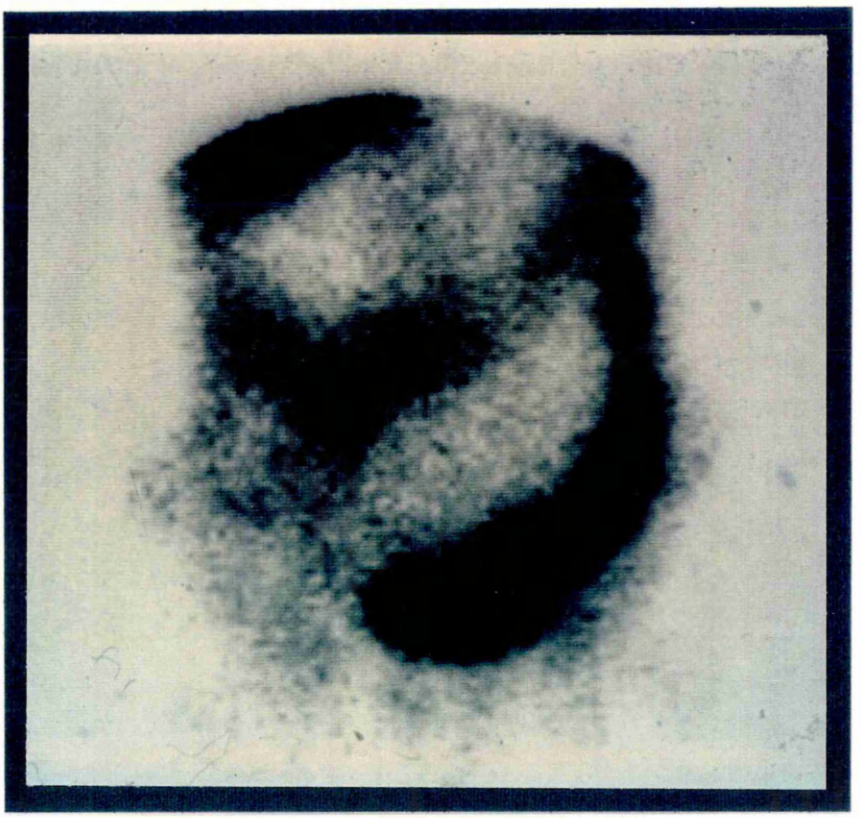


PLATE 5.3 Indium scan showing total colitis (scan score 9)

with stomas. The scoring for the Bristol Index was changed to 0 = normal stools, 1 = < 3 liquid stools per day, 2 = > 3 liquid stools per day ; for stoma patients 0 = normal stomal output, 1 = slightly increased output, 2 = greatly increased and very loose output. All patients had their erythrocyte sedimentation rate (ESR, Westergreen method), C-reactive protein (CRP, by nephelometry) and gastrointestinal protein loss measured by the $^{51}CrCL_3$ method (Van Tongeren & Reichert, 1966).

Statistical Analyses

The Spearman rank correlation coefficient (r_s) was calculated for the indium scan activity scores and the other indices of disease activity, and only $p < 0.05$ values were considered to be significant.

RESULTS

All patients had technically satisfactory scans with no pooling of leucocytes in the lungs.

Disease Activity

Twenty three sets of results are available (Table 5.1) and are summarised in Table 5.2 . Only the MOD CDI was calculated for the three stoma patients. There were no significant correlations between the indium scan activity scores and the other indices of disease activity - CDAI (r_s=0.25, p>0.1); MOD CDI (r_s=0.27, p>0.1); ESR (r_s=0.4, p>0.05); CRP (r_s=0.2,p>0.1); and $CrCl_3$ GI protein loss test (r_s=0.04, p>0.1) (Figures 5.1 to 5.5).

Disease Location

Of the five patients who had negative scans, three had extensive disease. Indium scanning showed correct location of disease in 58% of patients (Table 5.3).In one patient with small and large bowel disease the extent of the disease was underestimated. In two patients with small bowel disease alone the scans were reported as showing small and large bowel disease (patient 2) and only right colonic disease in patient 19. Radiology but not

	Median	*Range*
CDAI	215	70-440
MOD CDI	4	0-10
ESR	36	10-65
CRP	28	10-93
GI protein loss	60	11-255
Indium scan	2	0-6

(Normal values or values indicating quiescent disease
CDAI < 150, MOD CDI < 2, ESR < 20 mm/h, CRP < 10mg/l,
GI protein loss < 25 ml/24h, scan score =0.)

TABLE 5.2

Summary of Disease Activity Assessment

	Correct	*Incorrect*	*Negative*
Small bowel (6)	2	2	2
Small and large bowel (4)	2	1	1
Ileocaecal (3)	2		1
Large bowel (4)	3		1
Ileo-colonic anastomosis (2)	2		

TABLE 5.3

Location of Disease by Indium Scan

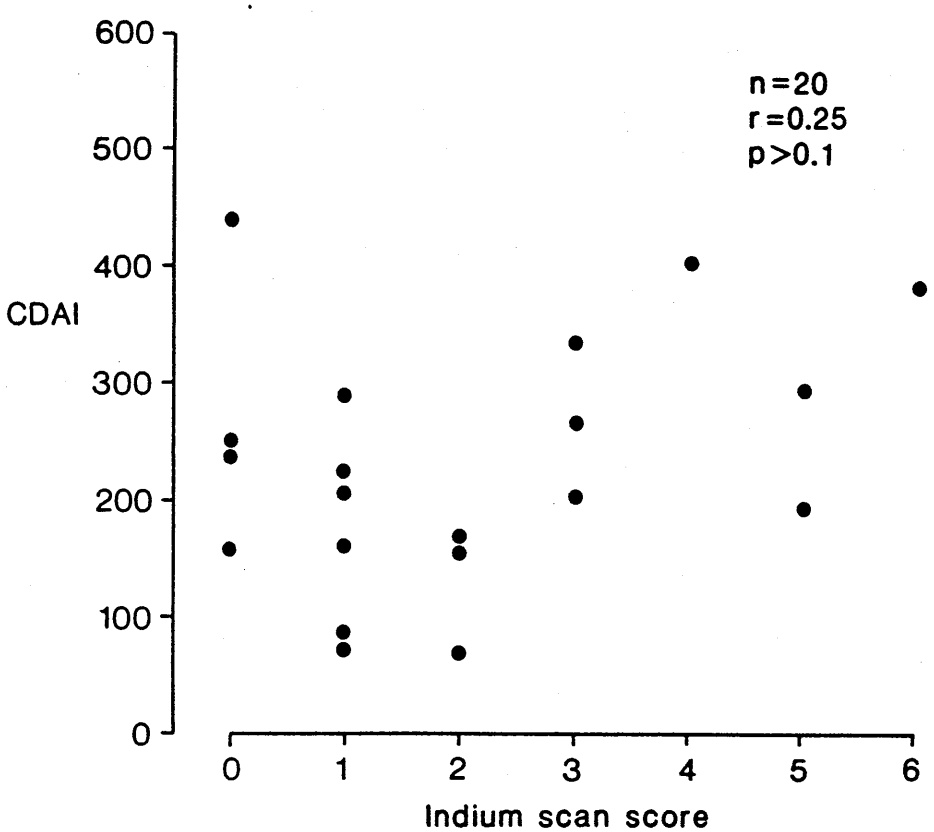


FIGURE 5.1

Correlation of Indium Scan Score and CDAI

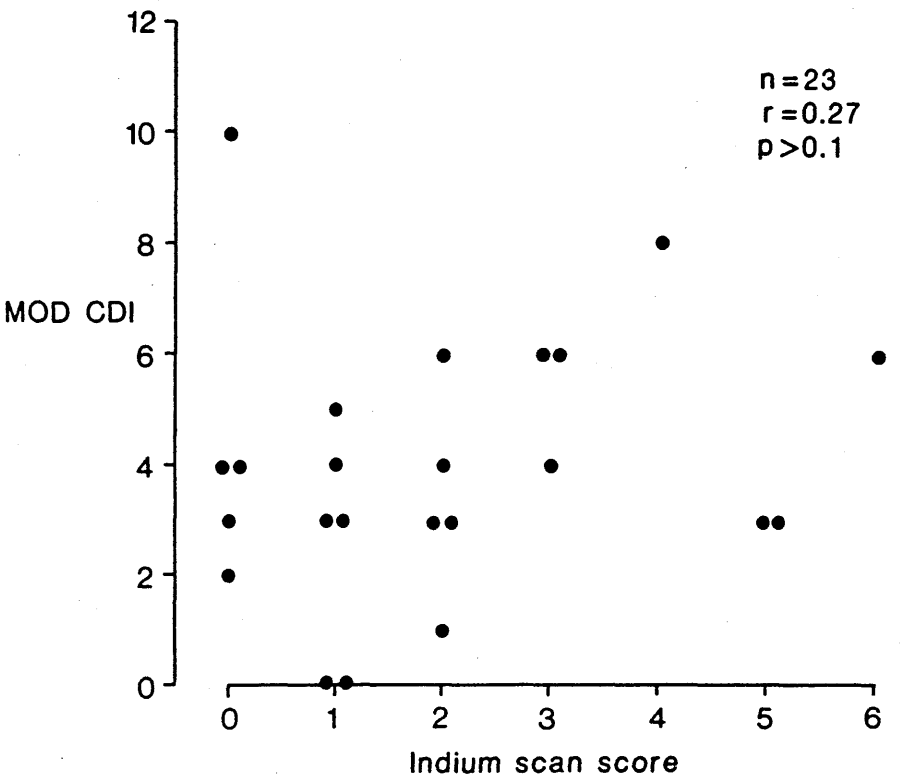


FIGURE 5.2

Correlation of Indium Scan Score and MOD CDI

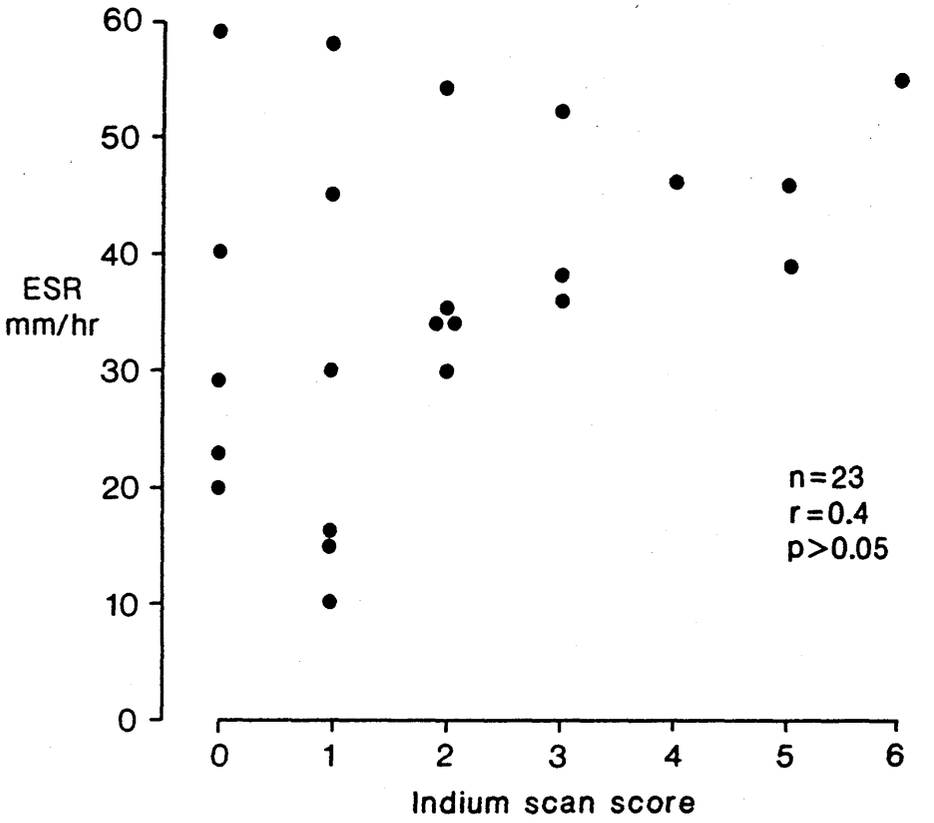


FIGURE 5.3

Correlation of Indium Scan Score and ESR

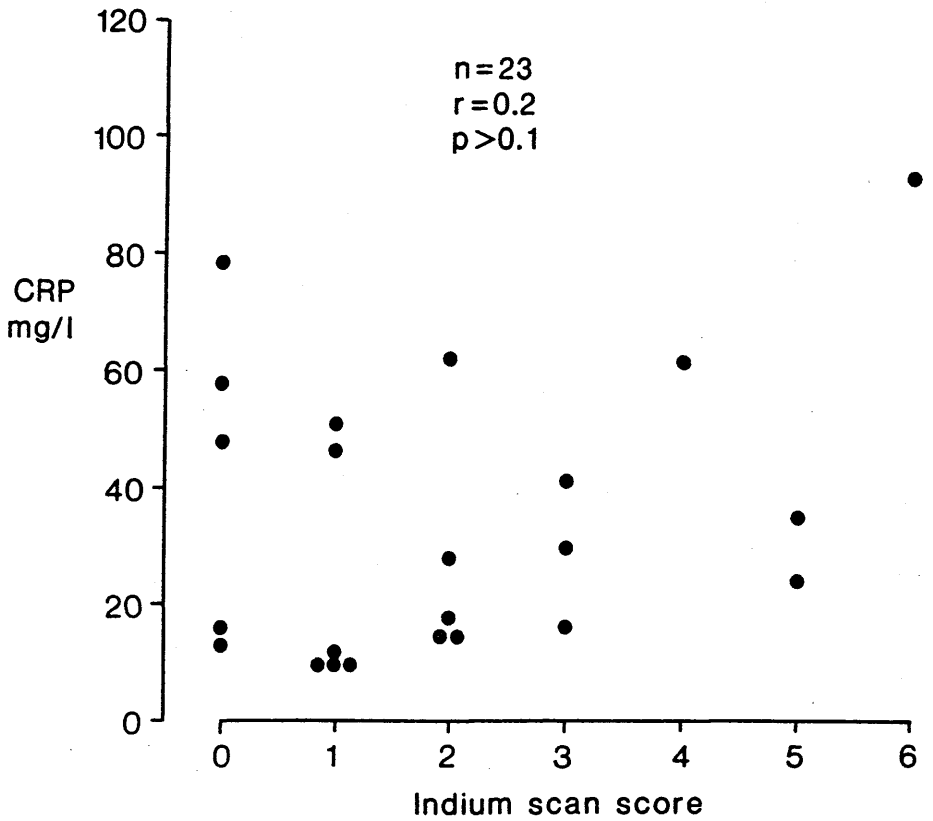


FIGURE 5.4

Correlation of Indium Scan Score and C-Reactive Protein

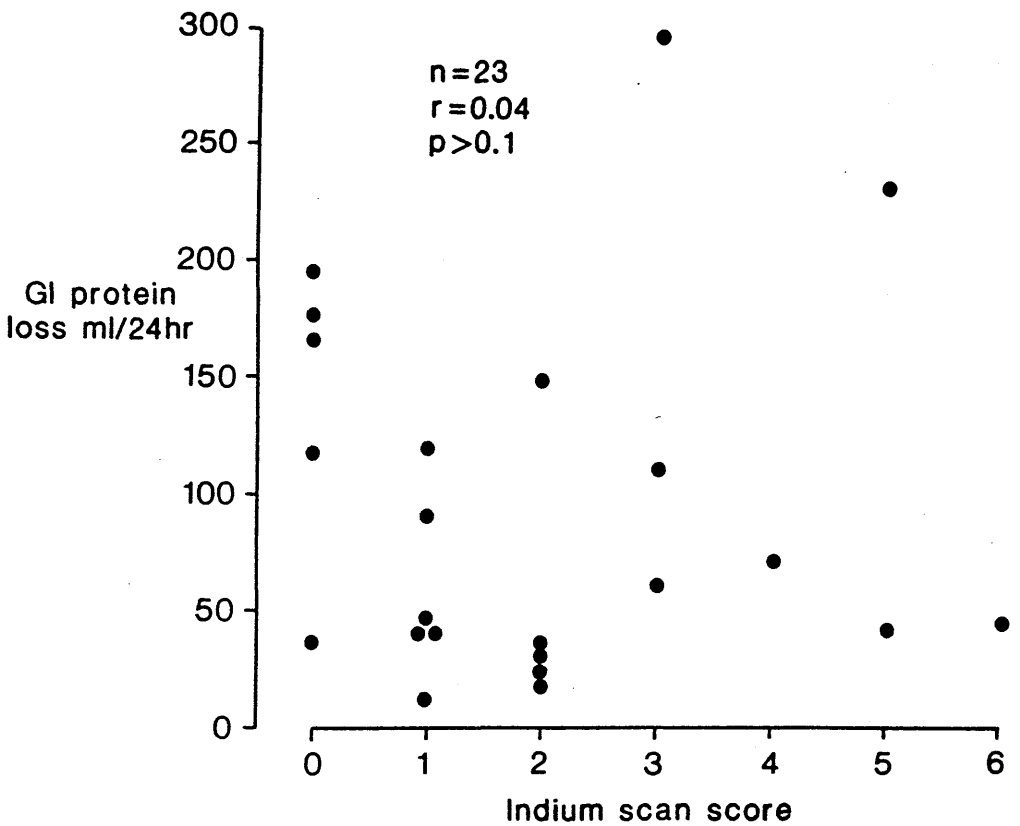


FIGURE 5.5

Correlation of Indium Scan Score and GI Protein Loss

colonoscopy had been performed on patient 2 and both investigations on the other patient.

DISCUSSION

The results of this study, which compared ^{111}Indium-oxine labelled mixed leucocyte scanning activity with other indices of disease activity and its assessment of disease extent, have failed to confirm previous encouraging results (Saverymuttu et al.,1982; Saverymuttu et al., 1983B; Saverymuttu et al., 1983C; Stein et al.,1983; Saverymuttu et al.,1986C). Buxton-Thomas et al. (1984) and Leddin et al. (1987) had found poor results with ^{111}Indium-oxine labelled mixed leucocytes. Five patients with unequivocally active disease had negative scans.

Indium scanning correctly located disease extent in only 58% of patients. The disease location accuracy was best for patients with colonic disease as had been found in previous studies (Saverymuttu et al.,1983B; Stein et al.,1983). This discrepancy could be explained by two reasons : poor scan technique or an actual limitation of indium-oxine mixed leucocyte scanning in detecting active inflammatory bowel disease.The first reason is unlikely as the scans had labelling efficiency of leucocytes of around 70%, comparable to other groups (Saverymuttu et al.,1983C; Saverymuttu et al.,1986A). Several groups have suggested that the scan technique can be improved by using a pure granulocyte preparation and substituting indium -

troponolone for indium oxine as the chelating agent (Saverymuttu et al.,1983C). Although Datz et al. (1985) found similar activities of both sets of leucocytes labelled by either indium-oxine or indium-troponolone, Fotherby et al. (1986), using Indium-troponolone showed an improvement in scan results from their previous study when indium-oxine had been used (Buxton-Thomas et al.,1984).

From this study standard indium-oxine mixed leucocyte scanning does not offer major advantages over the conventional methods of bowel immaging in inflammatory bowel disease. It may play a wider role in special circumstances, including severely unwell and toxic patients, very old and frail patients and in the investigation of intra-abdominal abscesses.

SUMMARY

Standard ^{111}Indium leucocyte scanning was compared with other indices of disease activity in 19 patients. There was poor correlation with he CDAI, MOD CDI, ESR, CRP and GI protein loss. Scanning correctly located disease extent in only 58% of patients.

CHAPTER 6

THE EFFECT OF BLOOD TRANSFUSION ON CROHN'S DISEASE ACTIVITY

INTRODUCTION

Recurrence After Surgery

The authors of the first reports on Crohn's disease (Dalziel, 1913; Crohn et al., 1932) considered that surgical resection offered a cure. However, it was not long before further studies reported early recurrence after resections (Felger & Schenk, 1940; Van Patter et al., 1954). Lennard-Jones & Stalder (1967), who were the first to use life-table analysis to investigate recurrence after surgery for Crohn's disease, found a cumulative recurrence rate of 23% after 5 years and 51% after 10 years. A recent study (Rutgeerts et al., 1984) found endoscopic evidence of recurrence in 72% of patients after one year following small bowel resection. Since then many other studies have looked at possible factors affecting recurrence after surgery : site of disease, with ileocolic disease having the highest recurrence (Wheelan et al., 1985); indications for surgery (Greenstein et al., 1988); and drug therapy after surgery (Wenckert et al., 1978).

Immunomodulating Effect of Blood Transfusion

Blood transfusion may cause immunosuppression in in the recipient : this is considered to be the mechanism of the improved graft survival in renal transplant patients (Woodruff & Van Rood, 1983) and the higher rate of recurrence following cancer surgery in patients who received blood in the perioperative period (Blumberg et al., 1986; Creasy et al., 1987). Blood transfusion could have a similar immunomodulating effect in Crohn's disease, which has been associated with many immunological abnormalities (Elson, 1988). The only previous study in Crohn's disease has been by Tartter et al. (1988) who examined the incidence of post-operative septic complications in patients who had received blood transfusions. They found that blood transfusion in the perioperative period was associated with an increased incidence of infection, even allowing for other factors including extent of disease and previous surgery. However, they did not examine if blood transfusion affected the disease activity or recurrence rate.

Blood transfusion is one of the oldest forms of artificial nutritional support. The potential effect of blood transfusion on disease activity in Crohn's patients has been ignored, which if present, could alter the therapeutic outcome of drug and diet trials.

AIM OF STUDY

The aim of the study was to determine if blood transfusion altered the relapse rate following surgical resections, and also in patients treated by medical methods.

PATIENTS AND METHODS

Patients

Patients were eligible for this study if they fulfilled the following criteria : an established diagnosis of Crohn's disease had been made by standard clinical, radiological, endoscopic and histological methods; they had required an admission for treatment of active Crohn's disease; they had responded to treatment and/or surgery and were off all drugs except maintenance therapy in the form of sulphasalazine-like drugs; they had been followed up for at least one year post admission. Patients who had received a blood transfusion for indications other than directly related to Crohn's disease were excluded.

Study Design

Details were recorded of disease activity (haemoglobin, C-reactive protein, ESR, albumin), treatment during

admission, duration of treatment, duration of disease remission, blood transfusion requirements, indications for blood transfusion, drug therapy before admission and drug therapy after admission. Indications for surgery were classified as either perforating (acute perforation, abscess formation, internal fistula) or non-perforating (intestinal obstruction, haemorrhage, failed medical therapy, toxic dilatation) (Greenstein et al., 1988).

Definition of Recurrence

Although there may be subtle differences between the terms recurrence, relapse or recrudescence, patients' outcomes are unchanged. For the purpose of this study, relapse has been used and is defined strictly as the appearance of gastrointestinal symptoms attributable to active Crohn's disease with objective laboratory, radiological and/or endoscopic evidence of active Crohn's disease.

Statistical Analyses

Results of patients' ages, distribution of disease, disease activity, and blood transfusion requirements were expressed as mean (sem). Demographic details of patients and results for disease activity were compared by using

the Student t test. Life-table analysis using the Kaplan-Meier (1958) method was used to calculate the cumulative relapse rate for different groups. Comparison of relapse rates between groups and treatment regimes were analysed by using the Chi square test. Results with $p < 0.05$ were considered to be significant.

RESULTS

Patients

207 patients fulfilled the criteria for this study. 151 (72.9%) patients did not receive a blood transfusion during their admission (NBT group), and 56 (27.1%) received a blood transfusion (BT group). The demographic details of the total, NBT and BT groups are shown in Table 6.1. There were no significant differences in age at the time of the study, age at presentation, duration of disease, or disease location.

Treatment Regimes

The treatment regimes for patients in the total, NBT and BT groups are shown in Table 6.2. Although there were more patients treated by surgical resection in the BT group (44.7%) compared with the NBT group (24.5%), this difference was not significant.

Maintenance Therapy

65.2% of the total group were taking maintenance therapy in the form of sulphasalazine (85.9% of patients on maintenance therapy) and mesalazine (14.1%). There were no significant differences in the number of patients taking

	TOTAL GROUP (n=207)	*NBT GROUP* (n=151)	*BT GROUP* (n=56)
Age at Study	35.2(1.6)	35.7(1.3)	33.9(2.1)
Age at Presentation	32.8(1.6)	33.1(1.2)	32.2(2.1)
Duration of Disease	2.5(0.3)	2.7(0.3)	1.8(0.3)
Gender (M/F)	83[40.1]/ 124[59.9]	62[41.4]/ 89[58.9]	21[37.5]/ 35[62.5]
Disease location :			
small bowel	53[25.6]	38[25.2]	15[26.7]
large bowel	73[35.3]	57[37.7]	16[28.7]
small and large	81[39.1]	56[37.1]	25[44.6]

(Key : results for age at study, age at presentation, duration of disease are expressed as mean(sem). Results in [ ] are % of groups)

TABLE 6.1

Patients' Demographic Details

		TOTAL (n=207)	*NBT* (n=151)	*BT* (n=56)
TREATMENT	MEDICAL	145(70)	114(76)	31(55)
	SURGICAL	62(30)	37(24)	25(45)

MEDICAL TREATMENT	*TOTAL* (n=145)	*NBT* (n=114)	*BT* (n=31)
Oral steroids	89(61)	65(57)	24(78)
Topical steroids	17(12)	16(14)	1(3)
Nutritional support	14(10)	10(9)	4(13)
Sulphasalazine alone	16(11)	15(13)	1(3)
Sulphasalazine and enteral nutrition	6(4)	5(4)	1(3)
Sulphasalazine and imtravenous nutrition	1(0.7)	1(0.9)	0
Mesalazine	2(1.3)	2(2)	0

SURGICAL TREATMENT	*TOTAL* (n=62)	*NBT* (n=37)	*BT* (n=25)
Right hemicolectomy	41(66)	27(73)	14(56)
Right hemicolectomy and small bowel resection	2(3)	2(5)	0
Small bowel resection	14(23)	6(16)	8(32)
Subtotal colectomy	5(8)	2(5)	3(12)

(Key : results in parentheses are % of group)

TABLE 6.2

Treatment Regimes for Total NBT and BT Groups

maintenance therapy between the NBT group (67.5%) and the BT group (58.9%) (Table 6.3).

Similar percentage of medically treated patients in both NBT and BT groups were taking maintenance therapy (X^2 = 1.07, $p > 0.05$). Although in the surgically treated patients there were fewer patients in the NBT group taking maintenance therapy (21.6%) compared with the BT group (40%), this difference was not statistically significant (X^2 = 2.45, $p > 0.05$).

Indications for Surgery

Patients in both NBT and BT groups were equally distributed between perforating and non-perforating indications for surgery (Table 6.4).

Blood Transfusion

In the BT group patients' mean (sem) tranfusion requirements were 3.4 (0.3) units. Table 6.5 shows the distribution of the number of units per patient and the ratio of whole blood to packed cells. Indications for transfusion were : correction of anaemia (76.8% : all 31 medical patients, 12 surgical patients); perioperative transfusion (8.9% : 5 surgical patients); and post-

	SASP & MES	*SASP*	*MES*
Total group (n=207)	135(65)	116(56)	19(9)
NBT group (n=151)	102(68)	87(58)	15(10)
BT group (n=56)	33(59)	29(52)	4(7)
NBT-MED group (n=114)	94(82)	81(71)	13(11)
BT-MED group (n=31)	23(74)	20(65)	3(10)
NBT-SURG group (n=37)	8(22)	6(16)	2(5)
BT-SURG group (n=25)	10(40)	9(36)	1(4)

(Key : results in parentheses are % of group; SASP = sulphasalazine; MES = mesalazine)

TABLE 6.3

Maintenance Therapy

	PERFORATING	*NON-PERFORATING*
TOTAL (n=62)	20 (32)	42 (68)
NBT (n=37)	10 (27)	27 (73)
BT (n=25)	10 (40)	15 (60)

(Key : numbers in parentheses are % of groups)

TABLE 6.4

Indications for Surgery

BLOOD TRANSFUSION (UNITS)	*PATIENTS (n = 56)*	*PACKED CELLS / WHOLE BLOOD*
1	1 (2)	1 PC
2	22 (38)	20 both PC
		1 both WB
		1 PC/WB
3	10 (18)	9 all PC
		1 all WB
4	18 (32)	18 all PC
6	1 (2)	All PC
8	1 (2)	All PC
9	1 (2)	6PC/3WB
10	2 (4)	1 7PC/3WB
		1 6PC/4WB

(Key : PC = packed cells; WB = whole blood; figures in parentheses are % of group)

TABLE 6.5

Blood Transfusion Requirements

operative transfusion (14.3% : 8 surgical patients).

Disease Activity

BT patients in the total group compared with NBT patients had significantly more active disease, assessed by the ESR ($p<0.01$) and serum albumin ($p<0.01$) (Table 6.6). The C-reactive protein levels were also slightly higher in the BT group ($p>0.05$). As expected the mean (sem) haemoglobin level in the BT group was lower than the NBT group [8.8 (0.2) v 11.9 (0.1)] ($p<0.01$). Similar differences in disease activity between the BT and NBT groups were also found in the medically treated patients (Table 6.7), but not in the surgically treated patients (Table 6.8).

Follow-Up Relapse Rate

The cumulative relapse rates for all the patients in both NBT and BT groups were not significantly different ($X^2=0.05$, $p>0.05$) (Figure 6.1). If only medically treated patients were analysed, there was a significant decrease in the relapse rate in the NBT group ($X^2=5.42$, $p<0.02$) (Figure 6.2). The opposite result was found in surgically treated patients, as the BT patients had a better relapse rate than the NBT patients ($X^2=6.71$, $P<0.01$) (Figure 6.3).

	NBT GROUP	*BT GROUP*	
Haemoglobin (g/dl)	11.9(0.1) [n=151]	8.8(0.2) [n=56]	*
C-Reactive Protein (mg/l)	41.4(4.7) [n=58]	56(10.8) [n=10]	
ESR (mm/h)	43.8(1.7) [n=122]	57(3.8) [n=49]	+
Albumin (g/l)	31.1(0.6) [n=71]	28.1(0.9) [n=23]	+

(Key : * = $p < 0.001$; + = $p < 0.01$; results are mean(sem); figures in [ ] parentheses are numbers of results)

TABLE 6.6

Disease Activity for Total Group

	NBT GROUP	*BT GROUP*	
Haemoglobin (g/dl)	11.8(0.2) [n=114]	8.1(0.2) [n=31]	*
C-Reactive Protein (mg/l)	43.5(5.6) [n=49]	64.4(14.1) [n=7]	
ESR (mm/h)	42.1(2.1) [n=92]	67.4(5.5) [n=28]	*
Albumin (g/l)	32.5(1.3) [n=56]	27.6(0.9) [n=14]	+

(Key : * = $p<0.001$; + $p<0.01$; figures in [ ] are number of results; results are expressed as mean(sem))

TABLE 6.7

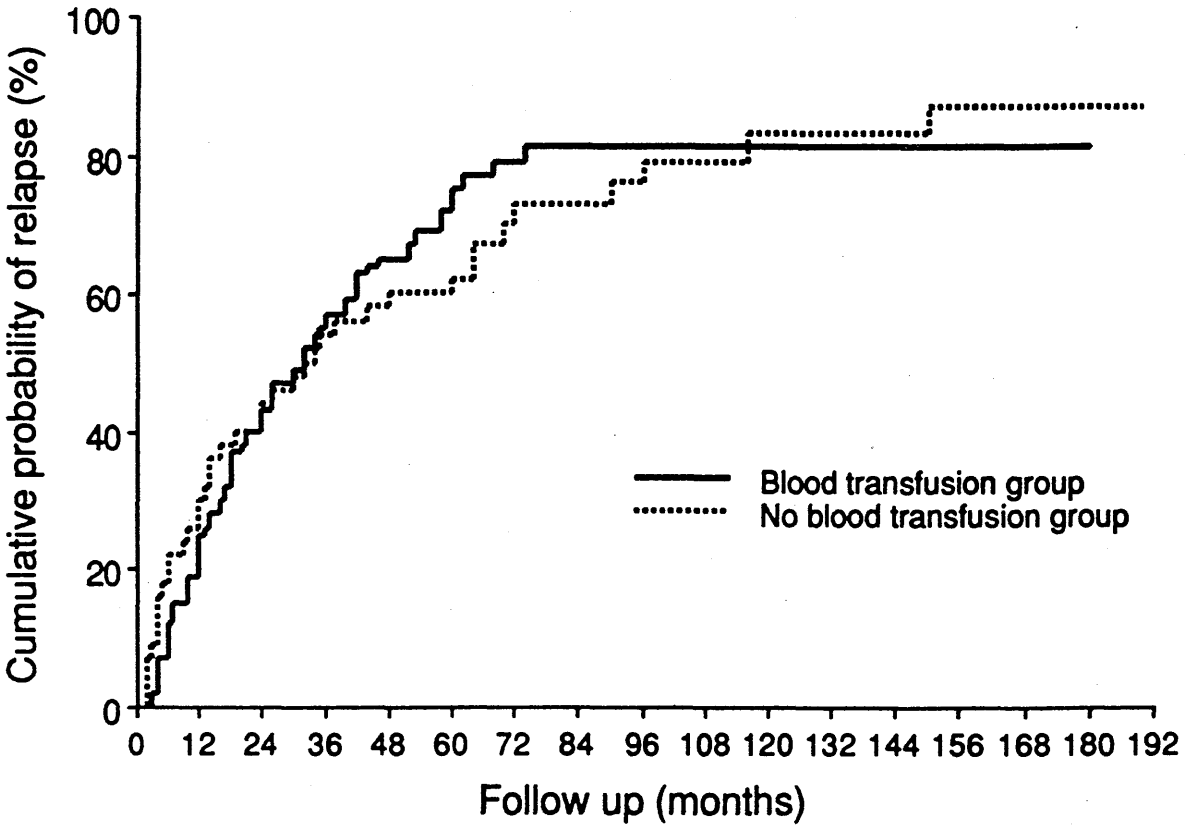
Disease Activity for Medically Treated Patients

	NBT GROUP	*BT GROUP*	
Haemoglobin (g/dl)	11.8(0.3) [n=37]	9.5(0.3) [n=25]	*
C-Reactive Protein (mg/l)	31 (4.1) [n=9]	27.7(4.9) [n=7]	
ESR (mm/h)	43.5(1.8) [n=30]	45.9(4.9) [n=21]	
Albumin (g/l)	31.8(1.2) [n=18]	28.9(1.7) [n=9]	

(Key;* = $p<0.001$; figures in [ ] are number of results; results expressed as mean(sem))

TABLE 6.8

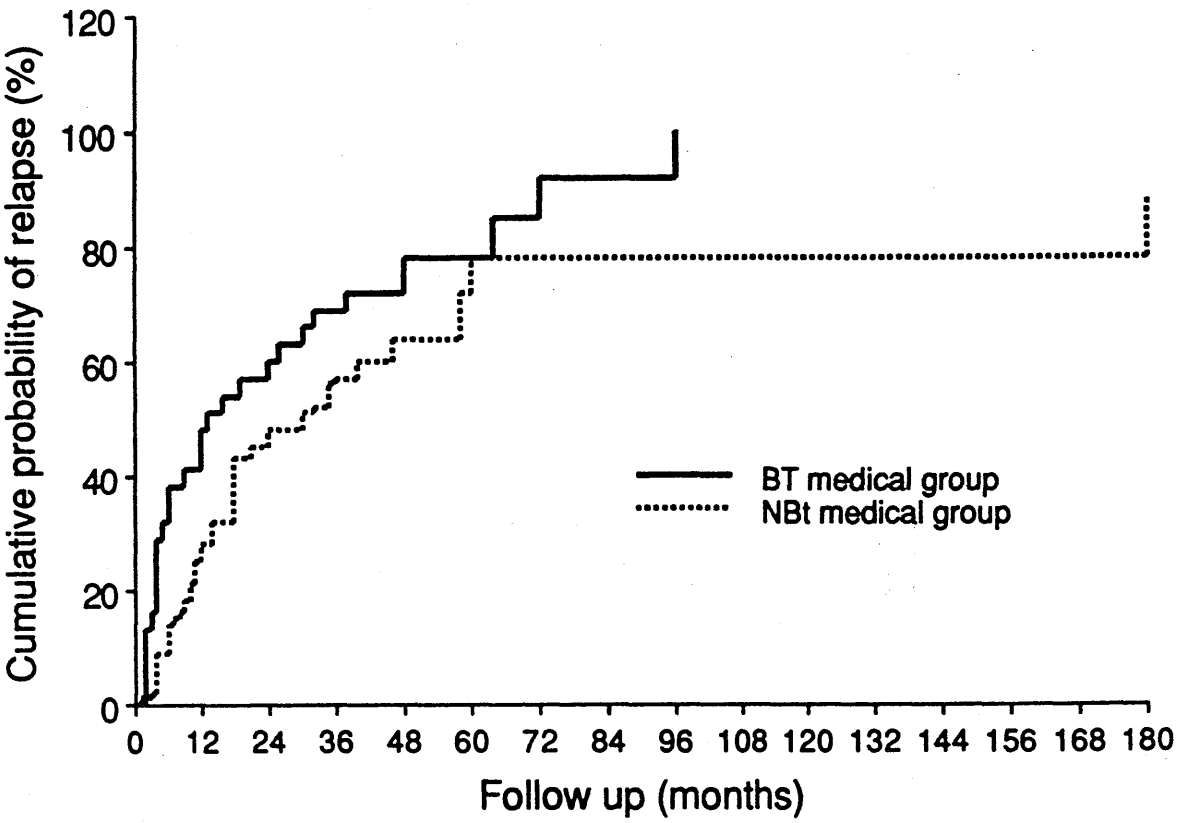
Disease Activity for Surgically Treated patients



(Key: NBT = no blood transfusion group; BT = blood transfusion group)

FIGURE 6.1

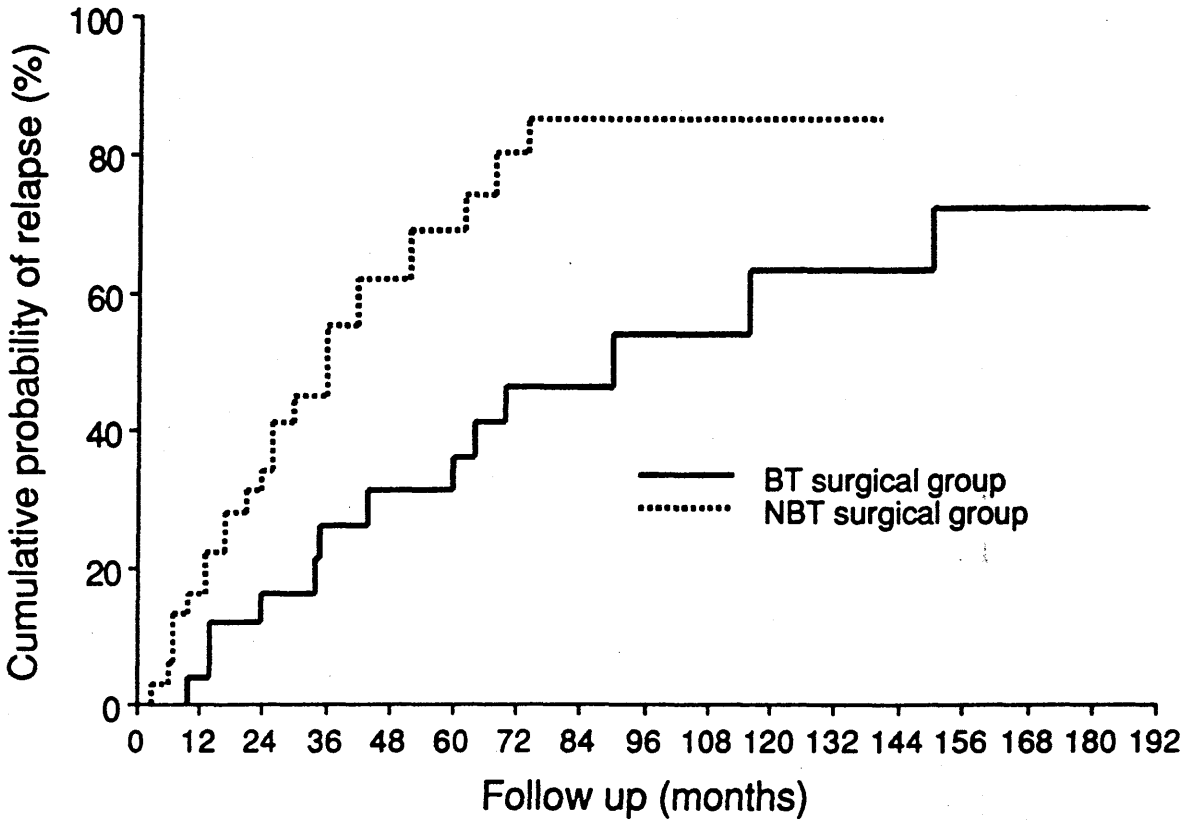
Cumulative Probability of Relapse for Total Group



(Key: NBT- medical group = medically treated patients who did not receive blood; BT-medical group = medically treated patients who received blood transfusion)

FIGURE 6.2

Cumulative Probability of Relapse for Medically Treated Group



(Key: NBT-surgical group = surgically treated patients who did not receive blood transfusion; BT-surgical group = surgically treated patients who received blood)

FIGURE 6.3

Cumulative Probability of Relapse for Surgically Treated Patients

DISCUSSION

Relapse Rates

This study has shown that blood transfusion does not affect the overall cumulative relapse rate for Crohn's disease. While medically treated patients who did not receive a blood transfusion (NBT-MED group) appeared to have a better relapse rate than patients who had received blood (BT-MED group), and surgically treated patients who had received blood (BT-SURG group) had a better relapse rate than surgical patients who had not received blood (NBT-SURG group), these discrepancies could be explained by differences in disease activity and maintenance therapy usage.

Disease Activity

The BT-MED group appeared to have more active disease at the time of admission (assesssed by ESR, CRP and albumin) then the NBT-MED group, which would be in keeping with the lower haemoglobin level and the requirement for blood transfusion. Although by definition of the criteria for entry into the study each patient had to achieve clinical remission, it is possible that the disease activity of the BT-MED group had not been suppressed completely and hence would be more likely to recur. The percentage of patients on maintenence therapy in the medically treated groups was

similar. While all the BT patients in the total group had more active disease, the relapse rates were the same for both groups.

The BT-SURG group relapse rate was better than the NBT-SURG group. Both groups had similar disease activity except that the BT group had lower haemoglobin levels. Fewer patients in the NBT-SURG group were on maintenance therapy compared with the BT-SURG group. Although the difference was not significant, it could have altered the long-term cumulative relapse rates. Previous studies, however, have failed to show any benefit from maintenence therapy following surgery (Wenckert et al., 1978; Summers et al., 1979).

Immune Mechanisms

The exact immunological mechanisms explaining the different outcomes in transfused patients following renal transplant and cancer surgery remain unclear. Creasy et al.(1987) have suggested that perioperative blood transfusion may impair the immunological surveillance of micro-metastases at the time of surgery. It is likely that there are different immune mechanisms affected by blood transfusion during transplant or cancer surgery.

Many different immunological abnormalities have been described in Crohn's disease (Elson, 1988). If immunological abnormalities varied considerably between patients with relatively inactive disease and very active disease, the immunomodulating effect of blood transfusion could depend on the degree of activity. This study has not found this as there were no significant differences between the NBT and BT patients in the total group, despite the BT group having more active disease.

SECTION IV

ASSESSMENT OF NEW ENTERAL LIQUID DIETS

CHAPTER 7

A STUDY OF NITROGEN UTILISATION, WEIGHT GAIN, FAECAL RESIDUE, HEPATIC LIPID CONCENTRATION OF RATS FED WITH NEW MODULAR ENTERAL LIQUID DIETS

INTRODUCTION

Elemental Diets and Small Bowel Function

The introduction of elemental diets for nutritional support was heralded as a significant advance in the management of patients with impaired gastrointestinal function (Russell, 1975). Elemental diets, composed of amino acids, simple sugars with very little lipid, were thought to offer advantages over whole protein and peptide diets. Nelson et al. (1981) demonstrated improved small bowel villus height and decreased crypt to villus ratio in rats fed with the elemental diets Vivonex and Flexical, and suggested that these changes resulted from improved survival of the mature enterocyte. Although the structure of the rat small intestine is altered by elemental diets (Nelson et al., 1981), small bowel function, assessed by water absorption using a perfusion technique, was not changed and in fact was worse with Flexical.

Peptide Diets

Potential advantages of elemental diets for patients with malabsorption or maldigestion (Russell, 1975) have not been demonstrated by subsequent animal and human studies. Silk et al. (1979) showed that normal subjects

absorbed orally administered mixtures of peptides and amino acids with equal efficiency. Elemental diets when compared with partially hydrolysed diets (a mixture of amino-acids and peptides) have been found to produce less weight gain and reduced nitrogen utilisation in rats (Main et al., 1984; Nelson et al., 1986; Maxton et al., 1987); in primates (Albino et al., 1985); and in patients (Meguid et al., 1984; Nasrallah et al., 1984).

Polymeric Diets

Young et al. (1980) compared the whole protein diet, Ensure, with the elemental diet, Vivonex, and partially hydrolysed diet, Flexical, in an isocaloric feeding study of rats over two weeks. Ensure-fed rats had greatest weight gain. Recognised disadvantages of elemental diets include unpalatability, diarrhoea due to hyperosmolality, higher costs and tendency to produce fatty livers (Young et al., 1981; Nelson et al., 1986). New modular elemental, polymeric whole protein, and peptide diets are available and offer greater flexibility of nutritional therapy.

AIMS OF STUDY

The aims of this study were to assess : the nutritional efficacy (weight gain, nitrogen utilisation) of the new modular diets, in particular the elemental diet, Elemental

028; the effect on faecal residue; and the development of fatty liver during feeding.

METHODS

Experimental Design

36 male Sprague Dawley rats were housed separately in matabolic cages, designed to limit coprophagia, and to allow separate collection of faeces and urine. Controlled feeding of the diet was possible and the animals were allowed free access to water. There were six test diets :the contol rat chow (Oxoid, Oxoid Limited, Basingstoke, UK) ; two elemental diets, Vivonex High Nitrogen (Eaton Laboratories, Woking, UK) and Elemental 028 (Scientific Hospital Supplies, Liverpool, UK) ; two peptide diets, Pepdite and MCT Pepdite (Scientifc Hospital Supplies, Liverpool, UK) ; and a polymeric diet, Enteral 400 (Scientific Hospital Supplies, Liverpool, UK).

The composition of the diets is shown in Table 7.1 . The diets are prepared using nitrogen, energy, vitamin and mineral " modjuls " from the SHS range. The peptides used for the Pepdite and MCT Pepdite diets are derived from hydrolysed non-milk protein and have mean chain lengths of 7.7 amino acids and molecular weight distribution of 5% > 2000, 9% 1000-2000 and 86% < 1000. L-amino acids are added to ensure a high biological value. The nitrogen source in Enteral 400 is whole protein (98%), derived from whey protein. Elemental 028 is composed of crystalline essential and non-essential amino acids.

Product	N.source	Carbohydrate source	Fat source	kcal : N	% Calorie Contribution by Fat
Oxoid 41B (Control diet)	Wheat, oats fish meal, milk	Lactose cereals	Not Known	115 : 1	Not known
Vivonex HN (VHN)	Amino acids	Glucose	Sunflower oil	150 : 1	0.78
Enteral 400 (E)	Whey protein Isolate	Maltodextrin	Arachis oil	190 : 1	39
Elemental 028 (ELE)	Amino acids	Maltodextrin	Arachis oil	187 : 1	15
Pepdite (P)	Soya Protein	Maltodextrin	LCT emulsion MCT emulsion	178 : 1	40
MCT Pepdite (MCT)	Soya Protein	Maltodextrin	MCT emulsion	178 : 1	40

Table 7.1 - Nutrient Composition of Test Diets

Each of the test diets were fed in isocaloric amounts (62 kcal/day) to 6 rats for 28 days. The diets varied in their kilocalorie to nitrogen ratio (Table 7.1), and since the rats were fed the same number of calories , a small ratio for the Oxoid and Vivonex HN diets indicated a relatively high nitrogen intake compared with the other diets.

Measurements

1. Body weight was measured every day and expressed as weight gain over 28 days as a percentage of starting weight.

2. Nitrogen balance was measured throughout the 28 days of the study. It was defined as the difference between nitrogen intake and nitrogen excretion measured by the micro-Kjeldahl technique (Fleck & Munro, 1965), on aliquots of each diet and on the excreta.

3. Nitrogen wastage, an approximate measure of nitrogen utilistaion, was defined as nitrogen excretion as a percentage of nitrogen intake.

4. Daily faecal residue was collected and dried, and weighed.

5. After 28 days of feeding the animals were sacrificed and the livers weighed and frozen for estimation of total

cholesterol (Abell et al.,1952) and lipid (van der Kamer et al., 1949).

Statistical Methods

Numerical data are expressed as mean (sem). Statistical analyses were performed using the Student t test and only results of $p < 0.05$ were considered to be significant.

RESULTS

Weight Gain

Mean weight gain (% of starting weight) ranged from 40 (3.5)% for the MCT Pepdite (MCT) group to 68 (3.4)% for the Enteral 400 (E) group (Figure 7.1), and was signicantly less for the peptide diets P and MCT compared with Oxoid (O) ($p<0.001$), Vivonex HN (VHN) ($p<0.001$), Enteral 400 (E) ($p<0.001$) and Elemental 028 (ELE) ($p<0.001$) (Table 7.2). This difference in weight gain could be partly explained by the reduction in dietary intake (% of diet not consumed) (Figure 7.2) in the P and MCT groups compared with the O, VHN, E and ELE groups (all $p<0.05$)(Table 7.2). Reduction in the dietary intake was found with all the rats in the P and MCT groups.

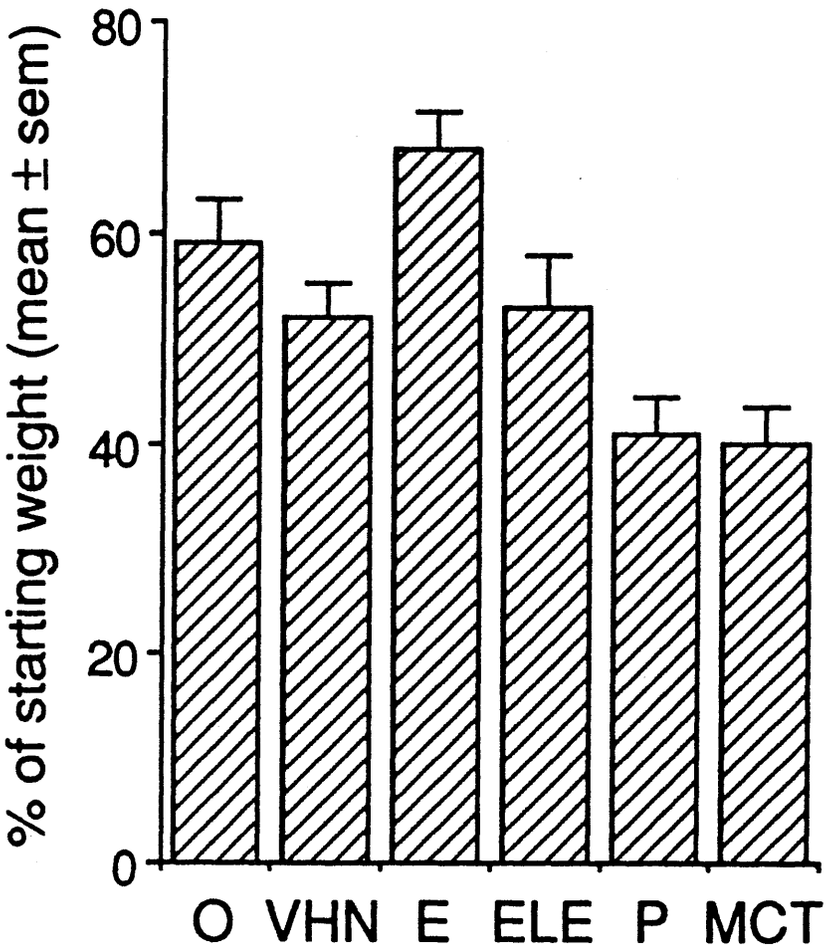
Nitrogen Utilisation

Nitrogen balance (mmol/24h)(Figure 7.3) of all the test diets was signicantly increased compared with the control diet (O) ($p<0.001$) as was VHN compared with E,ELE, P and MCT ($p<0.001$). Although the VHN group had the highest nitrogen wastage (nitrogen excretion as % of intake) (Figure 7.4), this difference was not significant. All test liquid diets had significantly reduced nitrogen wastage compared with the control diet, O ($p<0.001$, Table 7.2).

PEPDITE	OXOID (O)	VIVONEX HN (VHN)	ENTERAL 400 (E)	ELEMENTAL 028 (ELE)	PEPDITE (P)	MCT (MCT)
Weight gain (% of starting weight)	59(4.3)	52(3.3)	68(3.4)	53(4.9)	41(3.5)	40(3.5)
Nitrogen Balance (mmol/24h)	8.1(1.4)	24.9(1.4)	17.4(1.5)	14.7(0.6)	15.5(0.8)	16.9(0.9)
Nitrogen Wastage (Nitrogen excretion as % of intake)	71(4.5)	29(1.8)	23(2.1)	27(2.6)	22(1.6)	24(1.6)
Faecal Residue (mg/24h)	7280(166)	203(5)	262(29)	304(8)	386(22)	267(5)
Hepatic Lipid (mg/g liver)	47.9(2.9)	57.8(4.6)	41.6(1.8)	56.5(5.2)	42.7(4.5)	45.4(3.2)
Hepatic Cholesterol (mg/g liver)	3.8(0.5)	5.4(0.5)	4.7(0.2)	4.8(0.4)	3.9(0.5)	3.4(0.2)
Dietary intake (% of diet not consumed)	1.8(0.2)	0	0	0.7(0.5)	19(8.0)	17(8.4)

[Key: All results Mean(SEM)]

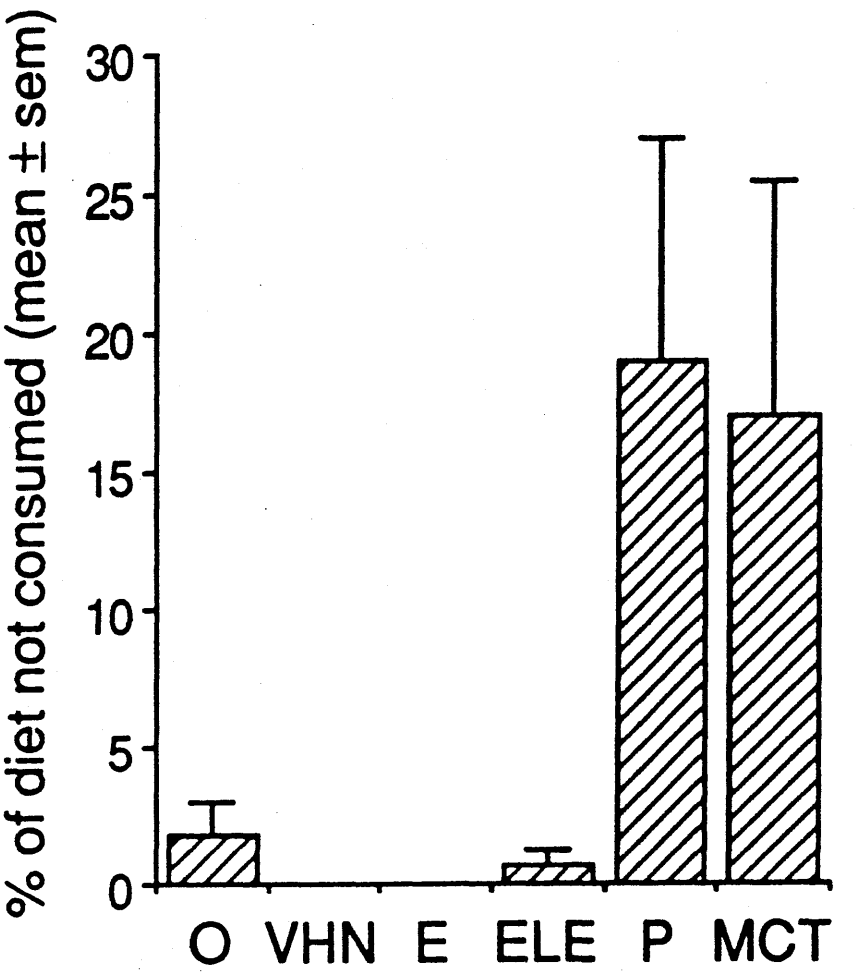
Table 7.2 - Results for Nutrogen Utilisation, Weight Gain and Hepatic Lipid Concentration



(Key: O=Oxoid; VHN=Vivonex High Nitrogen; E=Enteral 400;ELE=Elemental 028; P=Pepdite; MCT=Pepdite MCT; all results as mean(sem) % increase of starting weight)

FIGURE 7.1

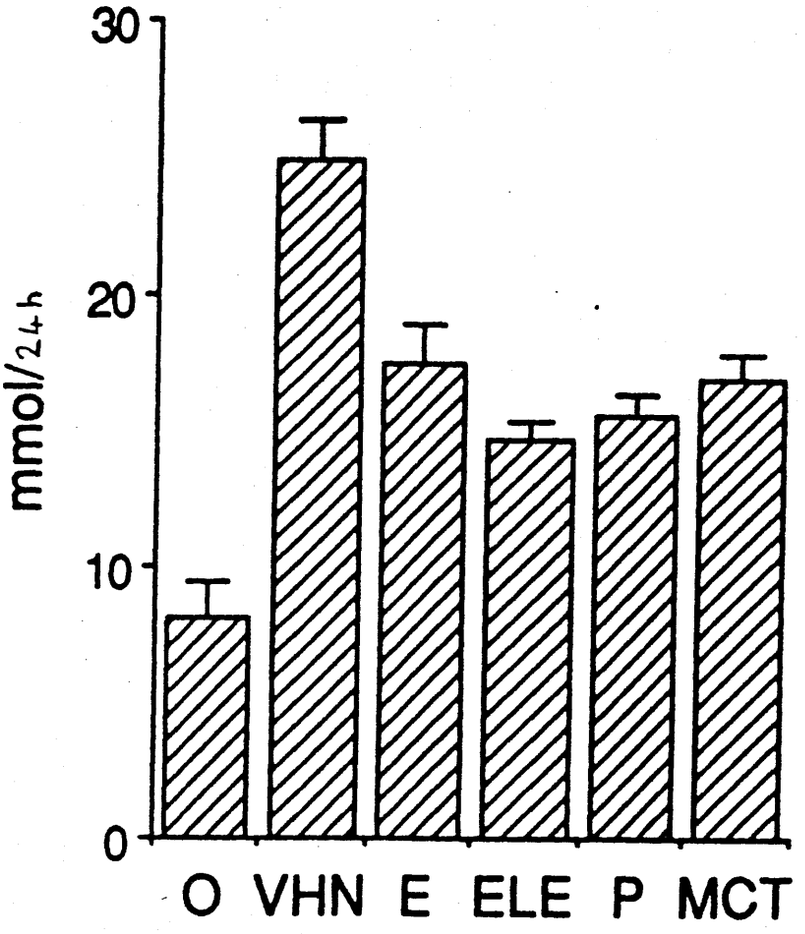
Weight Gain During Study



(Key: as in Figure 7.1; results as mean(sem) % of diet not consumed)

FIGURE 7.2

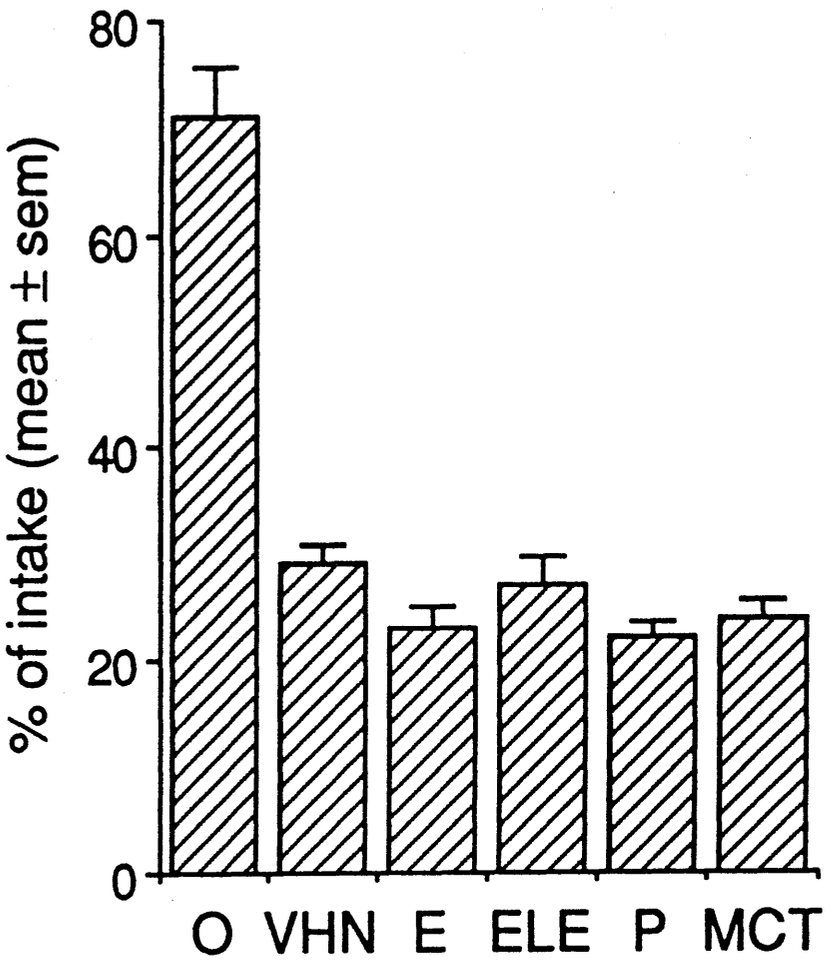
Dietary Intake



(Key: as in Figure 7.1; results as mean(sem) nitrogen balance mmol/ 24h)

FIGURE 7.3

Nitrogen Balance



(Key: as in Figure 7.1; results as mean(sem) % of nitrogen intake)

FIGURE 7.4

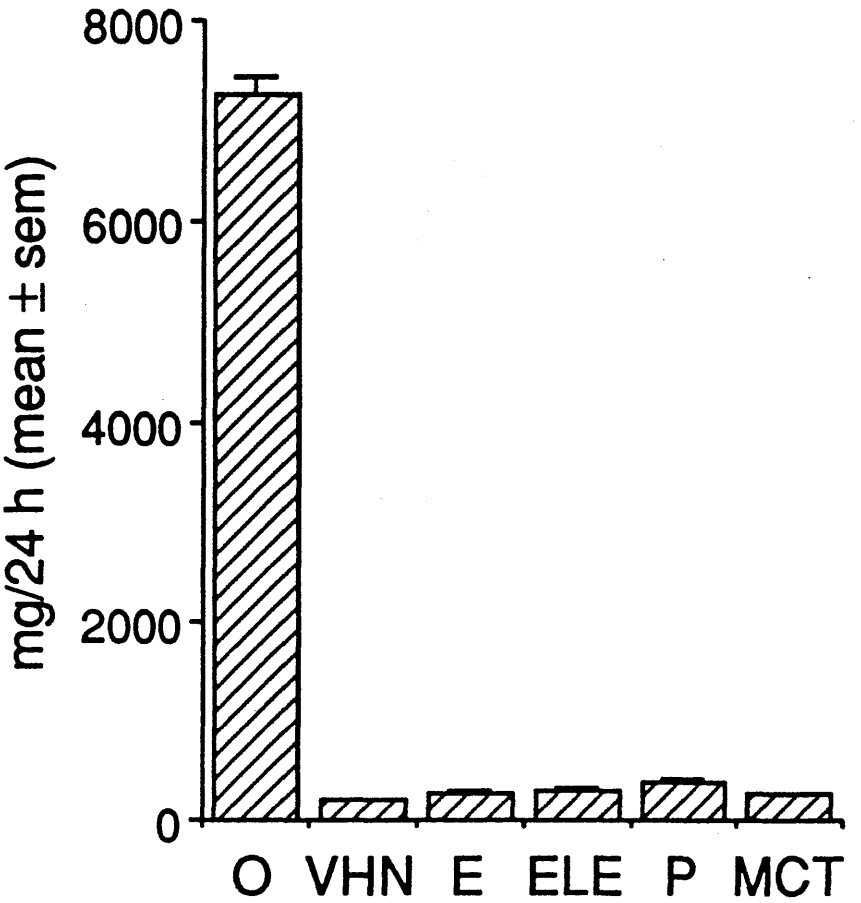
Nitrogen Wastage

Faecal Residue

All test liquid diets induced low faecal residue (<6% of control feed) (Figure 7.5). The faecal residue was significantly increased ($p<0.001$) in the P group compared with VHN,E,ELE and MCT (Table 7.2). The faecal residue in the VHN group was reduced significantly ($p<0.001$) compared with ELE, P and MCT but not E.

Hepatic Lipid

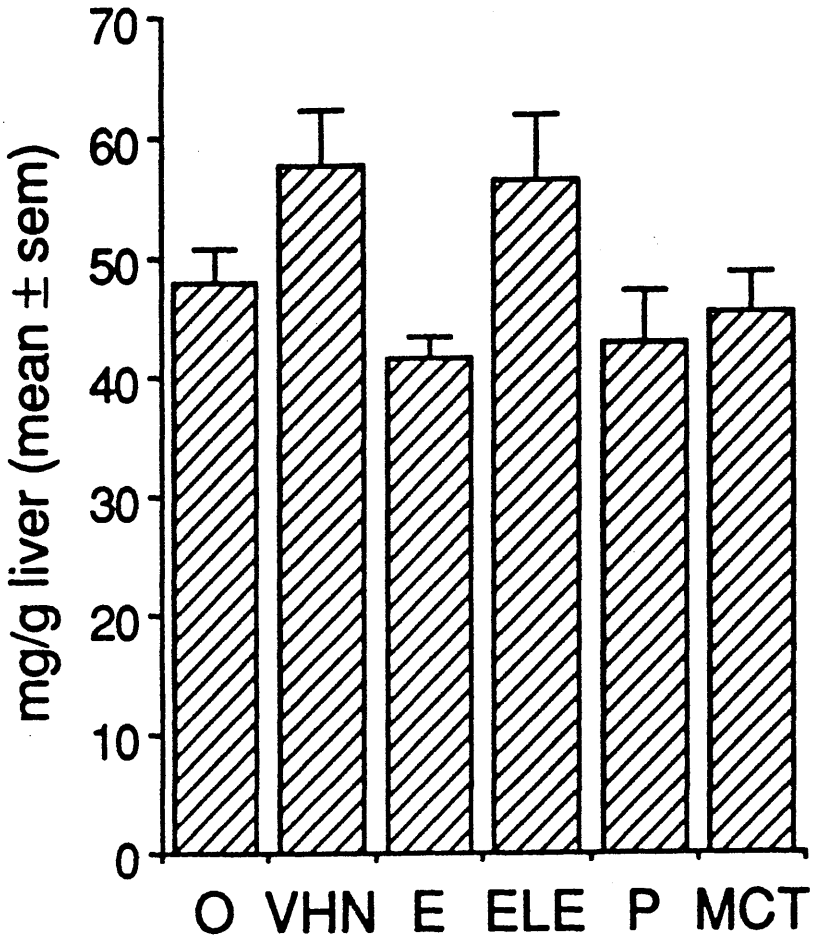
Hepatic lipid (Figure 7.6) was significantly increased ($p<0.05$) with the elemental diets VHN and ELE, compared with the polymeric and peptide diets (E and P). There was no significant difference between the elemental diets (Table 7.2). The hepatic cholesterol (Figure 7.7), although elevated in the elemental diets, was not significantly higher than the other groups except MCT.



(Key: as in Figure 7.5; results as mean(sem)
faecal residue mg/ 24h)

FIGURE 7.5

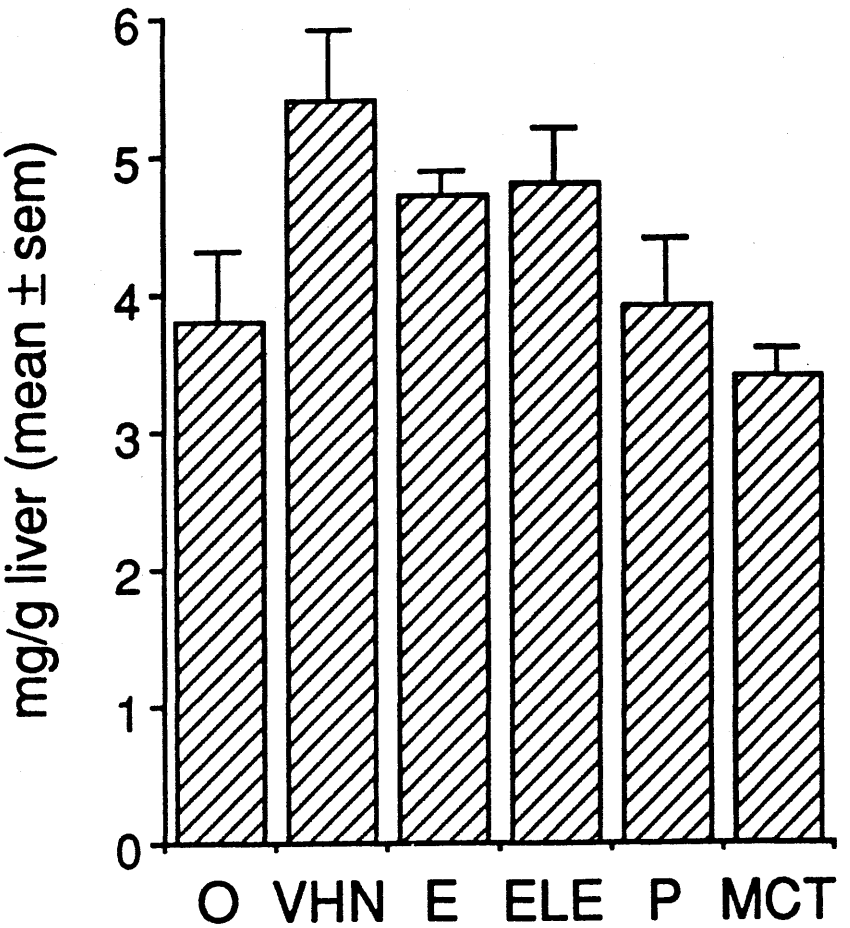
Faecal Residue



(Key: as in Figure 7.1; results as mean(sem) mg/ g liver)

FIGURE 7.6

Hepatic Lipid



(key: as in Figure 7.1; results as mean(sem) mg/ g liver)

FIGURE 7.7

Hepatic Cholesterol

DISCUSSION

Weight Gain

The weight gain of the rats fed the elemental diets, VHN (52(3.3)%) and ELE (53(4.9)%) was lower, although not significantly, than the polymeric diet group E (68(3.4)%). Other studies have found reduced weight gain with elemental diets (Young et al.,1980; Nasrallah et al.,1984; Nelson et al.,1986). Unexpectedly the peptide diet groups, P (41(3.5)%) and MCT (40(3.5)%) had significantly reduced weight gain compared with O, VHN, and E groups. The poor weight gain with the peptide diets has not been found with other studies (Nasrallah et al., 1984; Meguid et al.,1984; Albina et al.,1985) and can be explained by the very poor intake of the peptide diets by the rats during the study period. The presumed poor palatability of the peptide diets would be a disadvantage for human consumption.

Nitrogen Wastage

Elemental diets, comprising of only amino acids, in particular Vivonex, have been shown to have poor nitrogen utilisation, producing elevation in blood urea and increased urinary urea nitrogen (Smith et al.,1982; Jones et al.,1983; Meguid et al.,1984; Albina et al.,1985). Meguid et al. (1984) suggested that the high glutamine content of Vivonex stimulated the urea cycle. However in a controlled metabolic study using human volunteers, Albina

et al. (1985) found that glutamine was not responsible for the difference in nitrogen utilisation, which may be due to other factors in the Vivonex diet. Main et al. (1984), using the technique of neutron activation analysis to assess whole body nitrogen, found that Vivonex fed rats had significantly reduced whole body nitrogen compared with Flexical and Clinifeed fed rats, but Vivonex HN fed rats had improved whole body nitrogen. In this study I found that nitrogen balance was significantly increased with VHN compared with the other diet groups, mainly due to the high nitrogen content of the VHN group. The nitrogen wastage (an arbitrary assessment of nitrogen utilisation) was higher in the VHN group but not significantly greater than the other test liquid diets.

Faecal Residue

Elemental and other liquid diets contain no indigestable fibre and produce very low stool weight (Russell, 1975). This study showed that the faecal residue of the VHN diet group was significantly reduced compared with the other liquid test diets. Elemental 028, the other elemental diet tested in this study, produced a mean(sem) faecal residue of 304(8) mg/day (similar to the other peptide and polymeric diets), and significantly higher than VHN 203 (4.6) mg/day. This difference in faecal residue between the two elemental diets and the other diets may be due to

the carbohydrate composition of the diets. Main et al. (1984) have shown that bacteria form the main component of the faecal residue of liquid diets, and that feeding with Vivonex produces the lowest bacterial content. Vivonex's carbohydrate source is glucose which is absorbed in the proximal small bowel. The other diets, including Elemental 028, have more complex carbohydrates and the unabsorbed carbohydrate can be fermented by colonic bacteria to provide energy for bacterial proliferation (Nyman & Asp,1982).

Hepatic Lipid

The hepatic lipid was increased significantly in both elemental diet groups compared with all the diets. There were no significant differences between the elemental diets. Although the hepatic cholesterol was higher in the VHN and ELE groups, only the MCT group had hepatic cholesterol concentration which was significantly lower. Young et al. (1981) found that Vivonex but not Vivonex HN produced a significant increase in the lipid concentration compared with Flexical, Vital and control rat feed. In a study by Nelson et al. (1986), rats which were allowed ad libitum access to Vivonex and Flexical developed massive increase in hepatic lipid, assessed biochemically and histologically. Isocaloric feeding, in the same study, produced a lower increase in hepatic lipid. The increase

in the hepatic lipid with the elemental diets have been attributed to the high content of easily absorbed carbohydrate and reduced fat content, which is similar to fatty liver production during parenteral nutrition (Lee, 1988). However Elemental 028 has similar carbohydrate source (although in a higher amount) to the other modular liquid diets, although the fat content is lower.

CONCLUSION - Overall Nutritional Efficacy

In conclusion, the new Elemental 028 diet does not offer any advantages over Vivonex, and may produce slightly increased faecal residue. The polymeric diet, Enteral 400, performed well, producing the highest weight gain and satisfactory nitrogen utilisation similar to Elemental 028. Both elemental diets produce fatty livers, which raises some concern over their long-term use. The other modular diets do not appear to offer any nutritional advantages, and the peptide diets may be less palatable than the other diets.

SECTION V

CLINICAL APPLICATION OF ENTERAL NUTRITION IN CROHN'S DISEASE

CHAPTER 8

DOUBLE BLIND CONTROLLED TRIAL OF ELEMENTAL AND POLYMERIC DIETS AS PRIMARY THERAPY IN ACTIVE CROHN'S DISEASE

INTRODUCTION

Elemental Diet As Primary Therapy

Improvement in disease activity of patients with Crohn's disease by dietary methods would be an attractive method of treatment: not only is diet more natural than drugs but may also avoid potential side effects and improvement of the nutritional state of patients would also be expected. In the 1970's several reports were published of the possible value of elemental diets in Crohn's disease (Voitk et al., 1973; Giorgini et al., 1973; Rocchio et al., 1974; Goode et al., 1976; Axelsson & Jarnum, 1977).

Voitk et al. (1973) and Rocchio et al. (1973) reported individual patients who received elemental diets for nutritional support, and in whom the clinical outcome was considerably better than expected. This early success in treatment led to the concept of the use of elemental diet as "primary therapy" in active Crohn's disease (Voitk et al., 1973). Giorgini et al (1973) were the first to demonstrate radiological improvement following elemental

diet in a child with disease affecting the terminal ileum.

However many of the publications have been only case reports (Cucchiara et al., 1984; Pfeil et al., 1988) or uncontrolled studies (Morin et al., 1982). It was not until the middle 1980's that the use of elemental diet in active Crohn's disease was investigated by controlled trials (O'Morain et al., 1984; Saverymuttu et al., 1985B; Sanderson et al., 1987). Most publications have found that elemental diets with or without antbiotics are as successful as steroid therapy in producing remission of disease activity. Although Seidman et al. (1986) found that Vivonex was as effective as steroid therapy in inducing remission after three weeks treatment, most diet treated patients relapsed at an early stage.

Mechanisms of Action of Elemental Diets in Crohn's Disease

Elemental diets are considered to be hypoallergenic and may alter the immunological mechanisms and thus the disease activity in patients with Crohn's disease. However other mechanisms for the improvement in disease activity have been prposed including improvement in immune function following correction of malnutrition, alteration of bowel flora, and the low residue nature of the diets (Russell, 1975; Rhodes & Rose, 1986).

Non-Elemental Diets in Crohn's Disease

It is possible, however, that other non-elemental liquid diets which are at least of equal nutritional efficacy may share the same beneficial effect on disease activity. Harries et al. (1983A) have shown in a controlled trial of polymeric liquid supplements in a group of malnourished outpatients with Crohn's disease that the use of supplements have beneficial effects on nutritional parameters, immunological tests and disease activity.

These findings were not confirmed by Brignola et al.(1983) in a smaller study using the diet Precision. Imes et al. (1986) found a less encouraging response in a group of patients who were given Ensure, as several patients were unable to tolerate the diet due to side-effects. In a case report, Fernandez-Banares et al (1988) found that a 14 year old boy with small and large bowel Crohn's disease responded to a polymeric diet, although he had also received metronidazole. However Steinhardt et al. (1988) found in six patients with stable Crohn's disease fed for a week with lactalbumin or its hydrolysate that intestinal protein loss was reduced using the diet with the hydrolysate as the nitrogen source.

AIMS OF STUDY

The aims of this study were to investigate whether an elemental diet offered any advantages over a polymeric diet in active Crohn's disease and to determine the role of improvement in nutritional status on activity of Crohn's disease.

PATIENTS AND METHODS

Patients

Fourteen patients with active Crohn's disease were entered into the study, randomly allocated to receive either the elemental diet (ED) Elemental 028, or the polymeric diet (PD), Enteral 400 (Scientific Hospital Supplies, Liverpool, UK). Seven patients were started on each dietary regime. The mean (range) in years for the ED group was 33(15-58) which was similar to the PD group 38(23-62), as was disease location (Table 8.1).

	ED GROUP	*PD GROUP*
AGE (mean, range)	33(15-58)	38(23-62)
GENDER (F/M)	6/1	7/0
DISEASE LOCATION		
small bowel	1	1
ileocaecal	0	1
large bowel	2	1
small and large bowel	4	4
DURATION OF DISEASE		
[years, mean(sem)]	5.8(2.9)	2.4(1.4)

(Key : ED = elemental diet; PD = polymeric diet;
ED v PD $p > 0.05$)

TABLE 8.1

Clinical Details of Study Patients

The diagnosis of Crohn's disease was made by the usual clinical, radiological, endoscopic and histopathological criteria. All patients had been admitted to hospital with active Crohn's disease which for inclusion into this study was defined by the modified Crohn's disease index (MOD CDI, see Chapter 3 of this thesis) of greater than 2, with at least 2 abnormal laboratory indices for disease activity, whcih included ESR, CRP, gastrointestinal protein loss, and indium scan activity.

Patients were excluded from the study : if they had evidence of significant intestinal obstruction, clinically evident intra-abdominal sepsis, toxic megacolon; if they had received systemic steroids or immunosuppressive agents in the preceeding six months; or if they were not willing to have enteral nutrition for 28 days. Two patients, one in each group, were on sulphasalazine on admission, which was continued during the trial.

Disease Activity

A clinical scoring system, the modified Crohn's disease index (MOD CDI), was used (see Chapter 3 of this thesis). Clinical remmision at the end of the trial was defined as a MOD CDI of less than 2.

Laboratory assessment of disease activity was made by :the erythrocyte sedimentation rate (ESR - Westergreen method); C-reactive protein (CRP), measured by nephelometry (Hyland laser nephelometer); gastrointestinal protein loss, using the $CrCL_3$ clearance method (Van Tongeren & Reichert, 1966); and autologous mixed leucocyte scan (as descibed in Chapter 5 of this thesis). The MOD CDI was calculated and ESR and CRP measured before, weekly during the trial, and at the end of the trial. Gastrointestinal protein loss and indium scans were performed pre- and post-trial.

Nutritional Assessment

Full anthropometric and biochemical assessment of each patient's nutritional status was performed before the start of the trial, at weekly intervals during the trial and at the end. Anthropometric measurements were taken to calculate percentage ideal body weight (% IBW), triceps skinfold thickness (TST % standard), and mid-arm muscle circumference (MAMC % standard) (Shenkin & Steele, 1978). Blood samples were taken for analysis of albumin, calcium, phosphate, magnesium, zinc, copper, transferrin, iron, vitamins A, E, C, B_1, B_2, B_6, B_{12}, and red cell folate (See Appendix 4.1 for laboratory methods). Twice weekly 24

hour urine collections were taken for urinary magnesium, zinc and nitrogen. Nitrogen balance was calculated as the difference between daily nitrogen intake and daily nitrogen output (urinary nitrogen plus 3g nitrogen to cover faecal and other nitrogen losses) (Shenkin & Steele, 1978). A full dietary history was taken on admission before the start of the trial.

Enteral Liquid Diets

The composition of both Elemental 028 (ED) and Enteral 400 (PD) diets (Scientific Hospital Supplies, Liverpool, UK) is shown in Table 8.2. ED is an elemental diet containing crystalline synthetic amino acids. It is considered to be hypoallergenic as it is free from whole protein. The polymeric diet, Enteral 400, is a whole protein diet (98% whole protein) derived from whey protein isolate, and it is therefore not considered to be hypoallergenic. Although the fat sources differ between the diets, the carbohydrate (maize based), maltodextrin, and the mineral and electrolyte compostion of both are similar due to the modular nature of the diets.

Each patient was randomised to receive for 28 days 2.4 litres per day of either the ED or the PD by nasogastric tube, controlled by a pump system (Flexiflo II, Abbott

	ELEMENTAL 028	*ENTERAL 400*
Total Energy (kcal)	2400	2400
Carbohydrate (g)	467	345
Fat (g) - arachis oil	40	71
- M.C.T. oil	-	23
Protein (g)		
- whey protein isolate	-	69
- amino acids	72	-
Osmolality (mosm/kg)	810	349

(Key ; values per 2.4 litres of diet)

TABLE 8.2

Composition of Enteral Liquid Diets

Laboratories, Maidenhead, UK). Each patient was scheduled to receive 2400 kcal daily whether in the form of ED or PD (Table 8.2). The type of diet was known only to the dietetic staff. The double blind nature of the trial was achieved by the dietetic staff covering the food reservoir with a large plastic bag and wrapping tape around the giving sets from the pump. The patients were prevented from taking other dietary intake during the 28 day trial period, except for tea and coffee without milk.

Statistical Analysis

Most of the indices for disease activity were not normally distributed and the Wilcoxon Rank Sum Test was used to compare the disease activity pre- and post-trial between the two groups and also intra-group analyses. Comparison of the nutritiional status was made by the Student t test. Follow up of the patients and the time to relapse was compared by Chi square analysis with Yates correction. All results with $p < 0.05$ were considered to be significant.

RESULTS

Patients

Ten of the fourteen patients completed 28 days of feeding. Three patients in the ED group were withdrawn from the trial around 2 weeks and one PD group patient between 3 and 4 weeks. The 3 ED group patients were still included in the 2 week assessment. The reason for withdrawal in all patients was continuing disease activity. Dietary and nutritional assessments, and assessment of disease activity were made in all patients weekly until 4 weeks, or additionally at time of withdrawal from the study.

Dietary Intake

Patients in each group had a pre-trial assessment by the dietary staff of their calorie and protein intake (Table 8.3). Five patients in the ED group and 3 patients in the PD group had less than 90% of recommended daily intake (Passmore et al., 1974). During the trial only one patient in each group did not receive the recommended daily intake. There were no significant differences between the two groups with respect to the dietary intake during the study (Table 8.3).

	ED GROUP	*PD GROUP*
Pre-trial assessment of total daily calorie intake (kcal)	1655(203)	2023(817)
Pre-trial % RDA	71(6)	96(18)
Total daily calorie intake during trial (kcal)	2266(87)	2289(75)
Total daily nitrogen intake during trial (g)	10.9(0.2)	10.5(0.3)

(Key : all results mean (sem); all ED v PD comparisons $p > 0.05$; ED = elemental diet; PD = polymeric diet)

TABLE 8.3

Dietary Intake of Study Patients

Nutritionl Assessment

Nutritional assessment was performed on all patients pre-trial and weekly during the trial. Very few patients were significantly malnourished at entry to the study. Only 1 ED and 2 PD patients were less than 80% of their ideal body weight, and only 1 ED and 3 PD patients had serum albumin of less than 25 g/l. Several patients in both groups had minor trace metal and vitamin abnormalities. In both groups there was an overall improvement in nutritional parameters by the end of the trial. Only the patients in the PD group, however, showed a significant increase in weight during the trial. Most of the improvement in nutritional status had occured by the third week. There were no significant differences in the biochemical nutritional status between the groups, either before, during or after feeding (Table 8.4).

Disease Activity

At the start of the trial there were no significant differences between the groups in disease activity by both clinical scores and laboratory parameters (Table 8.5). The results for post-trial CDI score compared to the pre-trial assessment (ED v PD all patients, ED v PD only patients who completed 28 days feeding and PD intragroup analysis) were significantly improved for the PD group. At the end

	Pre-trial (n=14)	After 1 week (n=14)	After 2 weeks (n=14)	After 3 weeks (n=11, 3 ED withdrawn)	After 4 weeks (n=13,3 ED and 1 PD withdrawn)	Change from pre-trial after 2 weeks (n=14)	Change from pre-trial after 4 weeks (n=10,3 ED and 1 PD withdrawn)
Weight							
% IBW							
ED	84(79-98)	85(79-98)	84(80-87)	85(80-87)	86(80-88)	0(-3-3)	1(-2-4)
PD	80(68-113)	82(80-113)	84(71-113)	89(74-114)	*87(71-114)	3(-14-4)	3(1-8)
TST							
% Standard							
ED	85(73-103)	88(71-95)	88(72-94)	83(70-100)	84(67-97)	1(-9-3)	-6(-7-2)
PD	54(36-121)	53(36-121)	54(36-121)	54(36-121)	54(36-121)	0(-12-6)	0(-3-4)
MMC							
% Standard							
ED	86(80-94)	86(83-91)	87(84-91)	86(85-94)	86(79-91)	2(0-4)	-1(-3-2)
PD	84(76-113)	84(71-115)	82(71-102)	80(71-103)	81(80-103)	2(0-5)	3(-10-10)
Hb							
(11.5-15.5g/dl)							
ED	10.9(0.05)	11(0.4)	11.3(0.04)	11.5(0.06)	11.9(0.05)	-0.1(0.9)	0.7(0.6)
PD	11.1(0.9)	11.1(0.9)	10.9(0.6)	10.3(0.05)	10.7(0.6)	-0.1(0.7)	-0.7(0.9)
Albumin							
(35-50g/dl)							
ED	28(3)	28(3)	26(5)	28(4)	31(5)	1(1)	5(1.5)
PD	29(3)	31(3)	34(2)	35(3)	36(2)	4(1)	5(2)
Transferrin							
(2-4g/l)							
ED	2.1(0.1)	2.2(0.2)	1.9(0.3)	1.9(0.1)	2.2(0.2)	0.1(0.05)	0.4(0.1)
PD	1.9(0.2)	1.9(0.2)	2.3(0.1)	2.4(0.1)	2.4(0.1)	0.5(0.1)	0.8(0.2)
Calcium							
(2.2-2.6mmol/l)							
ED	2.42(0.05)	2.43(0.04)	2.45(0.04)	2.42(0.02)	2.44(0.01)	0.05(0.01)	0.04(0.01)
PD	2.50(0.04)	2.44(0.06)	2.44(0.04)	2.46(0.04)	2.46(0.04)	0.06(0.02)	0.07(0.01)
Phosphate							
(0.7-1.4mmol/l)							
ED	1.1(0.1)	1.2(0.2)	1.25(0.2)	1.3(0.1)	1.1(0.1)	0.12(0.04)	0.06(0.06)
PD	1.2(0.2)	0.9(0.3)	1.2(0.2)	1.2(0.1)	1.5(0.1)	0.2(0.05)	0.18(0.1)

Table 8.4 - Nutritional Assessment

Serum Mg (0.7-1.0 mmol/l)							
	ED	0.72(0.03)	0.74(0.04)	0.76(0.04)	0.77(0.05)	0.69(0.05)	0.11(0.04)	-0.03(0.01)
	PD	0.78(0.07)	0.87(0.06)	0.86(0.05)	0.88(0.05)	0.85(0.09)	0.14(0.08)	0.6(0.2)
Urinary Mg (2-11mmol/24h)							
	ED	1.5(0.3)	1.7(0.6)	2.6(0.9)	4.1(0.8)	2.2(0.6)	1.2(0.2)	0.9(0.2)
	PD	1.8(0.7)	2.6(0.8)	2.3(0.1)	1.8(0.7)	1.7(0.3)	0.7(0.3)	0.8(0.1)
Serum Zn (12-18umol/l)							
	ED	10.1(0.6)	10.1(0.8)	11(0.5)	12.1(0.08)	10.2(1)	0.4(0.1)	0.2(0.1)
	PD	11.6(2)	10.2(1.4)	9.1(1)	11.3(1.3)	12.1(1.5)	-1(0.3)	0.5(0.2)
Urinary Zn (4.6-10.6umol/24hr)							
	ED	6.1(1.1)	7.3(1.2)	9(1.4)	9.9(1.1)	6.8(1.6)	2.4(0.5)	1.5(0.9)
	PD	7.9(2.4)	16.3(3.4)	10.8(1.6)	8.6(1.7)	7.3(1.8)	3.0(0.6)	4.6(1.0)
Copper (10-15umol/l)							
	ED	23(2)	21(3)	19(2)	21(2)	17(4)	-1(0.3)	-2(0.3)
	PD	22(3)	21(2)	21(3)	23(3)	24(4)	0.2(0)	-1.1(0.2)
Iron (10-30umol/l)							
	ED	4.7(0.6)	4.2(0.1)	5.9(1.0)	5.0(1.0)	4.0(0.1)	0.8(0.1)	-0.5(0.2)
	PD	5.7(0.6)	6.9(1.1)	9.7(1.4)	11.1(1.0)	9.6(1.7)	3.4(0.4)	4(0.5)
Vitamin A (1-2.8umol/l)							
	ED	0.9(0.1)	1.1(0.2)	1.5(0.6)	1.3(0.4)	1.7(0.4)	1.0(0.04)	0.3(0.08)
	PD	1.2(0.1)	1.4(0.4)	1.5(0.3)	1.5(0.3)	1.4(0.1)	0.2(0.1)	0.1(0.05)
Vitamin E (14-39umol/l)							
	ED	18(1)	19(1)	20(2)	16(1)	20(1)	1(0.05)	0.6(0.01)
	PD	24(2)	26(2)	30(2)	31(2)	29(2)	2(0.08)	2(0.4)
Vitamin C (11-114umol/l)							
	ED	16(3)	18(2)	17(3)	20(2)	21(3)	0.5(0.1)	1.5(0.2)
	PD	22(4)	20(2)	21(3)	19(3)	23(1)	0.08(0.01)	1(0.1)

Table 8.4 Cont.

Vitamin B1							
(less than 25% activation)							
ED	10(3)	7(4)	8(2)	10(3)	12(7)	0.5(0.2)	1(0.3)
PD	11(4)	6(3)	3(1)	6(2)	4(2)	-4(0.5)	-3(0.4)
Vitamin B2							
(less than 60% activation)							
ED	14(6)	13(5)	16(2)	15(9)	14(2)	0.2(0.1)	0.1(0.05)
PD	28(6)	31(12)	10(4)	3(1)	16(3)	-4(0.6)	-3(0.5)
Vitamin B6							
(less than 150% activation)							
ED	29(17)	41(10)	28(8)	39(7)	33(3)	-2(0.3)	-0.5(0.1)
PD	75(20)	62(11)	41(8)	21(10)	28(12)	-8(0.5)	-7(0.4)
Vitamin B12							
(150-730pg/ml)							
ED	773(237)	784(204)	892(170)	794(194)	845(225)	102(46)	320(66)
PD	469(182)	456(173)	576(150)	436(104)	413(78)	180(54)	-40(30)
Red Cell Folate							
(106-614pg/ml)							
ED	393(129)	378(113)	384(174)	440(290)	325(69)	15(5)	-80(35)
PD	264(129)	270(93)	372(121)	367(145)	375(141)	82(40)	95(23)
Nitrogen Balance							
(g/day)							
ED		3.2(0.7)	2.8(0.6)	2.4(0.8)	2.1(0.6)		
PD		2.9(0.5)	1.8(0.7)	2.6(0.5)	2.9(0.7)		

[Key: ED = Elemental Diet; PD = Polymeric Diet; IBW = Ideal body weight; TST = Triceps skinfold thickness; MAMC = Mid-arm muscle circumference; Hb = Haemoglobin; Mg = Magnesium; Zn = Zinc; IBW, TST and MAMC expressed as median (range); All other parameters expressed as Mean (SEM); normal values in parentheses; * Pre and Post-trial for PD, $p<0.05$).

Table 8.4 Cont.

		PRE TRIAL (n=14)	AFTER 1 WEEK (n=14)	AFTER 2 WEEKS (n=14)	AFTER 3 WEEKS (n=11,3ED withdrawn)	AFTER 4 WEEKS (n=10,3ED and 1PD withdrawn)	CHANGE FROM PRE-TRIAL AFTER 2 WEEKS (n=14)	CHANGE FROM PRE-TRIAL AFTER 4 WEEKS (n=10,3ED and 1PD withdrawn)
CDI	ED	4(2-10)	4(1-6)	4(0-6)	2(0-3)	*2(0-3)	-2(-3-1)	-2(-7-[-2]
	PD	4(3-8)	2(0-3)	1(0-6)	1(0-6)	0(0-3)	-3(-5-2)	-3(-7-0)
ESR	ED	36(19-80)	40(10-76)	40(8-76)	42(5-50)	28(5-55)	-5(-15-5)	-12(-15-3)
	PD	54(29-80)	35(20-88)	55(20-100)	40(14-62)	32(10-80)	1(-32-26)	-15(-40-5)
CRP	ED	32(14-79)	26(10-70)	20(6-65)	7(8-65)	19(10-68)	-8(-23-7)	-15(-21-11)
	PD	30(15-93)	22(8-135)	7(6-44)	10(8-85)	14(8-98)	-22(-63-0)	-16(-83-32)
GI PROTEIN LOSS	ED	123(40-255)				55(36-230)		-25(-23-135)
	PD	34(15-118)				40(2-90)		-4(-20-22)
INDIUM SCAN	ED	2(0-5)				1(0-5)		0(-1-2)
	PD	2(0-5)				1(0-1)		-1(-5-0)

[KEY: ED = Elemental Diet; PD = Polymeric Diet; CDI = Crohn's Disease Index; ESR = Erythrocyte Sedimentation Rate; CRP = C-reactive Protein]
*ED v PD $p < 0.05$, PD group PRE v Post Trial $p < 0.05$. All results median, range.
Normal ranges CDI = 0, ESR = 15mm/h, CRP = < 10mg/l, GI protein Loss < 25ml/24h, Indium scan = 0.

Table 8.5 - Activity of Crohn's Disease

of 28 days feeding 5 (71%) of the PD group were in clinical remission (CDI < 2) compared with only 2 (29%) of the ED group. The other 2 ED patients had improved clinically with reduction in CDI score from 10 to 3 and from 6 to 3. There were no other significant differences in the other disease activity parameters, either comparing each group or pre- and post-trial results for each group.

Of the patients in clinical remission at exit from the trial the laboratory parameters of disease activity showed that 2 ED patients and 3 PD patients were in remission by the "simple" criteria of normal ESR and CRP, but that 1 of the ED patients still had an elevated GI protein loss of 36 ml/24 hours and 2 of the PD patients had indium scan scores of 1 or greater. Hence at exit from the trial only 1 of the ED patients and 1 of the PD patients fulfilled all the criteria of remission by laboratory parameters (ESR < 20mm/h; CRP < 10mg/l; GI protein loss < 25 ml 24h; Indium scan score < 1).

Of the patients who completed 28 days of feeding 2 ED patients required alternative therapy (1 steroid, 1 surgery), within a few weeks of stopping the trial and were not well enough to be discharged from hospital on resuming normal diet. Within 1 year the relapse rates for

the patients (ED v PD) who completed the trial were 100 v 66% ($p > 0.05$).

DISCUSSION

Diet Trial - Induction of Remission

This prospective controlled double-blind study of elemental and polymeric diet in active Crohn's disease has shown that the polymeric diet (PD) is as effective as the elemental diet (ED) in improving clinical and laboratory parameters of Crohn's disease. The polymeric and elemental diets given to the patients were of equivalent nutritional composition. The only differences being in the presentation of the protein source, being whole protein in the polymeric preparation and pure amino acids in the elemental preparaation.

Although this study demonstrated clinical and laboratory improvement in most patients in both dietary groups, a complete remission of disease, (as defined by CDI < 2, ESR < 20 mm/h, CRP < 10mg/l, GI protein loss < 25 ml/24h, and Indium scan score < 1), was only achieved in one patient in the elemental diet group and one patient in the polymeric diet group. Using less rigid criteria, as have been used in previous studies (O'Morain et al., 1984; Saverymuttu et al., 1985B; Sanderson et al., 1986), clinical remission occured in 5 (71%) of the PD group and only 2 (29%) of the ED group. It is not clear why the remission rates were not as good as these previous studies. This may be due to slightly smaller groups,

different study criteria or be an indication of the true therapeutic value of these diets.

Nutritional Assessment

Nutritional assessment showed slight improvement in all parameters tested, with a significantly greater increase in weight for the PD group. This improvement occurred steadily during the treatment period. Patients who had to be withdrawn from the study due to continuing or worsening symptoms also showed evidence of early nutritional improvement.

Ideal Diet Trial

Although other studies using elemental diet in active Crohn's disease have been controlled (O'Morain et al., 1984; Saverymuttu et al., 1985B; Sanderson et al., 1986; Seidman et al., 1986), they have not been double-blind nor has the elemental diet been given by naso-gastric tube under close supervision in hospital, as in this study.In the previous studies, after a period of stabilisation in hospital, usually one week, patients were discharged home to continue their elemental diet as sole therapy. Observation of the patients' "true diet" is extremely important and can only be effectively performed on an in-patient basis. In this study other dietary intake was not

accessible to the patients. Very few patients are tolerant of an elemental diet by mouth and often it has to given by naso-gastric tube, which requires effective hospital supervision in the short-term. To accurately assess the comparative efficacy of elemental and polymeric diets as "primary therapy" in active Crohn's disease, it is necessary to use a double-blind controlled model and to make sure the diets were given as sole therapy to patients.

It is also difficult to assess a controlled trial of dietary methods in active Crohn's disease because of the variable natural history of the disease, the possibility of spontaneous improvement and as the disease characteristics vary considerably. Some of these factors may have interfered with the results. However, this study has attempted to achieve controlled status in that both groups of patients had similar disease location and disease activity at entry to the study. The small number of patients who completed the study is somewhat disappointing, but reflects the strict entry criteria, in particular the exclusion of patients who had received steroid therapy, and the demanding patient co-operation for the study.

Conclusion

In conclusion, a nutritionally equivalent polymeric diet appears to be as effective as an elemental diet in improving clinical and laboratory evidence of activity in Crohn's disease and inducing remission in some patients.

Improvement occurring in Crohn's disease following the use of liquid diets may be a reflection of nutritional improvement rather than a specific effect of the diet itself. If this is so, polymeric diets, which are easier to use and cheaper than elemental diets, may be preferable to elemental diets.

CHAPTER 9

PRACTICAL ASPECTS AND THERAPEUTIC EFFICACY OF HOME ENTERAL NUTRITION

INTRODUCTION

Home enteral nutrition (HEN) for Crohn's patients was introduced for correction of nutritional deficiences before elective surgery (Goode et al., 1976). Since then the indications for HEN have expanded to cover refractory malnutrition, management of the short bowel syndrome and growth retardation (Main et al., 1980; McIntyre et al., 1983). However subsequent reports have included small number of patients, have not included results of long-term outcome and have avoided discussion of practical problems associated with HEN.

AIMS OF STUDY

The aims of this study were : to investigate the practical aspects of HEN and in particular all technical problems; to document the incidence of complications related to HEN; to determine patients' compliance of the technique and their impression of any change in their life-style produced by HEN; to determine the therapeutic efficacy of HEN; to assess the use of the new modular liquid diets in HEN.

METHODS

Patients

Sixteen patients (9 males, 7 females) were included in this study. The mean age was 21.9 years, (range 13-44). The location of Crohn's disease was confined to the small bowel (6), small and large bowel (7) and large bowel alone (3). Several patients were taking mineral supplements including zinc (4), magnesium (2), iron (5), and copper (1), and anti-inflammatory drugs which included sulphasalazine (8), mesalazine (1), prednisolone (6), and azathioprine (1).

Individual Patient Clinical Summaries

Patient 1 13 year old male who was diagnosed as having Crohn's colitis at the age of 12. Despite few gastrointestinal symptoms and little evidence of disease activity he failed to gain weight and although his height was within the 25th centile he was pre-pubertal. He was anorexic, consuming only 1650 kcals per day. HEN was started to to correct his poor oral intake in an attempt to stimulate puberty.

Patient 2 17 year old male who presented in 1986 with diarrhoea and was found to have Crohn's disease of small and large bowel. He had received steroids with some improvement in disease activity but remained underweight and anorexic. HEN was started for nutritional support.

Patient 3 40 year old male who had a right hemicolectomy for Crohn's disease in 1976. He required a further small bowel resection in 1980 for obstructive symptoms. He was subsequently found to have extensive small and large bowels disease. He presented in June 1986 with severe malnutrition and active disease. HEN was started after a period of inpatient intravenous nutrition to continue nutritional support.

Patient 4 28 year old female who had extensive small bowel Crohn's disease and required small bowel resections at the age of 24 and 26. She presented in June 1986 with severe anorexia and nutritional deficiency.

Patient 5 This 14 year old male presented with delayed stature, weight loss and anorexia in February 1984, and was found to have Crohn's disease of the distal ileum and proximal colon. Despite anti-inflammatory drug therapy he failed to gain weight or height and was started on HEN in October 1984.

Patient 6 17 year old female was found to have small bowel Crohn's disease in 1985, requiring continuous steroid therapy. She continued to have mildly active disease and gradually lost weight. HEN was started in November 1986 for nutritional support.

Patient 7 30 year old male who required a subtotal

colectomy for Crohn's disease in 1980. He developed abdominal pain in 1986 and was found to have disease affecting both small and large bowels. His symptoms improved with anti-inflammatory therapy but he failed to gain weight. HEN was started in November 1986.

Patient 8 26 year old female who was diagnosed as having anorexia nervosa at the age of 16. Subsequently she required a panproctocolectomy for severe colonic Crohn's disease at the age of 21, and a small bowel resection at the age of 22. In 1985 small bowel radiology showed disease affecting her mid ileum. By August 1985 she was malnourished and HEN was commenced.

Patient 9 25 year old female who had required a right hemicolectomy at the age of 20. She re-presented in 1986 with abdominal pain and diarrhoea and was found to have recurrence at the anastomosis. Despite anti-inflammatory therapy she failed to improve, but she refused sugery. HEN was started in June 1987 for nutritional support.

Patient 10 18 year old male who had required a right hemi-colectomy for Crohn's disease at the age of 14, followed by small bowel resection two years later. He had marked growth retardation. In October 1984 HEN was commenced in an attempt to reverse the growth retardation.

Patient 11 16 year old female of normal height who

presented in 1985 with diarrhoea and was found to have colonic Crohn's disease.She required continuous steroid therapy and by October 1986 had lost considerable amount of weight. HEN was commenced for nutritional support.

Patient 12 15 year old male who presented in February 1986 with diarrhoea and delayed stature. He was found to have Crohn's disease of the distal small bowel and large bowel. Steroid therapy improved his symptoms but he failed to gain weight. HEN was started in May 1986.

Patient 13 16 year old male who developed abdominal pain and weight loss and was found to have small and large bowel Crohn's disease in 1987. He was growth retarded and HEN was commenced in July 1988 in an attempt to reverse this.

Patient 14 44 year old male who had a subtotal colectomy for Crohn's disease in 1981. He developed recurrence of his Crohn's disease in the large bowel with a colo-cutaneous fistula. He was malnourished and HEN was started in June 1987 in an attempt to improve his malnutrition and heal the fistula.

Patient 15 27 year old female who required a right hemi-colectomy in 1985 for Crohn's disease. She developed recurrence of disease in the neo-terminal ileum and colon and became malnourished. She failed to improve with

steroids, and HEN was started in January 1987.

Patient 16 15 year old female who was found to have Crohn's disease of the distal small bowel and proximal colon in 1986. Steroid therapy improved her symptoms but she continued to lose weight. HEN was started in February 1987 in an attempt to reverse the malnutrition.

The primary indications for HEN were nutritional support (10), correction of growth retardation (5) and healing of fistula (1) (Table 9.1). Several of the 16 patients had a history of previous bowel resections, and 4 patients had required two or more resections.

Study Design

Each patient completed a dietary diary card before starting HEN and on follow-up. Nursing staff skilled in methods of nutritional support instructed each patient in the techniques of passing a nasogastric tube, the preparation of the enteral liquid feeds and the mechanics of the feeding pump. A questionnaire covering all practical aspects of HEN was completed in addition to a simple sleep diary. Most patients were studied in the latter stages of their periods of HEN. All patients were followed up regularly and anthropometric indices and

biochemical screens were checked.

All patients used the Flexiflo feeding system (Abbott Laboratories, UK), incluing the Flexiflo volumetric feeding pump. Patients used Vygon paediatric feeding tubes (Vygon UK Ltd) and checked position by aspirating gastric fluid.

RESULTS

Patient training

All patients were trained as inpatients and the time taken for training ranged from 1-2 days for 13 (81%) patients to 7 days for 3 (19%) patients.

Therapeutic Efficacy of HEN

Patients received HEN for a median period of 17 months (range 4-54) (Table 9.1). All patients, except patient 7, have stopped.

Types of Enteral Liquid Diets and Duration of Infusion

All patients fed themselves overnight. 8 patients used Ensure (Abbott Laboratories, UK), 4 patients used Elemental 028 (Scientific Hospital Supplies, Liverpool, UK) 1 patient used Osmolite (Abbott Laboratories, UK), 1 patient Enteral 400 (Scientific Hospital Supplies, Liverpool, UK), 1 patient Triosorbon (E.Merck Ltd, UK) and 1 patient Reabilan (Roussell, UK) (Table 9.2). The median volume of feed infused per night was 1000 mls (range 750 - 1500), infused over 10-12 hours (Table 9.2).

Preparation time for HEN

Every patient found that the daily preparation of the feed was easy to perform. Time to set up the feed and position the nasogastric tube ranged from 5 minutes (2), 10 minutes (6), 15 minutes (7) to 20 minutes (1). Only 2 patients required assistance from a relative.

PATIENT	*DURATION OF HEN (months)*	*INDICATION FOR HEN*	*REASON FOR STOPPING*	*RESULT*
1	21	pre-pub	post-pub	success
2	24	mal, act dis	well	success
3	14	post IVN maintain weight	weight loss	failure
4	9	mal	well	success
5	28	GR	gro norm	success
6	4	mal	well	success
7	54	mal, SB	-	success
8	28	mal, SB	well	success
9	4	mal, act dis	surgery	failure
10	30	GR, act dis	well gro norm	success
11	6	mal, act dis	well	success
12	16	GR	gro norm	success
13	30	GR, act dis	gro norm	success
14	17	fist, mal	fist healed	success
15	12	mal	well	success
16	6	mal	well	success

(Key : pre-pub = pre-pubertal; post-pub = post pubertal mal = malnutrition; act dis = active disease; GR = growth retardation; gro norm = growth normal; fist = fistula; post-IVN = post intravenous nutrition; SB = short bowel)

TABLE 9.1

Therapeutic Efficacy of HEN

PATIENT	DIET	FREQUENCY PER WEEK	VOLUME (mls)	INFUSION TIME (hrs)
1	Ensure	5	1000	10
2	Osmolite	5	1000	10
3	Elemental 028	7	1000	10
4	Elemental 028	7	1500	12
5	Triosorbon	5	1000	10
6	Ensure	7	1250	10
7	Ensure	7	1000	10
8	Elemental 028	4	1200	10
9	Ensure	7	750	10
10	Elemental 028	7	1500	12
11	Ensure	7	1250	10
12	Ensure	5	1000	10
13	Ensure	5	1000	10
14	Reabilan	7	1500	12
15	Ensure	7	750	10
16	Enteral 400	7	1200	10

TABLE 9.2

Enteral Liquid Diets and Infusion Times

Sleep Disturbance During HEN

Six patients complained of disturbed sleep during HEN, usually due to increased nocturnal arousal due to urination (4), defaecation (1) and noise of pump (1).

Problems with Equipment

Four patients complained that the Flexiflo pump was heavy for portable use. One of the patients also complained of the noise of the pump during sleep.

Complications of HEN

No patients experienced symptoms of cough, wheeze, dyspnoea, regurgiation or aspiration of feed. No patient required treatment for a chest infection during the periods of HEN. All patients felt that HEN was completely safe.

Patients' Assessment of the Efficacy of HEN

Eleven patients (69%) felt better on HEN which had improved their life-style (Table 9.3). Most attributed this to inproved daily activity and reduction in hospital admissions. Four patients (25%) felt no improvement and 1 patient (6%) felt worse on HEN.

Dietary Intake During HEN

Before starting HEN the dietary intake from the patients' daytime diet was very low with a mean (sem) intake of only 1240(70) kcals/day. This represented

PATIENTS	*BETTER LIFE STYLE*	*LESS HOSP ADM*	*IMPROVED SYMPTOMS*	*IMPROVED DAILY ACTIV*	*NO CHANGE*	*FAILURE*
1	*	*	*	*		
2	*	*	*			
3						*
4	*	*	*	*		
5		*			*	
6	*		*	*		
7					*	
8	*	*	*			
9					*	
10	*		*			
11	*		*	*		
12	*	*	*	*		
13	*		*	*		
14	*	*	*	*		
15		*			*	
16	*	*	*			

(Key : hosp = hospital; adm = admission; activ = activity)

TABLE 9.3

Patients' Assessment of the Efficacy of HEN

approximately 49% of the RDA. During HEN the daytime diet increased a little to 1307(85) kcal/day, but this increase was not significant (Table 9.4). The mean (sem) intake from HEN was 993(65) kcal/day and this represented 43(3)% of the total dietary intake. Despite the use of HEN, 2 patients failed to receive more than 1900 kcals/day.

Anthropometric Results

The anthropometric results are shown in Table 9.5. The mean (sem) increase in weight (kg) was 8.5(1.5), in skinfold (TST) was 1.3(0.4) mm, and in mid arm muscle circumference (MAMC) 1.7(0.4) cm. Weight increase expressed as % of pre-HEN weight was 25(3).

Therapeutic Goal

Therapeutic goal was achieved in 14 (88%) patients. Patient 3 did not maintain his weight on HEN and was switched over to home intravenous feeding. Although patient 5 relapsed on HEN his growth retardation was reversed. Patient 9 continued to have severe disease activity and failed to gain a significant amount of weight. During their period on HEN none of the patients received additional therapy for their Crohn's disease. At the end of HEN most patients disease activity had improved (see Chapter 11 and Table 11.6).

PATIENTS	*INTAKE FROM DAYTIME DIET (kcal/day)*	*INTAKE FROM HEN (kcal/day)*	*TOTAL INTAKE (kcal/day)*	*% OF TOTAL INTAKE FROM HEN .*
1	1650	700	2350	30
2	1480	1000	2180	32
3	800	1000	1800	56
4	650	1500	2150	69
5	1440	700	2140	33
6	1300	1250	2550	49
7	1800	1000	2800	36
8	980	1200	2180	55
9	1260	750	2010	37
10	1340	1500	2840	53
11	1460	1250	2710	46
12	1640	700	2340	30
13	1760	700	2460	28
14	1060	1250	2310	54
15	1180	700	1880	37
16	1460	1200	2660	45
TOTAL	1307(85)	993(65)	2251(94)	43(3)

(Key : total results expressed as mean (sem))

TABLE 9.4

Intakes from Daytime Diet and Liquid Diet During HEN

PAT	WEIGHT			TST			MAMC		
	pre	post	Δ	pre	post	Δ	pre	post	Δ .
1	45.1	61.0	15.9	4.8	6.0	1.2	19.3	21.0	1.7
	(71)	(93)	(22)	(38)	(45)	(7)	(76)	(80)	(4)
2	50.0	60.3	10.3	11.0	12.0	1.0	20.0	22.0	2.0
	(74)	(89)	(15)	(88)	(96)	(8)	(79)	(87)	(8)
3	70.0	61.2	-8.8	11.5	7.6	-3.9	21.6	18.4	-3.2
	(95)	(83)	(-7)	(92)	(61)	(-31)	(85)	(73)	(-12)
4	37.0	43.5	6.5	8.4	9.6	1.2	14.1	16.1	2.0
	(74)	(87)	(13)	(51)	(58)	(7)	(61)	(69)	(8)
5	29.0	41.0	12.0	6.0	9.0	3.0	14.4	18.4	4.0
	(54)	(76)	(22)	(48)	(72)	(24)	(57)	(73)	(16)
6	41.0	47.0	6.0	10.5	12.0	1.5	18.2	19.2	1.0
	(77)	(89)	(12)	(64)	(73)	(9)	(78)	(83)	(5)
7	43.0	52.0	9.0	3.5	7.3	3.8	16.5	19.8	3.3
	(62)	(75)	(13)	(28)	(58)	(65)	(65)	(78)	(13)
8	40.0	48.0	8.0	10.0	11.3	1.3	16.4	18.0	1.6
	(65)	(77)	(12)	(61)	(68)	(7)	(71)	(78)	(7)
9	44.7	45.7	1.0	8.2	9.0	0.8	15.4	15.5	0.1
	(77)	(79)	(2)	(50)	(54)	(4)	(66)	(66)	(0)
10	35.0	49.0	14.0	10.5	11.2	0.7	17.7	20.2	2.5
	(53)	(70)	(17)	(84)	(98)	(15)	(69)	(80)	(11)
11	41.0	48.0	7.0	10.1	12.0	1.9	16.0	18.0	2.0
	(82)	(96)	(14)	(61)	(73)	(12)	(69)	(78)	(9)
12	37.0	52.0	15.0	6.0	10.0	4.0	17.6	20.1	3.5
	(56)	(79)	(23)	(48)	(80)	(32)	(69)	(79)	(10)
13	29.0	43.0	14.0	5.5	7.0	1.5	16.4	19.0	2.6
	(44)	(65)	(21)	(44)	(56)	(12)	(65)	(75)	(10)
14	46.5	58.0	11.5	4.4	6.1	1.7	20.9	22.4	1.5
	(68)	(86)	(18)	(38)	(49)	(11)	(83)	(89)	(6)
15	43.0	47.0	4.0	8.0	7.8	-0.2	18.5	18.2	-0.3
	(80)	(88)	(8)	(48)	(47)	(-1)	(80)	(80)	(0)
16	30.0	40.5	10.5	4.2	6.0	1.8	15.0	17.1	2.1
	(56)	(75)	(19)	(25)	(48)	(23)	(65)	(74)	(9)

[Key : TST = triceps skinfold thickness; MAMC = mid arm muscle circumference; figures in parenthesis are the % of IBW or % standard results].

TABLE 9.5 Anthropometric Details of Individual Patients

DISCUSSION

This study has shown that the techniques of HEN can be easily taught to patients with Crohn's disease. Most of the patients mastered the technique within 1-2 days. Berezin et al. (1988) have shown similar results in a group of paediatric patients who were in fact instructed at home. Most of the patients did not encounter any major practical problems and they all remained complication-free during their period of HEN.

The success of HEN can be estimated by both the patients' assessment of the technique and if the therapeutic goals have been achieved. Eleven (69%) patients felt better on HEN and only 1 (6%) patient felt worse. Fourteen (88%) patients were considered to have attained their pre-HEN therapeutic goal. In particular, on HEN patients gained 25(3)% (mean, sem) of their ideal body weight (IBW) compared with their pre-HEN weight and post-HEN 50% of patients' weights were > 80% of their IBW compared with only 19% of patients pre-HEN. Interestingly without additional treatment for their Crohn's disease, most of the patients disease activity improved.

In summary, HEN offers a method of long-term nutritional support which does not require extensive training, is acceptable to patients who require little assistance, and

is free from complications. The main advantage of HEN compared with home intravenous feeding is the ease of administration and lack of complications.

CHAPTER 10

MAGNESIUM DEFICIENCY IN PATIENTS ON HOME ENTERAL NUTRITION

INTRODUCTION

Magnesium and Nutrition

Multiple nutritional deficiencies are frequently found in Crohn's disease (Beekan, 1975; Harries & Heatley, 1983B). As it is less common for a single deficiency to arise, the clinical manifestations from a particular deficiency can be masked by other deficiencies and also by underlying disease activity. However, the clinical aspects of pure magnesium deficiency have been studied using metabolic studies on human volunteers (Dunn & Walser,1966; Shils, 1969), and include irritability, lethargy, tetany and tremor. Cardiac arrhythmias can also arise (Iseri et al., 1975). The symptoms and clinical signs of magnesium deficiency can be reversed within hours of repletion (Shils, 1969).

Magnesium, an essential mineral, is required as co-factor in at least 300 enzyme systems involved in intermediary metabolism, including adenosine triphosphatase(ATP) (Shils, 1988). Only 1% of the total body magnesium is in extracellular fluid, the majority is distributed in bone (65%), muscle (27%) and other cells (7%). Magnesium is absorbed throughout the small bowel.

Approximately 30-50% of the ingested magnesium is absorbed and subsequently excreted in the urine (Graham et al., 1960).

Prevalence of Magnesium Deficiency in Crohn's Disease.

As magnesium is abundant in food magnesium deficiency in patients with Crohn's disease is usually seen in conditions producing high faecal outputs including severe diarrhoea, fistulas and short bowel syndrome. Booth et al. (1963) were the first to describe hypomagnesaemia in seven patients following small bowel resections, and further reports appeared later (Heaton & Fourman, 1965; Gerach et al., 1970). Nine of 63 patients (14%) with Crohn's disease had low serum magnesium (Beekin, 1975). Main et al. (1981) reported that 6 out 17 patients with severe Crohn's disease requiring intravenous nutrition had low serum magnesium, and 15 patients (88%) had low urinary magnesium. In this study magnesium deficiency was severe enough to produce symptoms in two patients.

Urinary magnesium excretion was below the normal range for Swedish adults in 32% of Crohn's patients who had undergone a small bowel resection (Hessov et al., 1983). Sjogren et al. (1988), using muscle biopsy intracellular analysis and intravenous magnesium infusions, found reduced magnesium stores in 30 patients with relatively

mild disease who were not particularly malnourished.

Assessing Magnesium Status

The variable prevalence rates for magnesium deficiency arise due to different patient populations and different methods of assessing magnesium status. In human volunteers who were made magnesium deficient, urinary magnesium fell within seven days of starting a magnesium deplete diet and stayed at a low level till repletion (Shils, 1969). Plasma magnesium fell more slowly. It is argued that as magnesium is an intracellular ion, low plasma levels may underestimate the frequency of magnesium deficiency (Lim & Jacobs, 1972). Several authors have suggested that tissue magnesium levels should be used. However studies have shown conflicting results. Abraham et al. (1986) have advocated the use of red blood cell and mononuclear cell magnesium levels. In another study, Sjogren et al.(1988) found that red blood cell magnesium levels of Crohn's disease patients who were magnesium deficient did not correlate with the other tissue levels including muscle, and were the same as normal controls. Only one out of ten chronic alcoholics with magnesium deficiency had a low red blood cell magnesium (Lim & Jacobs, 1972).

Pure magnesium deficiency in human volunteers is associated with normal muscle magnesium levels and Dunn &

Walser (1966) concluded that the lost magnesium must have arisen from bone. This finding was not confirmed by Lim & Jacobs study (1972) of ten chronic alcoholics who had low muscle magnesium levels but normal bone levels. Alfrey et al. (1974) found that muscle magnesium was directly related to muscle potassium level and may reflect changes in total body potassium rather than an accurate measure of total body magnesium.

More recently Holm et al. (1987) and Sjogren et al. (1988) have advocated the use of the magnesium load test, measuring the muscle magnesium level after an intravenous infusion of magnesium. This test is potentially dangerous as it involves an intravenous infusion of magnesium, in addition to being time-consuming and complicated. It is interesting to note from the study by Sjogren et al. (1988) that the basal urinary magnesium levels were statistically lower than the control group. A combination of plasma and urinary magnesium levels appears to be sufficient to assess magnesium depletion.

AIMS OF STUDY

The aims of this study were to investigate the magnesium intake of patients on home enteral nutrition (HEN), the contribution of the magnesium intake from HEN, and their magnesium status.

PATIENTS AND METHODS

Patients

Nine patients were investigated. There were 5 females and 4 males with a mean age of 26 years (range 16-40). The extent of their Crohn's disease was confined to the small bowel (5), small and large bowel (3), and large bowel alone (1). Two of the younger patients had short bowel syndrome with high faecal output and had growth retardation. All the patients were on overnight feeding, receiving between 650-1200 mls over 8-12 hours.

The patients received HEN for a median of 7 months (range 2-17 months). The types of enteral liquid diets used were Ensure (4 patients) (Abbott Laboratories,Maidenhead, U.K.), Elemental 028 (4 patients) (Scientific Hospital Supplies, Liverpool, U.K.) and Triosorbon (1 patient) (E. Merck Ltd, Alton, U.K.).

Assessing Magnesium Intakes and Deficiency

Total calorie and magnesium intakes were calculated from dietary assessment of daytime food intake (using the Salford University "Microdiet" Computer System), magnesium supplements and enteral liquid diets. A 10 ml blood sample was taken for serum magnesium and a 24h urine collection for urinary magnesium excretion, measured by atomic absorption spectrometry. Magnesium deficiency was defined as serum magnesium < 0.7 mmol/l and/or urinary magnesium <

2 mmol/24h. Magnesium status was determined before starting HEN and at follow-up, when magnesium deficient patients were allocated to Group 1 and magnesium replete patients to Group 2.

Statistical Analyses

Statistical analyses of the differences between both groups were performed using the Student t test, and p values < 0.05 were considered to be significant.

RESULTS

Magnesium Status

There were no significant differences in the magnesium status of the total patient group between the pre- feeding and follow-up assessments (Table 10.1). However, at follow-up, 4 patients (Group 1) were found to be biochemically magnesium deficient, although no patient had clinical magnesium deficiency (Table 10.2). Two patients in Group 1, both with short bowel syndrome and high faecal output, had been magnesium deficient before starting HEN. Five patients had normal magnesium status (Group 2).The diets used for HEN and the magnesium content of the diets are summarised in Table 10.3.

Dietary Intakes

There were no significant differences in the total calorie intake (kcal/day) between group 1 2850(300) (mean, sem) and Group 2 3150(400) and in the percentage of total calories derived from HEN 34(6) compared with 37(5)%.Total daily magnesium intake did not differ significantly between Group 1, 19.5(2.6) mmol/24h and group 2, 20.1 (2.1) mmol/24h. However, patients in group 1 had a significantly smaller percentage of total magnesium intake derived from HEN 32(4)% compared with Group 2 patients 47 (5)% ($p<0.05$) (Table 10.4). One patient in Group 1 was taking magnesium supplements (Maalox, Rorer

	Pre HEN		*Follow-up*	
	Serum Mg (mmol/l)	*Urinary Mg (mmol/24h)*	*Serum Mg (mmol/l)*	*Urinary Mg (mmol/24h)*
Total group	0.79(0.04)	2.5 (0.3)	0.76(0.03)	2.4 (0.6)
Group 1	0.73(0.04)	1.8 (0.2)	0.68(0.04)	1.1 (0.3)
Group 2	0.84(0.06)	2.9 (0.4)	0.82(0.02)	3.4 (0.8)

[Key : all results mean(sem)]

TABLE 10.1

Magnesium Status of Study Patients

	Pre HEN		*Follow-up*	
	Serum Mg (mmol/l)	*Urinary Mg (mmol/24h)*	*Serum Mg (mmol/l)*	*Urinary Mg (mmol/24h)*
Patients				
Group 1				
1	0.68	1.3	0.64	1.6
2	0.75	2.0	0.72	0.6
3	0.72	2.1	0.62	0.5
4	0.76	1.8	0.75	1.6
Group 2				
5	0.91	3.2	0.88	3.4
6	0.76	4.5	0.79	6.3
7	0.80	2.2	0.79	2.6
8	0.81	2.4	0.78	2.6
9	0.93	2.6	0.87	2.1

TABLE 10.2

Magnesium Status of Individual Patients

	Group 1	*Group 2*	*Mg content of diet (mmol per 1000 kcal)*
Ensure (Abbott)	1	3	8.5
Elemental 028 (SHS)	3	1	6.7
Triosorbon (Merck)	-	1	7.5

TABLE 10.3

Enteral Liquid Diets

Patients (liquid diet)	Daily food (mmol/24h)	Supplements (mmol/24h)	HEN (mmol/24h)	Total Mg intake (mmol/24h)	Percentage total from HEN
Group 1					
3 (Elemental 028)	16.2	-	7.4	23.6	31
4 (Elemental 028)	18.9	-	4.6	23.5	20
8 (Elemental 028)	7.3	-	5.6	12.9	43
9 (Ensure)	3.4	8.4	6.4	18.2	35
Group 2					
5 (Triosorbon)	10.2	-	7.5	17.7	42
6 (Ensure)	15.2	-	10.6	25.8	41
7 (Ensure)	5.5	-	8.5	14.0	61
10(Elemental 028)	16.0	-	8.0	24.0	33
11(Ensure)	8.5	-	10.7	19.2	56

Table 10.4 - Magnesium Intake

Pharmaceuticals, Eastbourne, U.K.).

DISCUSSION

Magnesium Deficient Patients

Four patients (44%) on long-term home enteral nutrition were found to have biochemical evidence of magnesium deficiency, although no patient had signs of magnesium deficiency. Two patients in group 1 who were magnesium deficient before starting HEN (patients 1 and 4) had short bowel syndrome with high faecal output. Only one of these patients (patient 4) had been taking magnesium supplements. Dietary intake of magnesium is usually well above the recommended daily allowance (RDA) (Mineral Elements, 1977) of 15 mmol per day. However this study has shown that some patients with Crohn's disease who require nutritional support have an inadequate magnesium intake from their diet. Five of the 9 patients (56%) had magnesium dietary intakes of 10 mmol/day or less. The inadequate oral intake was corrected by HEN and magnesium supplements in 3 of the 5 patients.

Magnesium Intakes

There were no significant differences in the total magnesium intakes between the two groups. However the percentage of the total magnesium intake from HEN was significantly less in Group 1. This may be partly

explained by the frequent use of Elemental 028 in Group 1 patients which has a lower magnesium content than the other liquid diets. Most patients starting HEN will have a precarious nutritional balance. It is important to check their magnesium status on a regular basis as the provision of HEN may not protect them from magnesium deficiency. Many patients on HEN may also require magnesium supplements.

CHAPTER 11

VITAMIN STATUS OF PATIENTS WITH CROHN'S DISEASE ON HOME ENTERAL NUTRITION

INTRODUCTION

Vitamin A Deficiency

Vitamin deficiencies can occur in Crohn's disease. Vitamin A deficiency has been reported in a few patients with Crohn's disease (Russell et al., 1973; Main et al., 1983), and has attracted some attention due to the effect of vitamin A on epithelial cells and the possible protective function on gut permeability (Dvorak, 1980). The previous studies have mainly involved outpatients with relatively inactive disease. Imes et al. (1987) found that serum retinal measurements were normal in 137 outpatients with Crohn's disease, despite 34% of patients taking less than the recommended daily allowance for vitamin A. Factors commonly found in vitamin A deficient patients were extensive small bowel disease and weight < 80% of ideal (Main et al., 1983).

Other Vitamin Deficiencies

Other heterogeneous groups of patients with Crohn's disease have been found to have deficiencies of folate,

vitamin B_{12}, and vitamin D (Rosenberg & Bowman, 1983). There is little information on complete assessments of multiple vitamin deficiencies in Crohn's disease, especially in patients with nutritional deficiencies who may require long-term enteral nutrition.

Vitamin Content of Liquid Diets

Fortunately the vitamin content of most commercial liquid diets used for HEN is much higher than the recommended dietary allowances (Shenkin, 1988). Berner et al. (1989) concluded that the high vitamin content of the commercial diets explained the near normal plasma vitamin levels in a group of patients with neoplasias who were totally dependent on HEN. It is unknown if the high vitamin content of the commercial diets would compensate for potential vitamin malabsorption in patients with Crohn' disease who are on long-term HEN.

AIMS OF STUDY

The aims of this study were to assess the vitamin status of patients with Crohn's disease before starting HEN, and on completion of HEN when they would be expected to be nutritionally replete.

PATIENTS AND METHODS

Patients

Sixteen patients (9 males, 7 females) with mean (range) age of 21.9 (13-44) years, were investigated. Full descriptions of the patients' clinical histories can be found in Chapter 9 of this thesis. The site of disease was small bowel (6), small and large bowel (7) and large bowel alone (3).

All patients were assessed before starting HEN and at the end of their course. Patient 7 was on continuous HEN at the time of his follow-up assessment. The mean (range) duration of HEN was 21.6 (4-54) months.

Patients' Diets During HEN

Eight patients were taking Ensure (Abbott Laboratories, Maidenhead, UK) as their liquid diet, one patient Osmolite (Abbott Laboratories), four patients Elemental 028 (Scientific Hospital Supplies, Liverpool, UK), one patient Enteral 400 (Scientific Hospital Supplies), one patient Reabilan (Roussell Laboratories, Uxbridge, UK), and one patient Triosorbon (E. Merck Ltd, Alton, UK).

Assessment of Dietary Intakes

Pre- and post-HEN assessments of calorie and vitamin intakes were made from the patients' daytime diets using the Salford University "Microdiet" Computer System. The calorie and vitamin intakes from HEN and from vitamin supplements were recorded. Intakes were compared with the Recommended Dietary Allowances (Passmore et al., 1974).

Nutritional Assessments

20 mls of blood was taken for measurement of vitamin A, E, C, B_1, B_2, B_6, B_{12}, and red cell folate using laboratory methods which are summarised in Appendix 4.1. Most of the water soluble vitamins were measured using enzyme activation analysis (Shenkin, 1988). Serum albumin and transferrin were also measured.

Disease Activity Assessment

Disease activity pre- and during HEN was measured using the modified Crohn's disease index (MOD CDI) and the C-reactive protein level.

RESULTS

Assessment of Dietary Intakes

The pre-HEN daytime dietary calorie was low at 1240(70) kcal/day [mean(sem)], which represented 49(4) % of the RDA (Table 11.1). During HEN the daytime dietary intake increased slightly to 1307(85) kcal/day. The total intake on HEN increased significantly to 2251(94) kcal/day ($p > 0.05$), which was 90(7)% of the RDA. The mean(sem) percentage contribution from HEN was 43(3)%.

Assessment of Vitamin Intakes

Three patients (study numbers 6, 7, 8) were receiving monthly vitamin B_{12} injections and two patients were on folate supplements (patients 8, 10). These patients were excluded from the group analyses of the vitamin B_{12} and folate levels. The vitamin contents of each enteral liquid diets are shown in Table 11.2. The estimated pre- and post-HEN vitamin intakes (% of RDA) are shown for individual patients in Table 11.3, and summarised for the whole group in Table 11.4

Patients 1 and 4 had acceptable pre-HEN vitamin intakes, having deficient intakes of only two vitamins (vitamins E and B_6). All the other patients in the group took < 90% of

	PRE - HEN	*DURING HEN*
Calorie intake from daytime diet	1240(70)	1307(85)
Calorie intake from daytime diet as % RDA	49(4)	52(5)
Calorie intake from HEN	-	993(65)
Total calorie intake	1240(70)	2251(94)
Total calorie intake as % RDA	49(4)	90(7)
% of total diet from HEN	-	43(3)

(Key : results expressed as mean(sem) kcal/day; RDA = recommended daily allowance)

TABLE 11.1

Daily Calorie Intakes

	DIETS					
	A	*B*	*C*	*D*	*E*	*F*
Calories (kcal)	1000	1000	1000	1000	1000	1000
Protein (g)	35	42	30	32	29	40
Fat (g)	35	35	16	39	39	40
Vit A	107	147	107	107	107	67
Vit E	230	320	201	150	210	50
Vit C	510	440	234	333	237	150
Vit B_1	125	133	125	125	125	58
Vit B_2	94	100	83	83	83	44
Vit B_6	111	122	106	111	106	61
Vit B_{12}	300	340	225	100	225	75
Folic acid	100	220	104	125	104	100

(Key : Diet A = Ensure; B = Osmolite; C = Elemental 028; D = Reabilan; E = Enteral 400; F = Triosorbon; all values per 1000 ml of diet; vitamin content as % RDA)

TABLE 11.2

Nutrient Content of Commercial Liquid Diets

PATIENTS	*VITAMIN A*				*VITAMIN E*			
	PRE HEN	*DURING HEN*			*PRE HEN*	*DURING HEN*		
		Diet	*HEN*	*Total*		*Diet*	*HEN*	*Total*
1	90	84	75	159	74	80	160	240
2	64	55	103	158	54	50	224	274
3	8	13	107	120	10	2	210	212
4	101	106	160	266	49	51	300	351
5	84	77	67	144	32	34	140	174
6	40	47	133	180	10	15	290	305
7	71	73	106	179	42	38	230	268
8	53	53	80	133	13	16	140	156
9	40	40	80	120	31	32	160	192
10	73	81	160	241	45	43	300	443
11	66	80	133	213	23	22	180	302
12	60	65	75	140	36	30	160	190
13	56	50	75	125	35	38	160	198
14	24	20	160	180	10	14	225	239
15	36	40	75	115	16	18	160	178
16	48	56	128	184	30	34	128	166

(Key : results expressed as % RDA; results < 90% RDA are underlined)

TABLE 11.3

Vitamin Intakes of Individual Patients

PATIENTS	*VITAMIN C*				*VITAMIN B_1*			
	PRE-HEN	*DURING HEN*			*PRE-HEN*	*DURING HEN*		
		Diet	*HEN*	*Total*		*Diet*	*HEN*	*Total*
1	800	960	357	1317	110	95	88	183
2	460	520	308	828	80	70	93	163
3	1240	866	234	1100	142	150	125	275
4	630	650	350	1000	158	142	192	334
5	496	530	106	636	75	67	42	109
6	660	33	633	666	75	71	158	229
7	8	12	506	518	42	50	125	175
8	50	63	280	343	92	108	92	200
9	100	113	380	493	25	33	92	125
10	363	403	350	753	130	142	197	333
11	36	37	593	630	42	33	158	191
12	360	325	357	682	76	84	88	172
13	130	125	357	482	64	52	88	140
14	20	26	500	526	33	40	188	228
15	260	310	357	667	56	48	88	136
16	380	415	284	699	82	84	150	234

(Key : results expressed as % RDA; results < 90% RDA are underlined)

TABLE 11.3 (Continued)

Vitamin Intakes of Individual Patients

PATIENTS	*VITAMIN B_2*				*VITAMIN B_6*			
	PRE-HEN	*DURING HEN*			*PRE-HEN*	*DURING HEN*		
		Diet	*HEN*	*Total*		*Diet*	*HEN*	*Total*
1	110	120	66	186	60	45	78	123
2	60	74	70	144	38	46	85	131
3	33	50	83	133	55	45	98	143
4	261	211	122	333	100	75	143	218
5	150	161	31	192	55	70	65	135
6	50	47	118	165	5	8	125	133
7	50	53	94	147	30	40	100	140
8	117	128	66	194	35	40	65	105
9	17	11	71	82	30	35	75	110
10	166	180	128	307	105	120	140	260
11	94	89	118	207	20	20	125	145
12	84	105	66	171	34	44	78	122
13	120	136	66	202	46	30	78	108
14	16	10	125	135	8	12	167	179
15	66	54	66	110	24	20	78	98
16	84	74	100	174	44	33	127	160

(Key : Results expressed as % RDA; results < 90% RDA are underlined)

TABLE 11.3 (continued)

Vitamin Intakes of Individual Patients

PATIENTS	VITAMIN B_{12}				FOLIC ACID			
	PRE-HEN	DURING HEN			PRE-HEN	DURING HEN		
		Diet	HEN	Total		Diet	HEN	Total
1	364	320	210	530	108	104	70	174
2	216	182	238	410	84	96	154	250
3	16	10	225	235	126	105	104	201
4	440	380	335	715	171	160	156	316
5	265	275	55	330	65	70	70	140
6	170	170	375	545	54	55	125	180
7	135	155	300	455	54	60	100	160
8	145	126	160	286	41	45	73	118
9	8	10	225	235	44	40	75	115
10	295	270	280	550	138	115	156	271
11	120	120	375	495	37	42	125	167
12	180	264	210	474	53	62	70	132
13	235	265	210	475	76	87	70	157
14	34	45	150	195	28	34	188	222
15	125	118	210	328	36	49	70	119
16	164	185	270	455	56	74	125	198

(Key : Results expressed as % RDA; Results < 90% RDA are underlined)

TABLE 11.3 (continued)

Vitamin Intakes of Individual Patients

VITAMINS	*PRE-HEN*	*DURING HEN*		
		Daytime Diet	*HEN*	*Total*
Vitamin A	57(6) [88]	59(6) [94]	107(8) [50]	166(9) [0]
Vitamin E	32(5) [100]	40(5) [100]	203(15) [0]	243(20) [0]
Vitamin C	375(85) [25]	292(76) [25]	378(41) [0]	670(69) [0]
Vitamin B_1	80(10) [69]	80(10) [69]	122(12) [31]	202(17) [0]
Vitamin B_2	92(16) [56]	93(15) [56]	87(7) [56]	180(16) [6]
Vitamin B_6	43(7) [87]	42(7) [93]	102(8) [50]	144(11) [0]
Vitamin B_{12}	182(30) [19]	181(27) [19]	239(21) [6]	420(35) [0]
Folic acid	73(10) [75]	75(9) [69]	108(10) [44]	183(15) [0]

(Key : intakes expressed as mean(sem) % RDA; results in [ ] parentheses are % of total group with intake < 90% RDA)

TABLE 11.4

Daily Intake of Vitamins for Total Group

the RDA of three or more vitamins. The poorest intakes were for vitamins A, E, B_1, B_6, and folate, in particular vitamins A and E (none of the group had normal vitamin E intakes). Intakes for vitamins B_{12} and C from the daytime diet were well within the RDA.

The vitamin intakes from HEN alone were above the RDA for vitamins C and E for the whole group, and for vitamin B_{12} in 15 patients. Patient 5 had a low vitamin B_{12} intake from HEN as the liquid diet he was on (Triosorbon) has a low vitamin B_{12} content. On HEN the vitamin intakes for all the patients were normal, and in most cases much higher than the RDA, except for one patient who had a low intake (82% of RDA) for vitamin B_{12}.

Assessment of Vitamin Status

The pre- and post-HEN vitamin status of individual patients is shown in Table 11.5, and summarised in Table 11.6. Pre-HEN, patients had low levels for only vitamins A, E and C. This was partly due to poor dietary intakes for these vitamins (Table 11.4), but the correlation coefficient for vitamin intakes and status was $r_s=0.44$ ($p > 0.05$).

HEN corrected the deficiencies in all but two patients -

PATIENTS	*VITAMIN A (1.0-2.8 umol/l)*		*VITAMIN E (14-39 umol/l)*		*VITAMIN C (11-114 umol/l)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	1.0	1.1	17	20	73	50
2	2.1	1.8	29	40	20	82
3	1.2	0.5	13	4	10	10
4	0.9	3.1	26	65	45	82
5	1.2	1.3	22	24	36	21
6	1.4	2.7	25	51	85	29
7	0.6	2.0	6	22	10	46
8	0.4	1.7	1	4	80	40
9	1.6	1.7	29	28	50	30
10	0.6	1.1	20	21	26	26
11	0.8	1.4	12	19	38	42
12	0.9	1.7	36	30	29	71
13	0.9	1.3	40	32	15	63
14	0.6	1.4	23	16	46	54
15	0.8	2.0	22	42	17	30
16	0.9	1.1	34	30	37	45

(Key : normal values in parentheses; results underlined represent deficient values)

TABLE 11.5

Vitamin Status for Individual Patients

PATIENTS	*VITAMIN B_1 (<25% act)*		*VITAMIN B_2 (<60% act)*		*VITAMIN B_6 (<150% act)*	
	Pre	*Post*	*Pre*	*Post*	*Pre*	*Post*
1	<2	8	14	9	60	97
2	3	4	9	2	14	29
3	36	8	23	23	47	13
4	3	10	15	8	30	35
5	8	12	8	28	63	52
6	12	2	19	2	65	32
7	6	5	32	27	42	32
8	13	6	12	15	17	36
9	6	2	32	11	42	21
10	16	8	46	30	32	33
11	12	10	44	30	60	34
12	7	10	8	16	58	38
13	4	3	36	12	80	46
14	2	14	30	9	57	45
15	9	15	40	15	98	101
16	19	15	21	18	72	60

(Key : normal values in parentheses)

TABLE 11.5 (continued)

Vitamin Status for Individual Patients

PATIENTS	*VITAMIN B_{12} (150-730 pg/ml)*		*RED CELL FOLATE (106-614 pg/ml)*	
	Pre	*Post*	*Pre*	*Post*
1	412	459	164	195
2	427	550	401	384
3	198	330	154	273
4	158	695	447	410
5	364	316	270	240
6 *	1008	900	299	285
7 *	730	672	265	335
8 *+	2238	2460	>1000	>1000
9	730	425	265	260
10 +	180	400	>1000	>1000
11	346	285	500	460
12	312	243	351	266
13	509	680	249	449
14	392	172	316	345
15	534	407	604	368
16	240	305	240	300

(Key : normal values in parentheses; * = patient on Vitamin B_{12} supplements; + = patient on folate supplements)

TABLE 11.5 (continued)

Vitamin Status for Individual Patients

patient number 3 who failed on HEN and required intravenous feeding, and patient 8 who remained low in vitamin E. While the intakes of the other vitamins (B_1, B_2, B_6, B_{12}, and folate) were low before starting HEN, all the patients had normal plasma vitamin levels.

For the whole group only the pre-HEN vitamin A level [mean(sem)] was low [0.9(0.1) umol/l]. The post-HEN vitamin A level [1.6(0.2)] is significantly increased ($p < 0.001$). Similarly the pre-HEN serum albumin [31.6(0.9) g/l] and transferrin [1.9(0.1)g/l] levels were significantly reduced compared with the post-HEN results, 38.2(1.5) ($p<0.001$) and 2.7(0.2) ($p<0.001$) respectively (Table 11.6).

Disease Activity

The mean(sem) pre-HEN and post-HEN CRP levels were 31.3(6.0) mg/l and 16(3.3) mg/l respectively (Table 11.6). Similarly the median(range) MOD CDI scores were 4(0-7) and 0(0-4). Both CRP and the MOD CDI scores indicated significant improvement whilst on HEN.

	PRE - HEN	*POST - HEN*	
Vitamin A (1.0-2.8 umol/l)	0.9 (0.1) [63]	1.6 (0.2) [6]	*
Vitamin E (14-39 umol/l)	22.2 (2.6) [25]	28 (0.2) [13]	
Vitamin C (11-114 umol/l)	38.6 (5.9) [13]	45.1 (5.3) [6]	
Vitamin B_1 (< 25% activation)	9.9 (2.2) [0]	8.3 (1.1) [0]	
Vitamin B_2 (< 60% activation)	24.3 (3.3) [0]	15.9 (2.3) [0]	+
Vitamin B_6 (< 150% activation)	52.3 (5.6) [0]	44 (6.1) [0]	
Vitamin B_{12} (150-730 pg/ml)	375 (60) [0]	415 (54) [0]	
Red cell folate (106-614 pg/ml)	333 (30) [0]	336 (20) [0]	
Serum albumin (40-52 g/l)	31.6 (0.9)	38.2 (1.5)	*
Serum transferrin (2-4 g/l)	1.9 (0.1)	2.7 (0.2)	*
C-reactive protein (< 10 mg/l)	31.3 (6)	16 (3.3)	+
MOD CDI (0)	4 (0-7)	0 (0-4)	*

(Key : All results are mean(sem), except median(range) for MOD CDI; figures in [ ] parentheses represent % of total group with subnormal levels; results pre and post HEN * = $p<0.01$; + = $p<0.001$)

TABLE 11.6

Pre and Post HEN Results for Vitamin Status and Disease Activity for Total Group

Correlation Between Vitamin A and Disease Activity

There was poor correlation between the pre-HEN vitamin A levels and pre-HEN serum albumin (r_S=-0.12, p=0.68), serum transferrin (r_S=0.2, p=0.52), CRP (r_S=0.21, p=0.56), and the MOD CDI (r_S=0.28, p=0.29). The correlation was equally poor between vitamin A and the disease activity indices in the post-HEN period - serum albumin (r_S=-0.05, p=0.86), serum transferrin (r_S=0.19, p=0.51), CRP (r_S=-0.49, p=0.053), and MOD CDI (r_S=-0.33, p=0.21).

DISCUSSION

Vitamin Intakes

Most of the patients in this study had low intakes of vitamin A, E and folate in the period before starting HEN. After supplementation with HEN, the vitamin intakes increased considerably and were above the RDA except for one patient who continued to have a low vitamin B_6 intake.

Vitamin Status

Despite the low dietary intake of vitamins before HEN, the plasma vitamin levels were remarkably normal except for vitamins A, E and C. There were significant increases in the plasma levels for vitamins A and B_2 after HEN. 63% of patients had low vitamin A levels before starting HEN. Although the low vitamin A levels could be partly explained by reduced retinal binding protein levels (which were not measured in this study), secondary to the acute phase response of active Crohn's disease (Shenkin, 1988), there was not a strong correlation between the vitamin A levels and serum albumin, transferrin and indices of disease activity. It is likely that some of the patients had true vitamin A deficiency.

Vitamin Content of Liquid Diets

The marked improvement in vitamin intake during HEN was due to the high vitamin content of the enteral liquid diets (Table 11.2). The vitamin contents of even 1000 ml of most of the diets are much higher than the RDA : with the exception of most of the vitamins in Triosorbon, the B_2 levels in Elemental 028, Enteral 400 and Reabilan.

SUMMARY

Vitamin status was assessed for 16 patients on HEN. Despite low intakes of most vitamins especially A, E and folate, plasma vitamin levels were generally within the normal range. The pre-HEN plasma vitamin levels for vitamin A and B_2 were low and improved with HEN. Home enteral nutrition is an effective method of correcting poor dietary vitamin intakes.

CHAPTER 12

RESPONSE OF GROWTH RETARDED ADOLESCENTS WITH CROHN'S DISEASE TO HOME ENTERAL NUTRITION

INTRODUCTION

Prevalence of Growth Retardation in Crohn's Disease

Crohn's disease in childhood and adolescence can be complicated by growth retardation and delayed puberty. Although this problem was recognised in early reports of Crohn's disease (Tanner, 1939), it is only recently that studies have found the prevalence to be as high as 17-33% (McCaffrey et al., 1970; Gryboski & Spiro, 1978; Puntis et al., 1984). The clinical significance of growth retardation in Crohn's disease is emphasised by the inclusion of a section of assessing growth in Lloyd-Still's index for disease activity in children (Lloyd-Still et al., 1979 : see Appendix 2.6).

Aetiology of Growth Retardation

While McCaffrey et al. (1970) found abnormalities in growth hormone secretion, later studies have failed to demonstrate significant abnormalities (Gotlin & Dubois, 1973; Layden et al., 1976; Tenore et al., 1977; Kelts et al., 1979; Kirschner et al., 1981A), and if present are thought to be unrelated to the under-lying disease activity (Farthing et al., 1981).

The use of steroids has been implicated as a cause of growth retardation. However Layden et al. (1976) found that several children treated on long- term steroids had normal growth, and Block et al. (1977) commented that many growth retarded children had never been treated with steroids.

Malnutrition is now regarded to be the prime cause for the growth retardation (Kirschner et al., 1981A). Although children with Crohn's disease have been found to have absorptive defects (Kirschner et al., 1978), poor oral intake is the main reason for the malnutrition (Layden et al., 1976; Kelts et al., 1979; Kirschner et al., 1981A).

There have been recent reports on the reversal of growth retardation in children with Crohn's disease treated by improved oral diet (Werlin, 1981; Kirschner et al., 1981A); short course of elemental diet (Morin et al., 1980); and intermittent elemental diet for one year (Belli et al., 1988).

AIMS OF STUDY

The aims of this study were to determine the efficacy of HEN in reversing the growth retardation in adolescents with Crohn's disease, and to assess if polymeric diets were as successful as elemental diets.

PATIENTS AND METHODS

Patients

Five male adolescent patients with Crohn's disease were recruited into this follow-up study. Their demographic details are described fully in chapter 9 (patients 1, 5, 10, 12, 13). Their mean age was 15.2 years (range 13-18), and disease was confined to small bowel (1), small and large bowel (3) and large bowel alone (1) (Table 12.1). Two patients were taking steroids, three were on sulphasazine or mesalazine and two were on iron and other mineral supplements. All had been taking medical therapy for at least 4 months.

All patients had significant growth failure with evidence of linear growth arrest or reduced linear growth (<4 cm/year), and/or bone age delay of greater than two years.

Nutritional Assessment

Previous heights and weights were recorded, and at clinic visits anthropometric measurements and assessments of pubertal development were made (Tanner et al., 1975). An X-ray of the left wrist was taken at the start of the feeding to assess the bone age. A full dietary history was assessed and a dietary card completed over three days before starting HEN.

Nutritional Support

All patients received inpatient instruction, and within 1-2 days were able to self intubate using a fine bore nasogastric tube (Vygon UK Ltd) and able to set up the pump with feed reservoir for overnight feeding. The enteral liquid diets were Ensure (3) (Abbott Laboratories, Maidenhead, UK), Elemental 028 (1) (Scientific Hospital Supplies, Liverpool, UK), and Triosorbon (1) (E. Merck Ltd, Alton, UK). (Table 12.1) The type of diet was determined by individual preference. Patients were followed up for at least 6 months post HEN.

RESULTS

Nutritional Support

The patients were on HEN for a mean (range) duration of 25 (16-30) months. Before starting HEN the mean (sem) daily dietary intake was 1526 (99) kcals, which represented only 56.6 (2.8) % of the recommended dietary allowance. Whilst on HEN the supplemented intake was 860 (160) kcal/day (Table 12.1), although most of the patients took around 700 kcal/night. The intake from HEN was 34.8 (4.6) % of the patients' total daily intake of 2426 (115) kcals, which represented 87(3.3) % of the recommended daily allowance (Passmore et al., 1974).

Reversal of Growth Retardation

The changes in weight, height and pubertal development are shown in Table 12.2. Patient 1's main indications for HEN were to correct his malnutrition and to reverse the delayed puberty. His growth velocity for the previous year had been slightly low at 4 cm/year, but on starting HEN he was at the 97th percentile for height (Figure 12.1). During his period on HEN he grew a further 9 cms. Although during HEN he gained 18 kg in weight over 2 years, he remained at the 75th percentile (Figure 12.2). His pubertal development progressed from 2+ to 5.

Patient 5 was markedly underweight , with short stature.

PATIENTS	*1*	*5*	*10*	*12*	*13*
Site of Disease	L	S+L	S	S+L	S+L
Duration of disease (years)	1	0.5	4	0.3	1
Chronological age (years)	13	14	18	15	16
Bone age (years)	11	11	14	12.5	12
Pre-HEN growth velocity (cm/yr)	4	0	0	1	0.5
Pre-HEN daytime diet (kcal/day)	1650	1440	1340	1640	1760
Pre-HEN daytime diet as % of RDA	63	55	47	57	61
Liquid diet	Ensure	Triosorbon	E028	Ensure	Ensure
Calorie intake from HEN (kcal/day)	700	700	1500	700	700
Total calorie intake during HEN (kcal/day)	2350	2140	2840	2340	2460
% of total intake from HEN	30	33	53	30	28
Total diet as % of RDA	89	81	99	81	85

(Key : L = large bowel; S - small bowel; E028 = Elemental 028; RDA = Recommended Dietary Allowance)

TABLE 12.1

Patients' Demographic Details and Dietary Intakes

PATIENTS	*1*	*5*	*10*	*12*	*13*
HEIGHT					
Pre-HEN	165(97)	138(<3)	144(<3)	149(<3)	153(<3)
6 months	169(90)	142(<3)	148(<3)	151(<3)	161(<3)
12 months	170(90)	144(<3)	150(<3)	153(<3)	166(10)
18 months	171(90)	146(<3)	154(<3)	156(<3)	168(10)
24 months	172(75)	149(<3)	160(<3)	-	169(25)
30 months	-	150(<3)	163(3)	-	173(25)
6 months post HEN	174(75)	154(<3)	165(10)	160(3)	175(50)
WEIGHT					
Pre-HEN	45.1(75)	29(<3)	35(<3)	37(<3)	29(<3)
6 months	50(75)	37(<3)	44(<3)	41(<3)	40.5(<3)
12 months	53.7(75)	39(<3)	44.5(<3)	47(<3)	40(<3)
18 months	60(75)	41(<3)	46(<3)	52(10)	41(<3)
24 months	61(75)	42(<3)	50.5(3)	-	41(<3)
30 months	-	41(<3)	49(<3)	-	43(<3)
6 months post HEN	63(75)	48(3)	52(3)	54(10)	46(<3)
PUBERTY RATINGS					
Pre-HEN	2+	2	3	2	2
6 months	2+	2	3	2	2
12 months	3	2	4	3	3
18 months	4	3	5	4	3
24 months	5	4	5	-	4
30 months	-	4	5	-	4
6 months post HEN	5	5	5	4	4

(Key : numbers in parentheses are percentiles; height in cm; weight in kg.)

TABLE 12.2

Height Weight and Puberty Ratings

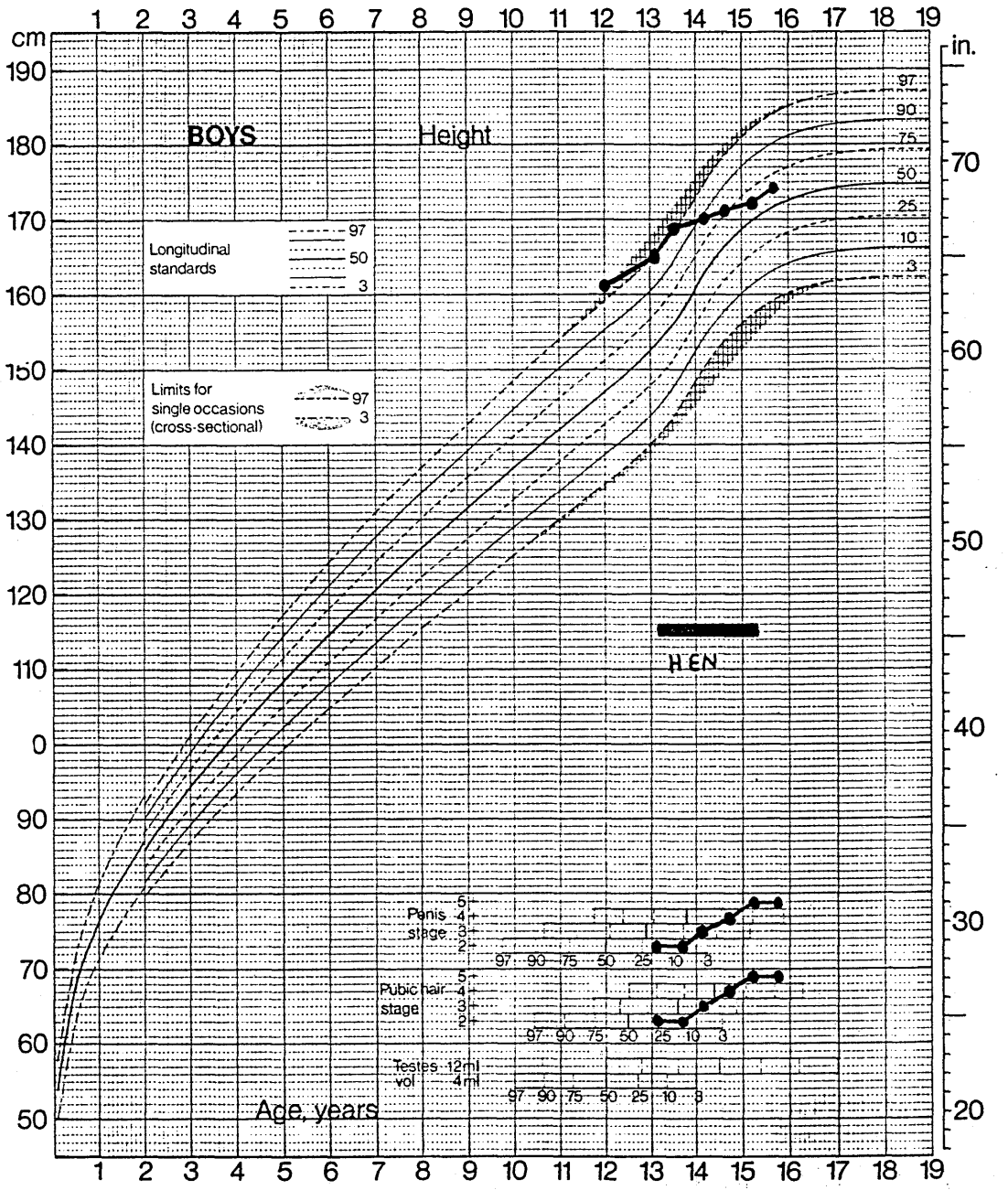


FIGURE 12.1

Height and Pubertal Development Chart for Patient 1

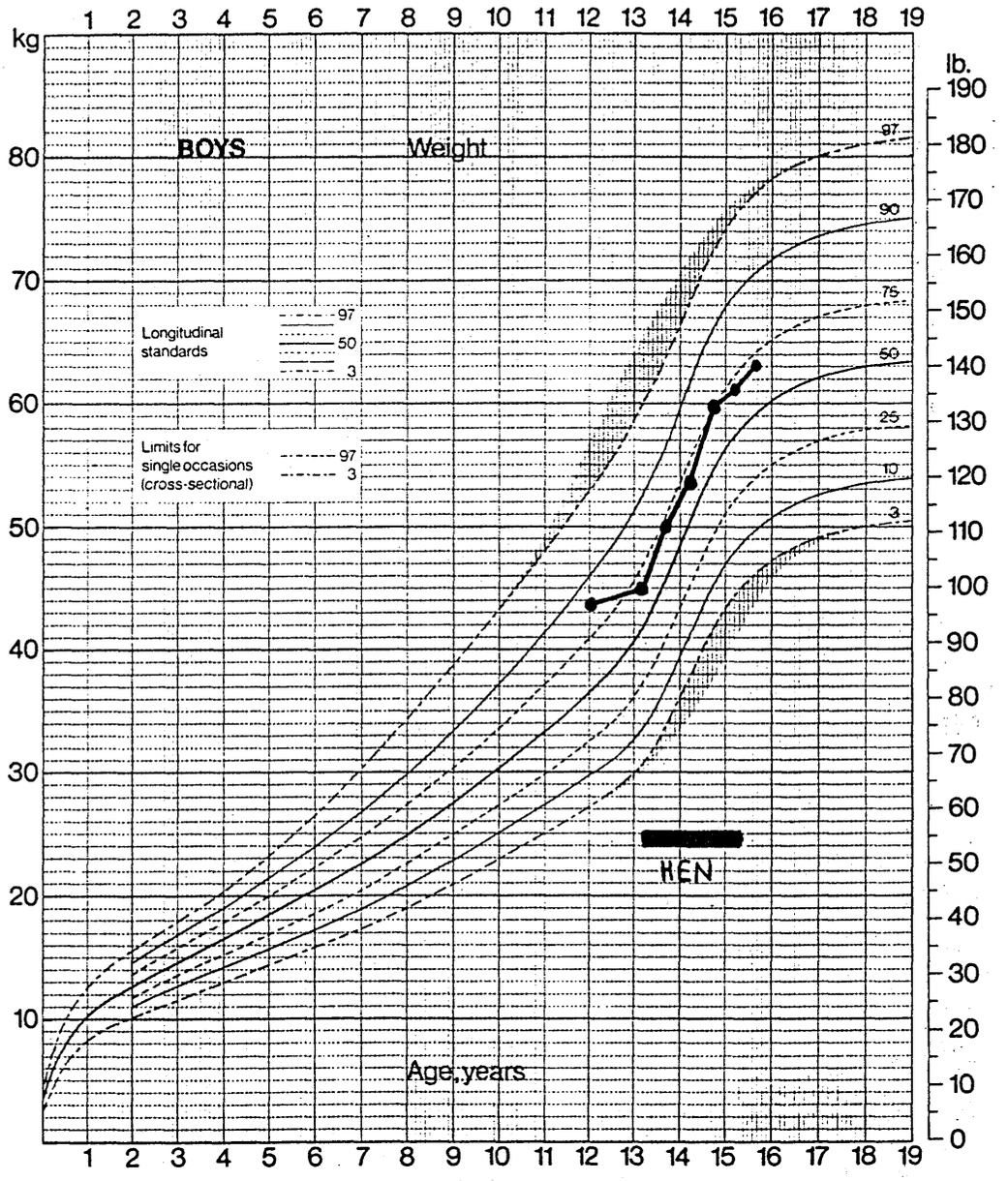


FIGURE 12.2

Weight Chart for Patient 1

He increased his height by 12 cm whilst on HEN for 30 months (Figure 12.3), although still remaining below the 3rd percentile. His weight initially increased on HEN but then plateaued at around 40-41 kg (Figure 12.4). At the latter stages of his period on HEN he developed obstructive symptoms and required a right hemicolectomy. Following this resection he gained a further 7 kg in weight, with an increase in height. His pubertal development was delayed until his weight had climbed to around 40 kg. Even following his resection his height remained below the 3rd percentile, despite a growth velocity of 5-7 cm/ year. He refused further HEN at that stage. Fortunately during the 18 months post resection he had achieved catch up height and had reached the 10th percentile.

Patients 10, 12 and 13 were all similar with pre-HEN heights and weights below the 3rd percentile. After a period of HEN all managed to undergo reversal of their growth retardation, and were within their 3rd and 10th percentile for age. Patient 13's weight continued to be below the 3rd percentile despite an increase of 14 kg. The improvement in growth continued after HEN was stopped (Figures 12.5 to 12.10).

The summaries for the changes in weights, heights and pubertal developments are shown in Table 12.3. The mean

PATIENTS	*1*	*5*	*10*	*12*	*13*
Increase in height (cm)	7	16	19	7	20
Increase in weight (kg)	17.9	19	17	15	14
Growth vel before HEN (cm/yr)	4	0	0	1	0.5
Growth vel on HEN (cm/yr)	3.5	6.4	7.6	4.7	8
Change in pubertal score	+3	+3	+2	+2	+2

(Key : vel = velocity)

TABLE 12.3

Increase in Height, Weight and Pubertal Development During HEN

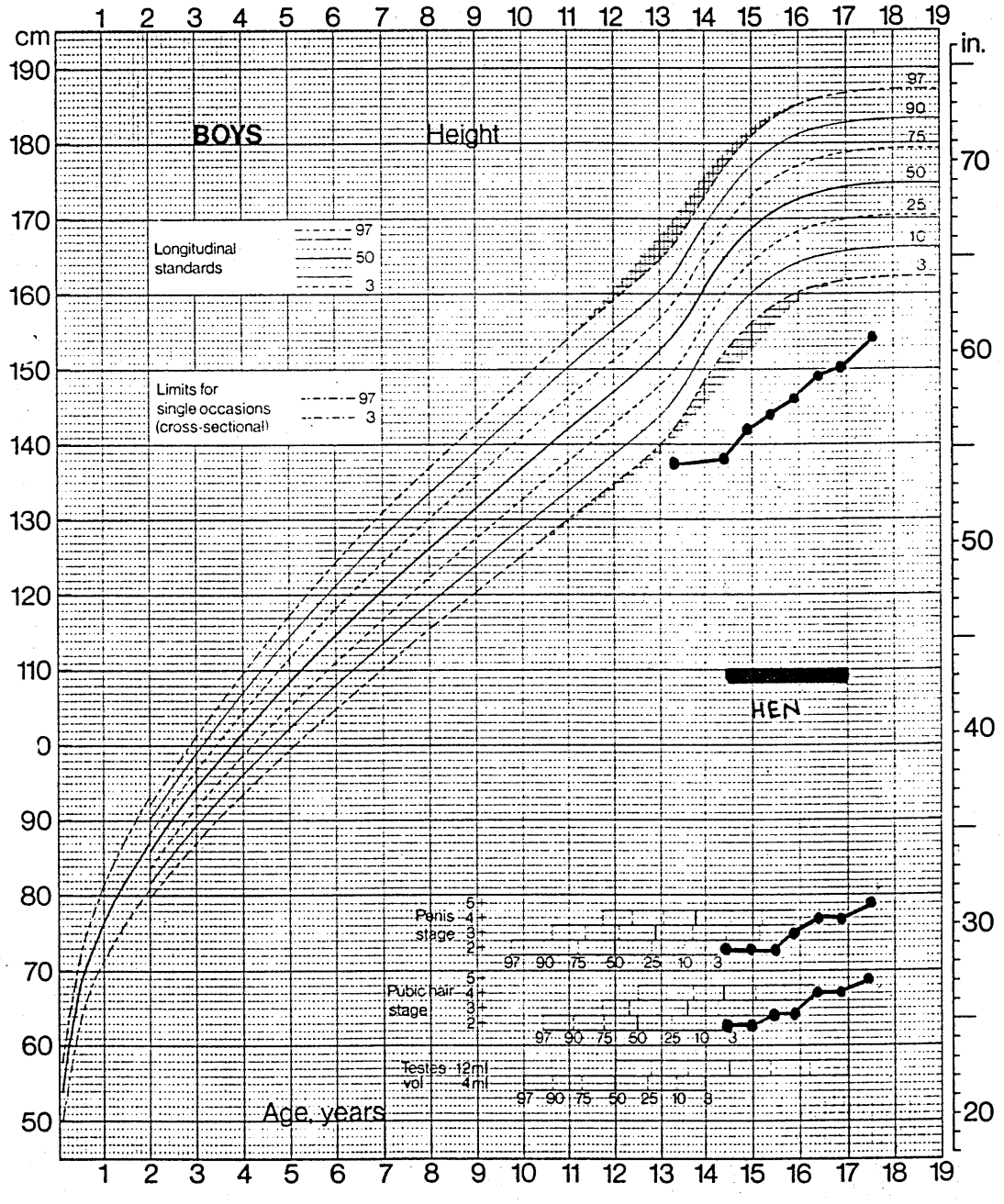


FIGURE 12.3

Height and Pubertal Development Chart for Patient 5

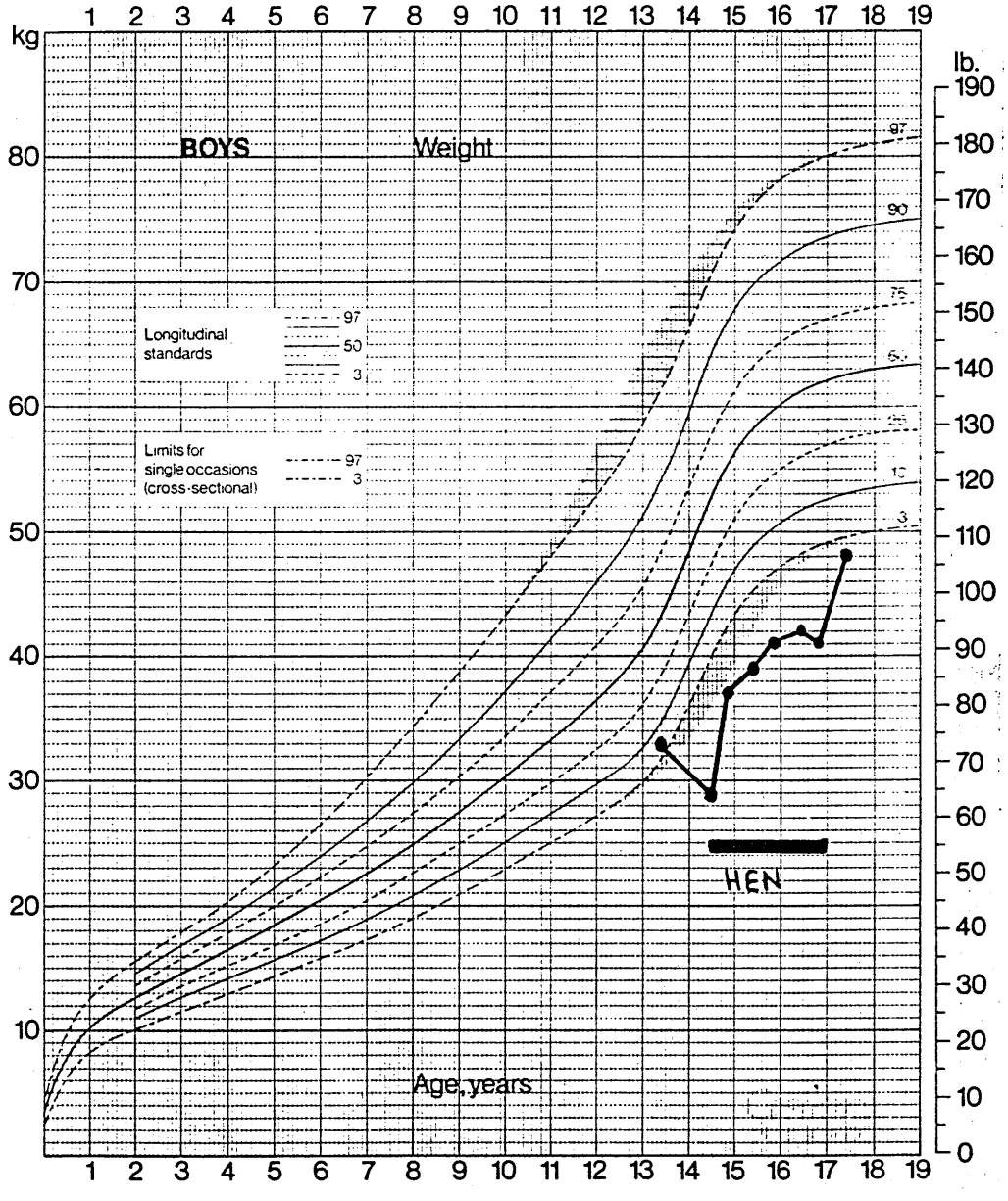


FIGURE 12.4

Weight Chart for Patient 5

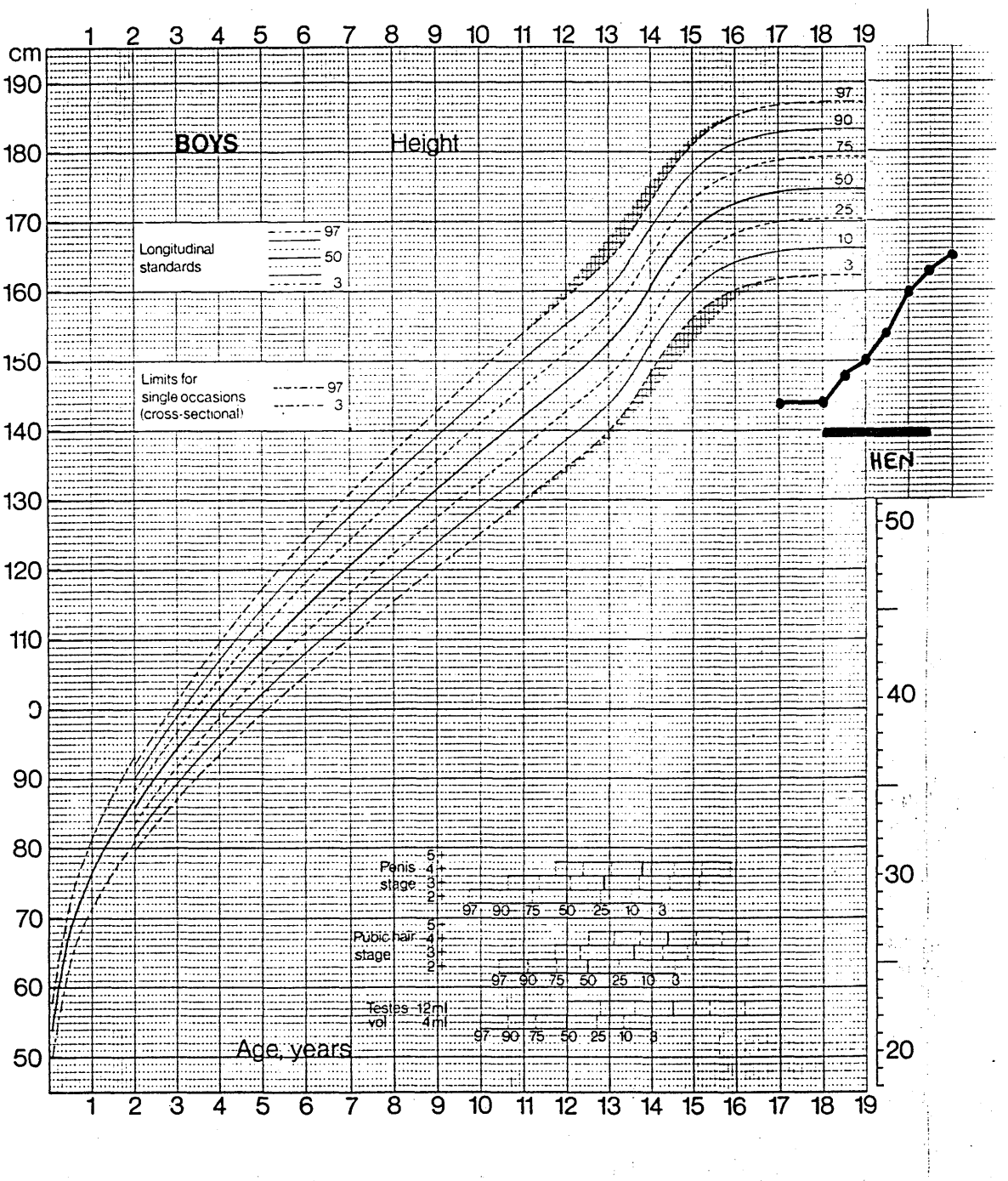


FIGURE 12.5

Height and Pubertal Development Chart for Patient 10

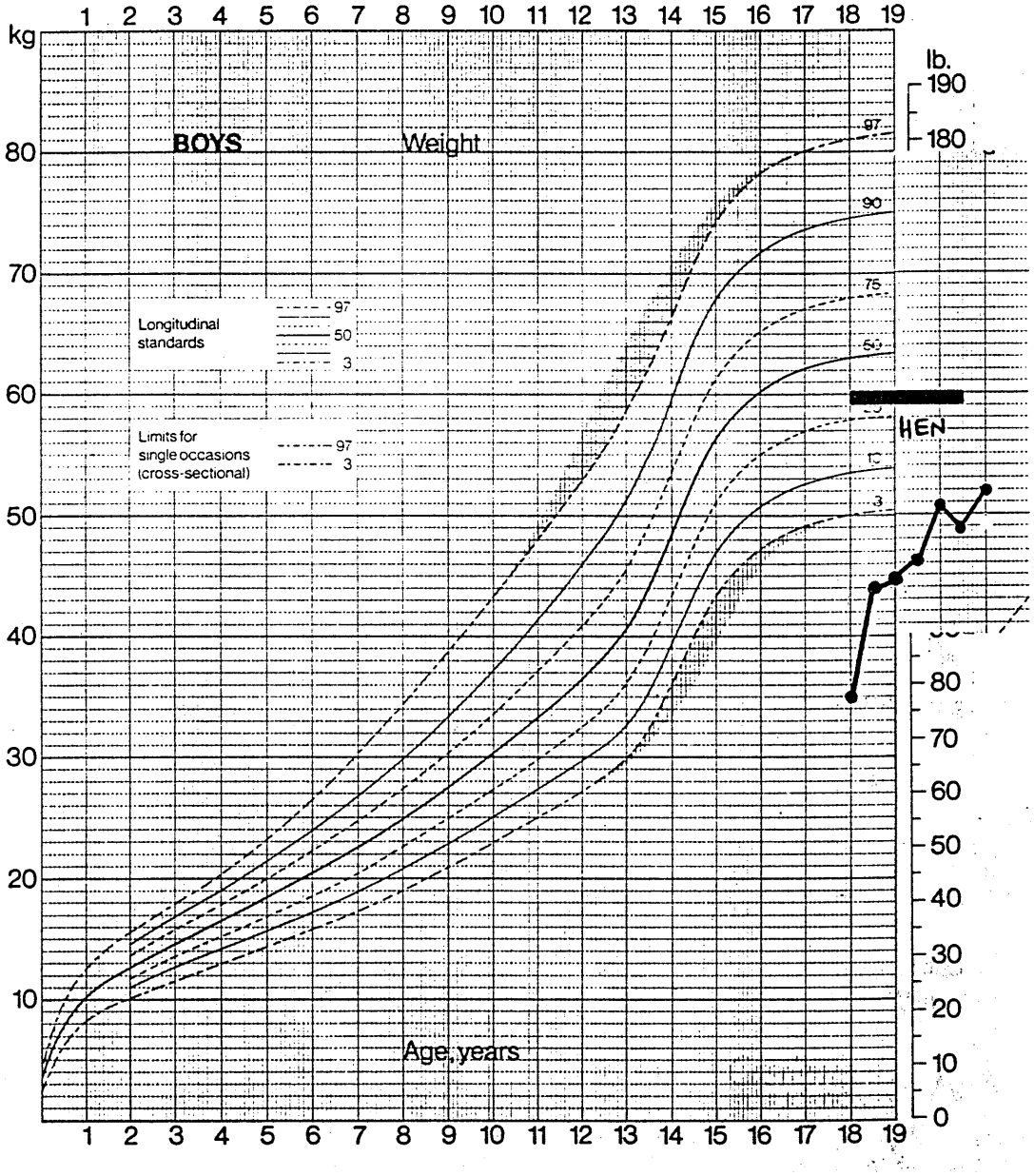


FIGURE 12.6

Weight Chart for Patient 10

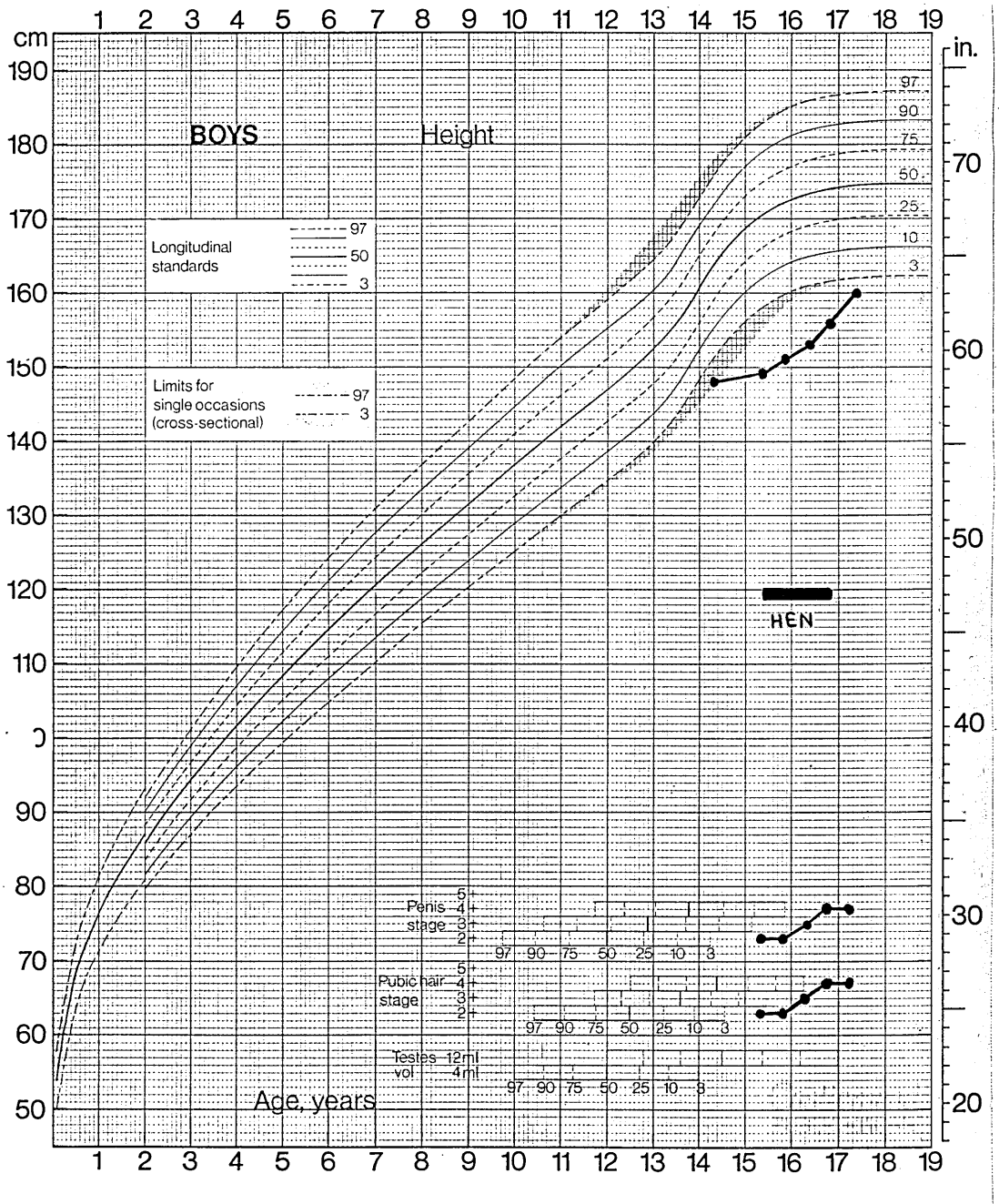


FIGURE 12.7

Height and Pubertal Development Chart for Patient 12

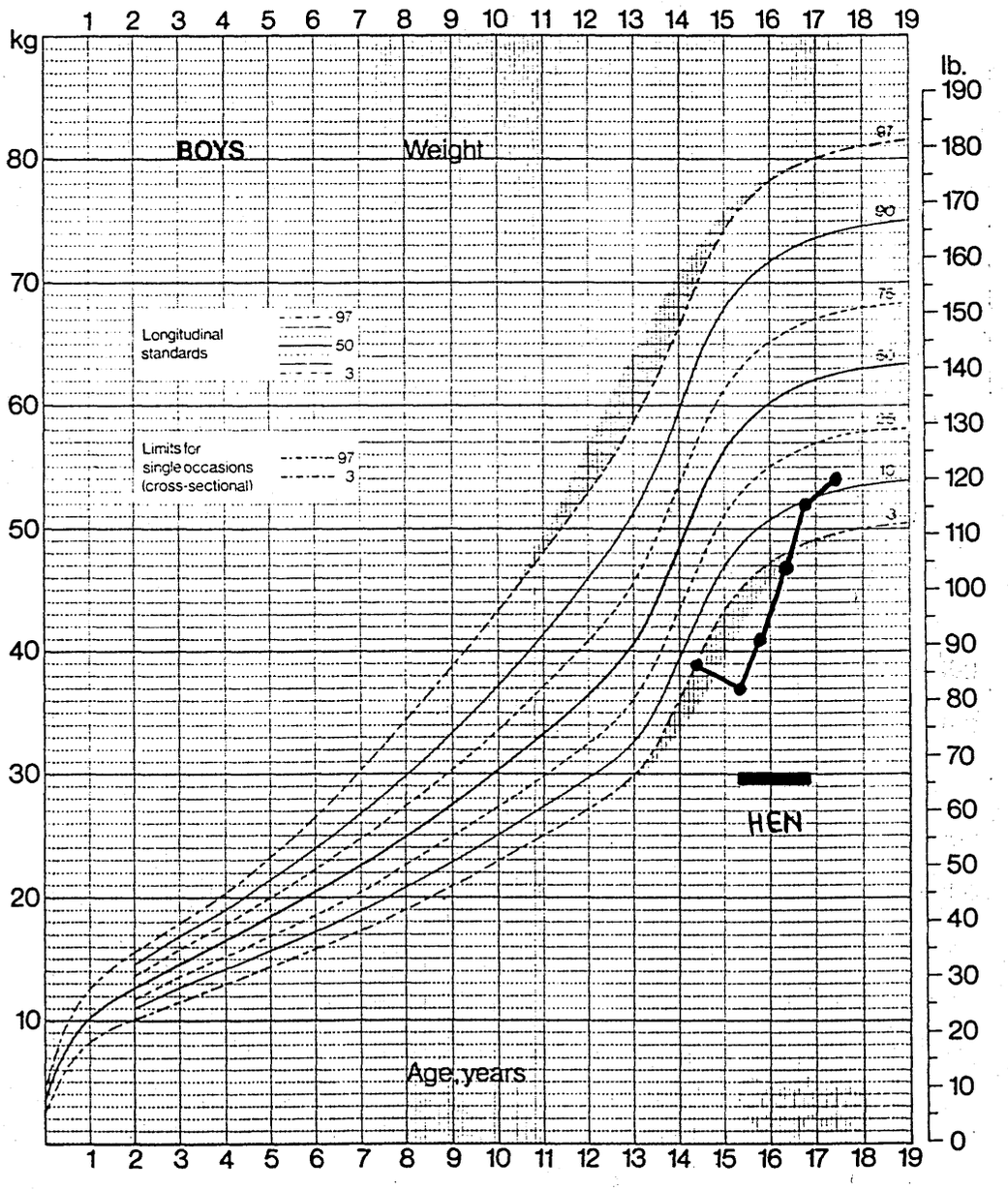


FIGURE 12.8

Weight Chart for Patient 12

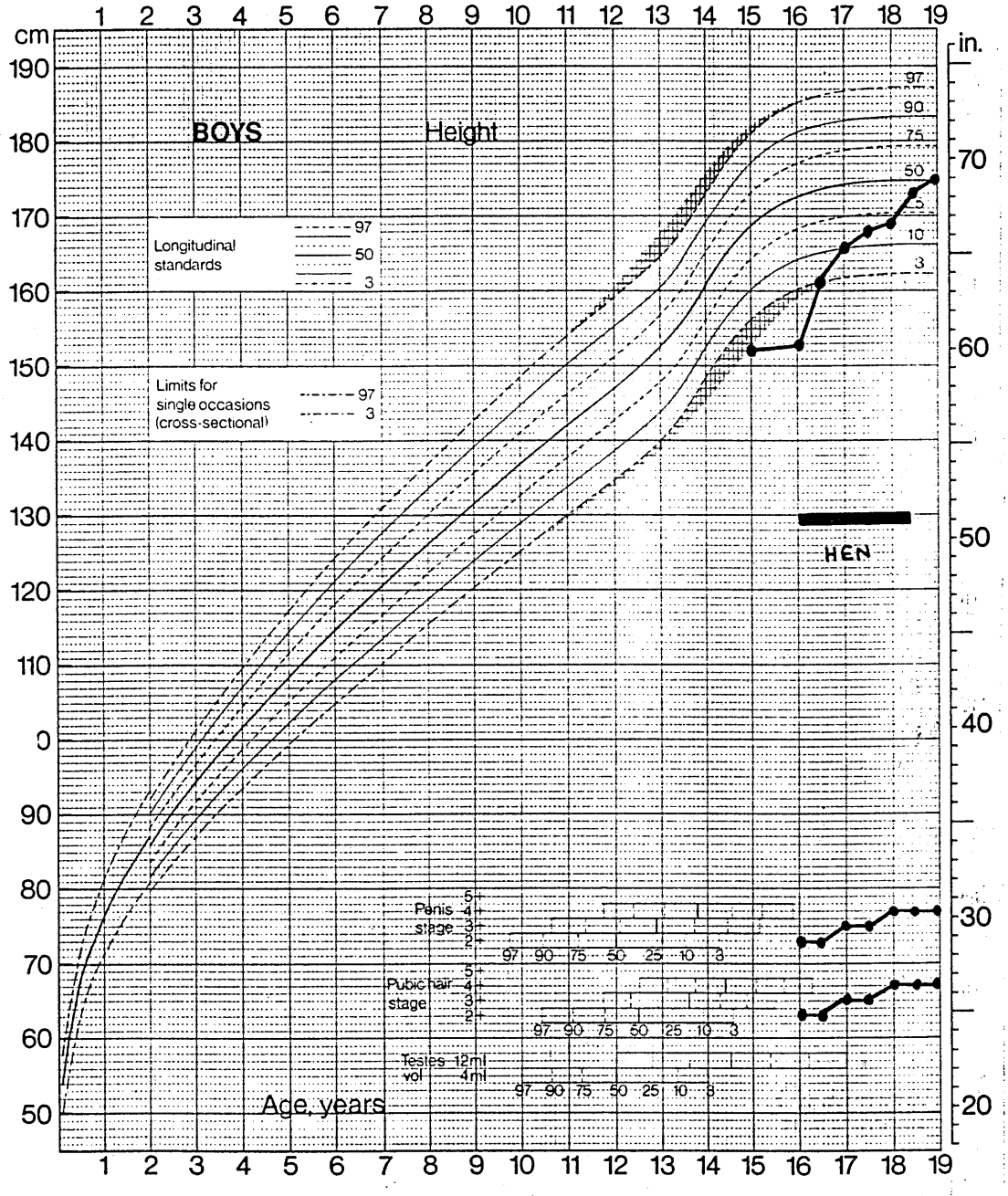


FIGURE 12.9

Height and Pubertal Development Chart for Patient 13

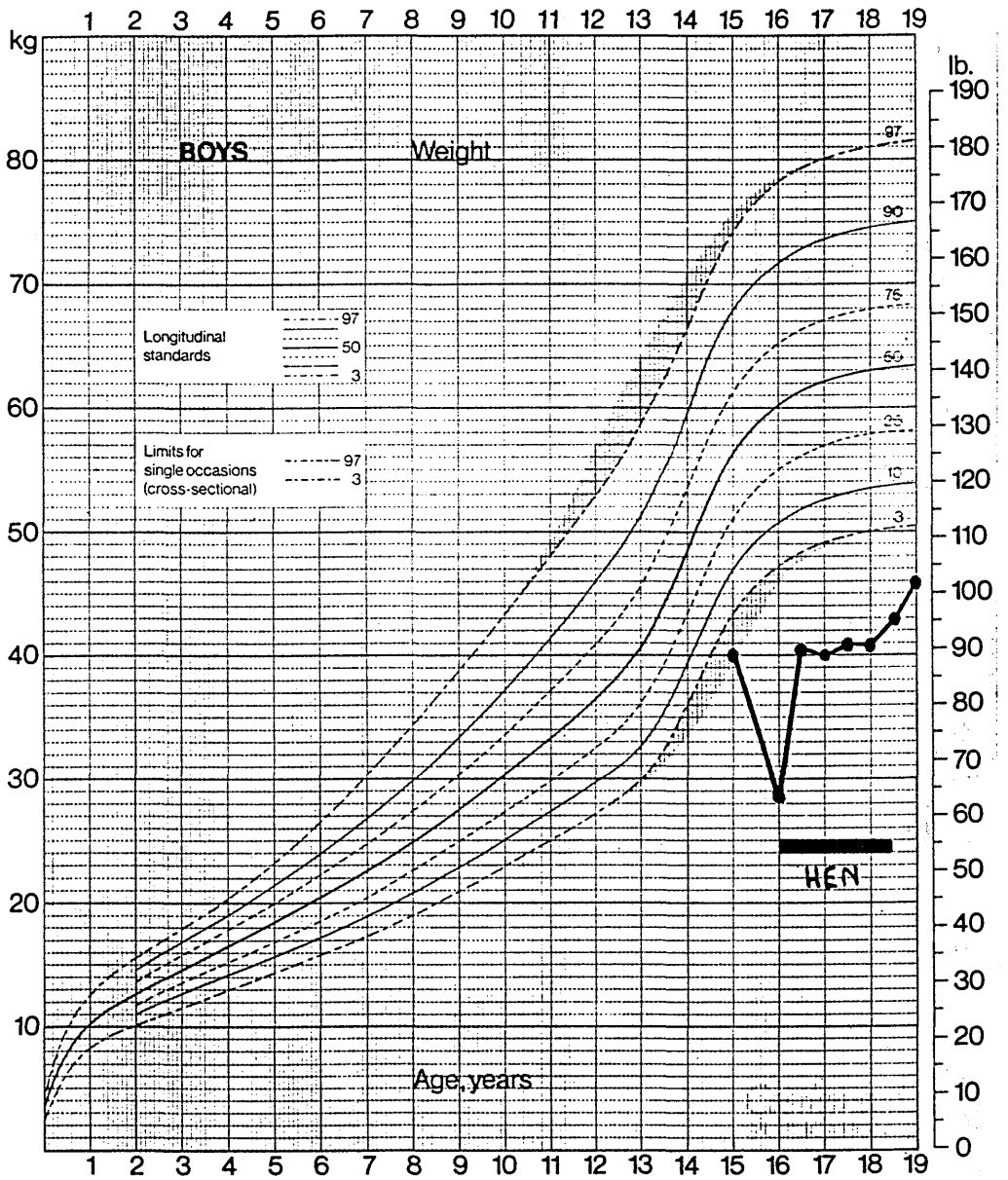


FIGURE 12.10

Weight Chart for Patient 13

(sem) increase in height was 13.8 (2.9) cm, and in weight was 16.6 (0.9) kg. Patients on HEN had a growth velocity of 6.1 (0.9) cm/year, compared with the pre-HEN growth velocity of 1.1 (0.7) cm/year. The pubertal development progressed by 2.4 (0.3).

DISCUSSION

Reversal of Growth Retardation

This study has shown that growth retardation and delayed puberty in patients with Crohn's disease can be reversed with additional dietary intake using HEN. All patients before starting HEN had very low mean (sem) dietary intakes of only 1526 (99) kcal/day, which represented 56.6 (2.8)% of their recommended intakes for age and height (Passmore et al., 1974). Using a modest increase in dietary intake at 860 (160) kcals/day from HEN , the mean (sem) total dietary intake rose to 87(3.3)% of the recommended intake.

The total calorie intake in this study was lower than reported by Kelts et al. (1979), who fed their patients 75 kcal/kg/day by a combination of oral diet and intravenous feeding (mean intake of 136% of expected dietary intake), and by Werlin (1981), who gave 3000 kcal/day via enteral nutrition to two patients. Kirschner et al. (1981A), using supplemented oral diets, increased their patients' dietary intakes from 56% of the recommended intake to 91 % (an increase from 1535 to 2493 kcal/day) and found a good response. The dietary intakes from the study by Kirschner et al. (1981A) were similar to my results. It is unlikely that many patients would be able to tolerate more than 3000 kcals/day using oral diets and supplemented HEN.

Catch-Up Growth

Of the four patients who had marked growth retardation, only one patient (patient 13) managed to attain an increase in height to the 50th percentile. The other patients remained in the 3rd-10th percentiles. There has been concern over the possible inability of therapeutic modalities, including surgery (Homer et al., 1977) and HEN (Werlin, 1981), to correct for the "catch-up" growth in growth retarded Crohn's patients, especially following puberty.Patient 5 in this study remained below the 3rd percentile after stopping HEN and also following surgery, but within the next eighteen months his height had reached the 10th percentile. Kirschner et al. (1981A) also found that several patients were able to reach their pre-illness height percentile.

It is unlikely that the improved growth in this study arose from the onset of puberty, as the reversal of growth retardation occurred at an earlier stage compared with the pubertal development.

In the 1970's surgical resection was considered to be the best form of treatment for growth retardation in Crohn's disease (Block et al., 1977). Later, when evidence that poor calorie intake was the main factor in the aetiology of growth retardation, intravenous feeding was

attempted with success (Layden et al., 1976; Kelts et al., 1979). Subsequent studies (Werlin, 1981; Kirschner et al., 1981A) and this study, have shown that additional calorie intake in the form of HEN can produce equally good results. Belli et al. (1988) have also shown that intermittent HEN therapy (1 month out of 4 months) using elemental diets can improve growth retardation.

Polymeric Diets

Although several studies have used elemental diets (Kirschner et al., 1981A; Belli et al., 1988) for reversal of growth retardation, this study and others (Werlin, 1981; Kirschner et al., 1981A) have shown comparable results with polymeric diets, which are generally easier to tolerate and are less expensive. The most important factor to correct growth retardation and delayed puberty in adolescents with Crohn's disease appears to be the requirement to rectify reduced calorie intakes.

SUMMARY

Five male adolescents with Crohn's disease, complicated by short stature and delayed puberty, received HEN for a mean period of 25 months, in an attempt to correct poor oral dietary intakes. All responded to HEN although three patients demonstrated poor "catch-up" growth and remained below the 10th percentile for height.

SECTION VI

CONCLUSION

CONCLUSION

The principle aims of the thesis have been achieved : links between Crohn's disease activity and nutritional problems were studied; in particular malnourished patients were found to be able to mount an appropriate acute phase response; and enteral nutrition improved disease activity, both in the short term and also during periods of long-term home enteral nutrition.

It was not my intention at the start of these studies to identify the ideal, "gold standard" method of assessing Crohn's disease activity : this task may be completely impractical and even inappropriate for Crohn's disease, which has so many heterogeneous features. Further, while I had not planned to create a new index for assessing disease activity, I was interested in determining which of the present routine indices and tests were suitable for use in diet trials, and for patients with stomas.

The modified Crohn's disease index (MOD CDI), appeared to be the most flexible index for my studies, and should provide an accurate assessment for all types of patients and in different clinical conditions. This index, in addition to the CRP level should be able to provide an adequate assessment of disease activity.

I found that the standard indium-oxine mixed leucocyte scanning provided very little additional information and feel that it has a limited role in the assessment of disease activity. At the start of these studies I was unable to include faecal indium excretion as a method of disease activity assessment. While Saverymuttu et al. (1986C) have suggested that faecal indium excretion may be the "best" method of assessing bowel inflammation, its use is limited by the complicated technique, difficulty of stool collection and inability to perform serial estimations.

I was disappointed with the small number of patients in the diet trial, which is a recognised problem with such a trial. Both polymeric and elemental diets appeared to improve disease activity, with Enteral 400 having a better overall remission rate. However, I suspect that several patients had not entered full remission , which led to early relapse.

The results of the long-term home enteral nutrition studies were more encouraging, in that most patients showed an improvement in disease activity and reduction in the rate of hospital admissions whilst on HEN without additional therapy. This improvement seemed to persist for 6 months or longer in most cases. As the improvement was

more marked with patients on long-term enteral nutrition, it is likely that the main effect was due to an improved nutritional state, which would not have been so marked with the shorter diet trial. Future diet trials may have to concentrate on longer term feeding.

Nutritional problems and Crohn's disease are so inextricably linked that every patient with Crohn's disease should be considered at risk and nutritional support, in its simplest form, commenced at an early stage and maintained for a long period. Hopefully easier management of Crohn's disease patients would result, and emaciated patients with Crohn's disease would become rarities.

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APPENDIX 2.1

WILLOUGHBY INDEX

CLINICAL FEATURES

- Lassitude
- Nausea
- Abdominal pain
- Rectal bleeding
- Wound sepsis
- Fistula
- Anal disease
- Arthropathy
- Skin rash
- Mouth ulcers
- Ocular inflammation

(graded 0-3 where 0 = absent; 1 = mild, no limitation of activities; 2 = moderate, some limitations of activities; 3 = severe, considerable limitation of activities)

STOOL FREQUENCY

Graded 0 - 2

LABORATORY PARAMETERS

Haemoglobin < 12 g/dl (males)
< 11.5 g/dl (females)

ESR > 20 mm/h

Albumin < 3.5 g/100 ml.

(one point for each of the abnormal parameter.Theoretical maximum score of 38)

APPENDIX 2.2

De DOMBAL INDEX

	Mild Attack	Severe Attack
LOCAL FEATURES		
Bowel actions	2-3 /day	6 or more/day
Pain	occasional/mild	continuous/severe
Rectal bleeding	negligible	macroscopic blood in stools
SYSTEMIC FEATURES		
Pulse rate	< 90/min	> 100/min
Temperature	< 99^{o}F	> 100^{o}F
Haemoglobin	> 80 %	< 70 %
Weight loss	< 1/2 stone	> 1 stone

(Attacks intermediate in severity graded as moderate)

APPENDIX 2.3

TALSTAD INDEX

DISEASE ACTIVITY PARAMETER	SCORE 1	2	3	4
Diarrhoea (motions / day)	3-5	6-10	>10	-
Fever (^{o}C)	38-39	> 39	-	-
Tachycardia	-	>100/min	-	-
Abdominal pain	slight	mod	severe	-
Weight loss	5-10 kg	>10 kg	-	-
Fistula	-	present	-	-
X-ray of colon	slight	mod	sev	toxic
Proctoscopy	slight	severe	-	-
ESR (mm/h)	10-30	> 30	-	-
Hb (g/100ml)	10-11.8	< 10	-	-
Leucocyte count (10000/ul)	-	> 1	-	-
Thrombocyte count (100000/ul)	-	> 4	-	-
Total protein (g/100ml)	<6.5	< 5.5	-	-
Albumin (g/100ml)	<3.3	< 2.5	-	-
Serum iron (ug/100ml)	< 70	< 50	-	-
TIBC (ug/100ml)	<270	<200	-	-
Schilling test	-	< 10%	-	-
Serum folic acid (mg/ml)	<3.0	-	-	-

(maximum score of 38. Mod = moderate; sev = severe)

APPENDIX 2.4

CROHN'S DISEASE ACTIVITY INDEX (INDEX)

ITEM	MULTIPLIED BY
Number of liquid/soft stools per week	2
Sum of 7 daily ratings of abdominal pain (0=none, 3=severe)	5
Sum of 7 daily ratings of well being (0=generally well, 4=terrible)	7
Number of associated problems - arthritis/arthralgia - iritis/uveitis - erythema nodosum/aphthous stomatitis - anal fissure/fistulas/abscesses - other fistula - fever over 100^{o}F during last week	20
Taking opiate antidiarrhoeal (0=no, 1= yes)	30
Abdominal mass (0= none, 5=definite)	10
Haematocrit deficeit (males: 47-HCT females:42-HCT)	6
Body weight (% below standard) Add (underweight) or subtract (overweight)	1

TOTAL SCORE =

APPENDIX 2.5

O'DONOGHUE INDEX

SYMPTOMS

Well being
Abdominal pain
Bowel frequency
Rectal bleeding

PHYSICAL SIGNS

Recent weight loss
Pyrexia
Abdominal mass
Abdominal tenderness
Anal lesion
Fistulas
Joint, eye or mucocutaneous lesion

(all scores = absent (0); mild with no limitation of activities (1); moderate with some limitation ofactivities (2) ; severe, with considerable limitation of activities (3).Abdominal mass scored 0=absent, 1=present)

LABORATORY TESTS

Haemoglobin
White blood count
ESR
Serum albumin

(all scored 0-2)

Theoretical maximum score of 39

APPENDIX 2.6

LLOYD-STILL INDEX

General activity (10)

10	normal school attendance bowel motions < 3 per day
5	lacks endurance bowel motions 3-5 per day misses < 4 weeks school/year
1	fever, home tutor bowel motions > 5 per day severely restricted activity

Physical examination and complications (30)

Abdomen	10	normal
	5	mass
	1	distension, tenderness
Proctoscopy/perianal	10	normal, no fissures
	5	friability, 1 fissure
	1	ulcers, pseudopolyps, bleeding, multiple fissures, fistulas.
Arthritis	5	nil
	3	one joint/arthralgia
	1	multiple joints
Skin/stomatitis/eyes	5	normal
	3	mild stomatitis
	1	erythena nodosum, pyoderma, severe stomatitis, uveitis

Nutrition (20)

Height	10	> 2 ins/year	Weight	10	normal
	5	< optimal %		5	no gain
	1	no growth		1	weight loss

X-Rays (15)

15	normal
10	ileitis, colitis to splenic flexure
5	total colon or ileocolonic involvement
1	toxic megacolon, obstruction

APPENDIX 2.6 contd

Laboratory (25)

Haematocrit	5	> 40	ESR	5	normal
	3	25-35		3	20-40
	1	< 25		1	> 40

White blood count			Albumin		
	5	normal		10	normal
	3	< 20,000		5	3.0 g/l
	1	> 20,000		1	< 2.5 g/l

APPENDIX 2.7

CROHN'S DISEASE INDEX (CDI)

A. General well being (0 = very well - 5 = terrible)

B. Abdominal pain (0 = none - 3 = terrible)

C. Number of liquid stools / day

D. Abdominal mass (0 = none - 3 = definite and tender)

E. Complications - arthralgia, uveitis, erythema nodosum, aphthous ulcers, pyoderma gangrenosum, anal fissure, new fistula, abscess (score 1 per item)

APPENDIX 2.8

ACTIVITY INDEX (AI)

ITEM	MULTIPLY BY
Serum albumin	- 5.48
ESR	0.29
Quetelet index	- 0.22
Abdominal mass (1 = none - 5 = diameter > 12 cm)	7.83
Sex (1 = male, 2 = female)	- 12.3
Temperature ^{o}C	16.4
Stool consistency (1 = well formed - 3 = watery)	8.46
Resection (1 = no, 2 = yes)	- 9.17
Extraintestinal lesion (1 = no, 2 = yes)	10.7

Constant - 209

TOTAL =

APPENDIX 2.9

NEW CROHN'S DISEASE ACTIVITY INDEX (NCDAI)

ITEM	MULTIPLY BY
Average daily number of liquid or very soft stools over the past week (3-5 stools = 1, over 5 = 2)	4
Average daily temperature over the past week (38-39^{o}C = 1, > 39 = 2)	5
Anal fistula or anorectal abscess (=2)	2.5
Serum iron [0.1 x (150 - serum iron)]	1.5
C-reactive protein	4
$Alpha_2$- globulin	1.5
Seromucoids	1

APPENDIX 2.10

OXFORD INDEX

Pain present
Bowels > 6/day or blood and mucus
Perianal complications
Fistula
Other complications
Mass present
Waisting/ emaciation
Temperature above 38 C
Abdominal tenderness
Haemoglobin below 10 g/dl

(score 1 for each feature, where present)

APPENDIX 2.11

CAPE TOWN INDEX

ITEM	SCORE
Diarrhoea	0 = none - 3 = > 6/day
Abdominal pain	0 = none - 3 = severe
Well being	0 = normal - 3 = terrible
Local complications	1 = skin tag, 2 = sinus 3 = fistula.
Systemic complications	1 = stomatitis, 2=arthralgia 3 = arthritis, uveitis, rash
Temperature ^{o}C	0 = < 37,1 = < 38, 2 = < 39, 3 = > 39
Weight compared with last weight.	2 = < 95%, 3 = < 90%
Abdominal mass	2 = indefinite, 3 = certain
Abdominal tenderness	1 = mild, 2 = moderate, 3 = severe
Haemoglobin (g/dl)	0 > 12, 1 = < 12, 2 = < 11, 3 = < 10

APPENDIX 2.12

WRIGHT SIMPLE INDEX

CLINICAL PARAMETERS

Diarrhoea
Pain
Systemic manifestations
general well-being

GRADES
1 = well
2 = mild symptoms
3 = moderate symptoms
4 = severe symptoms
5 = acutely ill
6 = fulminating attack

APPENDIX 2.13

CROHN'S ACTIVITY GROUP SCALE

VARIABLE	COEFFICIENT
Haemoglobin (g/dl)	0.3255
Serum carotene (ug/dl)	0.0112
Prednisolone (tablets/day)	-0.2594
Serum iron (ug/dl)	0.0050
Weight (kg)	0.0930
Age (year)	-0.0406
Mean red cell volume (fl)	0.0415
% ideal weight	-0.0296
Sex (1 = male, 2 = female)	1.6653
Serum phosphorus (mg/dl)	-0.4870
Triceps skinfold thickness (mm)	-0.0396
Serum calcium (mg/dl)	0.3418
Duration (years)	0.0274
Serum vitamin C (umol/l)	-0.0051
Total lymphocytes	-0.0001
(Constant)	-14.2213

APPENDIX 4.1

LABORATORY METHODS FOR MEASURING PROTEINS AND MICRONUTRIENTS

Albumin, calcium, phosphate	SMAC analyser
Magnesium, zinc, copper	Atominc absorption spectrometry (Perkin-Elmer model 3030)
Transferrin	Immunoturbometric method
Iron	Colourimetric method (Hitachi 704)
Vitamins A, E and C	Spectrophotometry (Perkin-Elmer MPS 32)
Vitamins B_1, B_2 and B_2	Red cell enzyme activation
Vitamin B_{12} and red cell folate	Radioimmunoassay
Urinary nitrogen	Micro-Kjeldahl method